MONASH University

Epidemiology and prevention of sexually transmissible infections among gay and bisexual men in the era of HIV pre-exposure prophylaxis

Michael William Traeger

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School of Public Health and Preventative Medicine

Department of Epidemiology and Preventative Medicine

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Abstract

HIV pre-exposure prophylaxis (PrEP), the use of antiretroviral medications by people without HIV to reduce their risk of HIV acquisition, is a highly efficacious HIV prevention strategy. In Australia, PrEP was first available through large implementation trials which enrolled more than 20,000 people nationally from 2016, and from 2018 became available through Australia's universal healthcare scheme. PrEP has significantly impacted the sexual and overall wellbeing of gay and bisexual men (GBM) in Australia, leading to increased comfort in condomless sex with partners with HIV and reductions in serosorting.

While traditional combination approaches to HIV prevention, including behavioural risk reduction, regular testing, and condom use, also help prevent other sexually transmitted infections (STIs), newer biomedical prevention strategies, such as PrEP and Treatment as Prevention (or Undetectable = Untransmissible) have led to a decoupling of HIV and STI prevention. In Australia, HIV and STI epidemics among GBM are now diverging, with HIV infections steadily declining as STI infections increase.

The overarching aims of my PhD were to explore the impact of PrEP implementation in Australia on the epidemiology of non-HIV STIs among GBM and improve understanding of the sexual and health-seeking behaviours of GBM using PrEP, to help guide Australia's response to increasing STIs. This thesis comprises of two literature reviews and five empirical studies. The first two studies are epidemiological analyses of data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS), a nation-wide sentinel surveillance system for blood borne viruses and STIs. Representing the largest STI incidence studies of PrEP users (>22,000) and GBM (>100,000) globally, these studies found stabilising trends in chlamydia and gonorrhoea among PrEP users, but high rates of syphilis reinfection across groups of GBM suggesting increasing syphilis transmission between sexual networks of GBM with and without HIV, influenced by changes in PrEP use and serosorting.

The third study is a systematic review and meta-analysis of studies of hepatitis C among GBM using PrEP. This meta-analysis found that high rates hepatitis C in early PrEP studies were likely reflective of risk-based PrEP eligibility criteria and higher community hepatitis C viraemia at the time of study. Later, larger studies, and studies which occurred in settings where hepatitis C direct-acting antiviral treatments (DAAs) were widely available (such as in Australia), found significantly lower rates of hepatitis C among PrEP users. Findings support the hypothesis that uptake of DAAs among GBM translates to less hepatitis C transmission in PrEP users.

The fourth study is a latent class analysis of participants from a large Australian PrEP implementation study. This study identified four distinct classes of PrEP users based on their behaviours and attitudes to STIs and STI prevention. Most PrEP users belonged to two groups distinguished by highly disparate attitudes towards STIs but with similar rates of a recent bacterial STI. Findings suggest that attitudes towards STIs among GBM using PrEP in Australia vary considerably, and likely influence their receptivity to different STI prevention strategies.

The final study is a mathematical modelling study based on gonorrhoea transmission among gay and bisexual men in Victoria, Australia. which explored the estimated impact of a hypothetical antimicrobial gel-based intervention for reducing gonorrhoea incidence. The introduction of a moderate-efficacy intervention could have benefits for population-level gonorrhoea prevention, even when the intervention is considerably less efficacious than condoms and uptake contributes to reduced condom use.

This thesis provides real-world data on the interplay between widespread PrEP uptake and STI epidemiology, including the interplay between HIV prevention, STI testing, sexual networks, behaviours, and attitudes towards STIs. The thesis provides empiric evidence to inform STI prevention strategies, and novel insights into how these may be targeted to maximise impact in the era of PrEP. These findings can also guide other countries planning to scale up PrEP to effectively plan for and address the impact of PrEP implementation on other STIs.

Publications during candidature

Peer-reviewed publications included as thesis chapters (4)

Traeger MW, Guy R Asselin J, Patel P, Carter A, Wright E, Grulich A, McManus H, Fairley CK, Chow EPF, McNulty A, Finlayson R, Bell C, Owen L, Marshall L, Russell D, O'Donnell D, Donovan B, Hellard ME, Stoové MA. Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis following nation-wide pre-exposure prophylaxis implementation in Australia: an analysis of sentinel surveillance data. *The Lancet Infectious Diseases*. Online 25 May 2022. doi:10.1016/S1473-3099(22)00175X

Traeger MW, Murphy D, Ryan K, Asselin J, Cornelisse V, Hellard M, Wright E, Stoové M. Latent class analysis of sexual behaviors and attitudes to sexually transmitted infections among gay and bisexual men using PrEP. *AIDS and Behavior*. (2021). doi:10.1007/s10461-021-03529-w

Traeger MW, Tidhar T, Holt M, Williams C, Wright E, Stoové M, Scott N, Hellard M. The Potential Impact of a Gel-based Point-of-sex Intervention in Reducing Gonorrhoea Incidence among Gay and Bisexual Men: a Modelling Study. *Sexually Transmitted Diseases*. 2020; 47(10): 649-657. doi:10.1097/OLQ.0000000000001239

Traeger MW, Stoové MA. Why risk matter for STI control: who are those at greatest risk and how are they identified? *Sexual Health.* Accepted 26 Apr 2022.

Submitted manuscripts included as thesis chapters (2)

Traeger MW, Harney BL, Sacks-Davis R, van Santen D, Cornelisse VJ, Wright EJ, Hellard ME, Doyle JS, Stoové MA. Incidence and prevalence of hepatitis C among HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP): a systematic review and meta-analysis. Submitted to *Lancet HIV*.

Traeger MW. Trends in Syphilis testing and incidence gay and bisexual men in Australia from 2012-2021. Submitted to *Lancet Infectious Diseases.*

Peer-reviewed publications related to doctoral research (6) [Included in Appendices]

Traeger MW, Patel P, Guy R, Hellard M, Stoové M. Changes in HIV pre-exposure prophylaxis prescribing in Australian clinical services following COVID-10 restrictions. *AIDS*. 2021;35(1):155-157. doi:10.1097/QAD.0000000000002703

Traeger MW, Cornelisse VJ, Asselin J, Price B, Roth NJ, Willcox J, Tee BK, Fairly CK, Chang CC, Armishaw J, Vujovic O, Penn M, Cundill P, Forgan-Smith G, Gall J, Pickett C, Lal L, Mak A, Spelman TD, Nguyen L, Murphy DA, Ryan KE, El-Hayek C, West M, Ruth S, Batrouney C, Lockwood JT, Hoy JF, Hellard ME, Stoové MA, Wright EJ. Association of HIV Pre-exposure Prophylaxis with Incidence of Sexually Transmitted Infections among Individuals at High Risk of HIV Infection. *Journal of the American Medical Association.* 2019;321(14):1380-1390. doi: 10.1001/jama.2019.2947

Ryan KE, Asselin J, Fairley CK, Armishaw J, Lal L, Nguyen L, Murphy D, **Traeger MW**, Hellard M, Hoy J, Stoové M, Wright E. Trends in HIV and STI testing among gay bisexual and other men who have sex with men following rapid scale-up of PrEP in Victoria, Australia. *Sexually Transmitted Diseases.* 2020; 47(8): 516-24. doi: 10.1097/OLQ.0000000000001187

Cornelisse VJ, **Traeger MW**, Wright EJ, Murphy D, Stoové M, Hellard M, Sacks-Davis R, Asselin J, Fairley CK, Doyle J, Sasadeusz J. Low incidence of hepatitis C among a cohort of HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Melbourne, Australia, and the contribution of sexual transmission. *Journal of Acquired Immune Deficiency Syndromes*. 2021;87(4):1011-1015. doi: 10.1097/QAI.0000000000002685

Donovan LC, Fairley CK, Aung ET, **Traeger MW**, Wright EJ, Stoové MA, Chow EPF. The presence or absence of symptoms among cases of urethral gonorrhoea occurring in a cohort of men taking HIV pre-exposure prophylaxis in the PrEPX Study. *Open Forum Infectious Diseases*. 2021;8(6):ofab263. doi: 10.1093/ofid/ofab263

Harney BL, Sacks-Davis R, van Santen DK, **Traeger MW**, Wilkinson A, Asselin J, El-Hayek C, Fairley CK, Roth N, Bloch M, Matthews G, Donovan B, Guy R, Stoové M, Hellard ME, Doyle JS. The incidence of hepatitis C among gay, bisexual and other men who have sex with men before and after the availability of direct acting antivirals in Australia, 2009-2019. *Clinical Infectious Diseases.* Online 25 October 2021. doi: 10.1093/cid/ciab720

<u>Other peer-reviewed publications during candidature (11)</u>

Traeger MW, Doyle JS, van Santen DK, Sacks-Davis R, Asselin J, El-Hayek C, Pedrana A, Wilkinson AL, Howell J, Membrey D, Didlick J, Donovan B, Guy R, Hellard ME, Stoové MA. Impact of COVID-19 lockdown restrictions on hepatitis C testing in Australian primary care and community health services providing care for people who inject drugs. *Journal of Viral Hepatitis.* Online 20 June 2022. doi:10.1111/jvh.13723

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Laher F, Richardson SI, Smith P, Sullivan PS, Abrahams AG, Asowata OE, Bitangumutwenzi P, Dabee S, Dollah A, Fernandez N, Langat RK, Bose DL, Likhitwonnawut U, Mullick R, Resop RS, Sutar J, Thompson-Hall AN, **Traeger MW**, Tuyishime M, Wambui J, Bekker L, Kaleebu P, McCormack S, O'Connor DH, Warren M, Torri T, Thyagarajan B. HIV prevention in a time of COVID-19: A report from the HIVR4P // Virtual conference 2021. *AIDS Research and Human Retroviruses*. 2022 May;38(5):350-358. doi: 10.1089/AID.2021.0138

Wilkinson AL, van Santen DK, **Traeger MW**, Sacks-Davis R, Asselin J, Scott N, Harney B, Doyle JS, El-Hayek C, Howell J, Bramwell F, McManus H, Donovan B, Guy R, Stoové M, Hellard M, Pedrana A. Hepatitis C incidence among patients attending primary care health services that specialise in the care of people who inject drugs, Victoria, Australia, 2009 to 2020. *International Journal of Drug Policy.* 2022Mar 25;103:103655. doi:10.1016/j.drugpo.2022.103655

Howell J, **Traeger MW**, Williams B, Layton C, Doyle J, Latham N, Draper B, Bramwell F, Membrey D, McPherson M, Stoové M, Roney J, Thompson A, Hellard M, Pedrana A. Point-of-care hepatitis C testing in needle and syringe exchange programs increases linkage to care and treatment uptake among people who inject drugs: An Australian pilot study. *Journal of Viral Hepatitis*. 2022;29:275-384. doi:10.1111/jvh.13664

Wilkinson AL, Pedrana A, **Traeger MW**, Asselin J, El-Hayek C, Nguyen L, Polkinghorne V, Doyle JS, Thompson AJ, Howell J, Scott N, Dimech W, Guy R, Stoové M, Hellard M. Real world monitoring progress towards the elimination of hepatitis C virus in Australia using sentinel surveillance of primary care clinics: an ecological study of hepatitis C virus antibody tests from 2009 to 2019. *Epidemiology and infection.* 2021 Dec 6;150:e7. doi:10.1017/S0950268821002624

Van Santen DK, Asselin J, Haber NA, **Traeger MW**, Callander D, Donovan B, El-Hayek C, McMahon JH, Petoumenos K, McManus H, Hoy J, Hellard M, Guy R, Stoové MA. Improvements in transition times through the HIV cascade of care among gay and bisexual men with a new HIV diagnosis in New South Wales and Victoria, Australia: the longitudinal HIV cascade (2012-2019). *The Lancet HIV.* 2021 Oct;8(10):e623-e632. doi: 10.1016/S2352-3018(21)00155-7

Doyle JS, van Santen DK, Iser d, Sasadeusz J, O'Reilly M, Harney B, **Traeger MW**, Roney J, Cutts JC, Bowring AL, Winter R, Medland N, Fairley CK, Moore R, Tee BK, Asselin J, El-Hayek C, Hoy JF, Matthews CV, Prins M, Stoové MA, Hellard ME. Mirco-elimination of Hepatitis C among People with HIV Coinfection: Declining Incidence and Prevalence Accompanying a Multi-center Treatment Scale-up Trial. *Clinical Infectious Diseases.* 2021 Oct 5;73(7):e2164-e2172. doi:10.1093/cid/cia1500

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Veronese V, **Traeger MW**, Oo ZM, Tun TT, Oo NN, Maung H, Hughes C, Pedrana A, Stoové M. HIV Incidence and Factors Associated with Testing Positive for HIV among Men Who Have Sex with Men and Transgender Women in Myanmar: Data from Community-based HIV Testing Services. *Journal of the International AIDS Society.* 2020;23(2). doi:10.1002/jia2.25454

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and two submitted publications. The core theme of the thesis is the epidemiology and prevention of sexually transmitted infections among gay and bisexual men in the context of HIV pre-exposure prophylaxis. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the within the School of Public Health and Preventative Medicine under the supervision of Prof. Mark Stoove, Prof. Margaret Hellard and A/Prof. Edwina Wright. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 3 to 8 my contribution to the work involved the following:

Thesis chapter	**Publication title**	**Publication status**	**Nature and % of student contribution**	**Co-author name(s) and % of co-author contribution***	**Co-authors, Monash student Y/N***
3	Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis in Australia following nation-wide pre-exposure prophylaxis implementation: an analysis of sentinel surveillance data	Published	75%; conceptualisation, methodology, data analysis, interpretation, manuscript preparation, review, and editing	Rebecca Guy, 3% Jason Asselin, 1% Prital Patel, 1% Allison Carter, 1% Edwina Wright, 1% Andrew Grulich, 1% Hamish McManus, 1% Christopher Fairley, 1% Eric Chow, 1% Anna McNulty, 1% Robert Finlayson, 1% Charlotte Bell, 1% Louise Owen, 1% Lewis Marshall, 1% Darren Russell, 1% Darryl O'Donnell, 1% Basil Donovan, 1%	

Thesis chapter	Publication title	Publication status	Nature and % of student contribution	Co-author name(s) and % of co-author contribution*	Co-authors, Monash student Y/N*
				Margaret Hellard, 3% Mark Stoové, 3%	
4	Syphilis testing, incidence, and reinfection among gay and bisexual men with and without HIV in Australia over a decade spanning HIV PrEP implementation: an analysis of surveillance data	Submitted	75%; conceptualisation, methodology, data analysis, interpretation, manuscript preparation, review, and editing	Rebecca Guy, 3% Caroline Taunton, 3% Eric Chow, 1% Jason Asselin, 1% Allison Carter, 1% Mark Bloch, 1% Christopher Fairley, 1% Anna McNulty, 1% Vincent Cornelisse, 1% Phillip Read, 1% Louise Owen, 1% Nathan Ryder, 1% David Templeton, 1% Darryl O'Donnell, 1% Basil Donovan, 1% Margaret Hellard, 3% Mark Stoové, 3%	
5	Incidence and prevalence of hepatitis C among HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP): a systematic review and meta-analysis	Submitted	65%; conceptualisation, literature search, abstract screening, data extraction, data analysis, interpretation, manuscript preparation, review, and editing	**Brendan Harney, 10%** Rachel Sacks-Davis, 2% Daniela van Santen, 2% Vincent Cornelisse, 2% Edwina Wright, 2% Margaret Hellard, 2% Joseph Doyle, 8% Mark Stoové, 8%	**Y**
6	Latent Class Analysis of Sexual Behaviours and Attitudes to Sexually Transmitted Infections among Gay and Bisexual Men using PrEP	Published	75%; conceptualisation, methodology, data analysis, interpretation, manuscript preparation, review, and editing	Dean Murphy, 2%; Kathleen Ryan, 2%; Jason Asselin, 2%; Vincent Cornelisse, 2%; Anna Wilkinson, 3%; Margaret Hellard, 2%; Edwina Wright, 2%; Mark Stoové, 10%	
7	The potential impact of a gel-based point-of-sex intervention in reducing gonorrhoea incidence among gay and bisexual men: a	Published	50%; conceptualisation, methodology, data collection, interpretation, manuscript	Tom Tidhar, 20% Martin Holt, 2% Chris Williams, 2% Edwina Wright, 2% Mark Stoové, 8% Nick Scott, 8%	

Thesis chapter	Publication title	Publication status	Nature and % of student contribution	Co-author name(s) and % of co-author contribution*	Co-authors, Monash student Y/N*
	modelling study		preparation, review, and editing	Margaret Hellard, 8%	
8	Why risk matters for STI control: who are those at greatest risk and how are they identified?	Published	80%; conceptualisation, literature review, manuscript preparation, review and editing	Mark Stoové, 20%	

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Michael Traeger

Date: 23 December 2022

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Mark Stoové

Date: 23 December 2022

Awards and scholarships received during candidature

2022 Young Leader Award, Australasian Sexual & Reproductive Health Alliance (ASRHA) (2022)

Fulbright Future Scholarship, Australian Fulbright Commission (2022)

Gilead Australia Fellowship (2022)

New Investigator Scholarship (high-scoring abstract), INHSU Conference (2021)

Harold Mitchell Postgraduate Travel Award, Burnet Institute (2021)

Conference scholarship, INHSU Conference (2021)

Conference scholarship, 11th IAS Conference on HIV Science (IAS2021) (2021)

New Investigator Award (high-scoring abstract), International HIV Research for Prevention (HIVR4P) Conference (2021)

Conference scholarship, HIV Research for Prevention (HIVR4) Conference 2021

Early Career Award Winner – Best oral presentation (Epidemiology, Prevention and Health Promotion Theme), 2020 Australasian HIV&AIDS and Sexual Health Conferences (2020)

Alfred Research Alliance Research Prize - Clinical/Public Health: Highest impact factor publication in 2019

Geoffrey Stewardson Travel Fellowship, Burnet Institute (2020)

Conference scholarship, International AIDS Conference (2020)

Postgraduate Scholarship, National Health and Medical Research Council (2020)

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List of abbreviations

Ab	antibody
ACCESS	Australian Collaboration for Coordinated Enhanced Sentinel Surveillance
AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
CDC	Centres for Disease Control and Prevention
CI	confidence interval
CT	*Chlamydia trachomatis*
DAAs	direct-acting antivirals
GBM	gay and bisexual men
GPs	general practitioners
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
HR	hazard ratio
HSV	herpes simplex virus
IRR	incidence rate ratio
MBS	Medicare benefits scheme
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NG	*Neisseria gonorrhoeae*
OR	odds ratio
PBAC	pharmaceutical benefits advisory committee
PBS	pharmaceutical benefits scheme
PCR	polymerase chain reaction
PSI	point-of-sex intervention
RNA	ribonucleic acid
STI	sexually transmissible infection
TasP	treatment as prevention
U=U	undetectable=untransmittable
WHO	World Health Organization

Notes on terminology

Gay men, bisexual men and other men who have sex with men

This thesis focuses on the epidemiology and prevention of sexually transmitted infections (STIs) among men who identify as gay and bisexual in Australia. Since the start of the HIV epidemic, the term men who have sex with men (MSM) has been used in public health discourse with the aim of detaching clinical diagnosis and treatment with stigma associated with homosexual behaviour. However, over time, many have acknowledged that using the term MSM may obscure social dimensions of sexuality, undermine the self-labelling of gay and bisexual men, and may contribute to erasure of gay and bisexual identity.[1] Nevertheless, in many settings, some MSM do not identify as gay or bisexual, and reject being labelled as such.[2] The choice of terminology in research and public health discourse should depend on how data are collected, who is included, and on local contexts of preferred terminology among communities being researched.

Throughout this thesis, I use the term gay and bisexual men (GBM) to describe the population of interest. The majority of MSM in Australia, and almost all participants included in the PrEPX Study (presented in Chapter 6 and mentioned throughout the thesis) self-identify as GBM. Where appropriate, I have used 'gay and bisexual men and other men who have sex with men' in contexts where not all individuals in question may identify as gay or bisexual. Where intentional or global research is referenced or collated, or where international guidelines are discussed, the original terminology is retained (e.g. the World Health Organization uses MSM to describe one of its five key populations for HIV and other STIs). In chapters which present published work, terminology is reflective of the preferred terminology of the journals in which chapters are published.

People with HIV and people without HIV

Exploring and reporting research outcomes and trends in disease disaggregated by HIV status is important for epidemiological research. Different terms have been used during the HIV epidemic to describe individuals of different HIV status. HIV-positive and HIV-negative, or HIV-seropositive and HIV-seronegative, have been used since the 1980's. Across the HIV sector and other fields, preferred terminology now reflects a shift towards person-centred language, which aims to prioritise placing

the person first to avoid defining someone by their illness or disease. For example, the use of 'people living with HIV' (PLWHIV) is now preferred over 'HIV-positive people'.[3]

Throughout the introduction and discussion of this thesis, I have incorporated simplified person-centred language by using "gay and bisexual men with HIV" and "gay and bisexual men without HIV", when comparing or discussing specific outcomes or characteristics by HIV status. In some chapters which present published work, terminology is reflective of the preferred terminology of the journals in which chapters are published.

Sero-different sex and relationships

A key focus of this thesis is the interplay between PrEP implementation and sexual networks, specifically sexual networks influenced by individuals' HIV status. Multiple terms are still used in the literature to describe sex or relationships between people with different HIV statuses. The terms discordant, sero-discordant, and sero-noncondordant, are commonly used in research and HIV guidelines, however many people consider these terms stigmatising given, the negative connotations of 'discordance' within with context of intimate relationships or between people of different sero-status. Throughout the introduction and discussion of this thesis, I have used the term sero-different to describe sex between GBM with different HIV statuses.

Chapter 1

Introduction

1.1 HIV elimination among gay and bisexual men

1.1.1 HIV epidemiology and prevention among gay and bisexual men

The first cases of Acquired Immune Deficiency Syndrome (AIDS) were diagnosed among gay men in 1981 in the United States.[4] In the 40 years since the Human Immunodeficiency Virus (HIV) was identified, there have been an estimated 75.7 million people diagnosed with HIV globally, with 32.7 million deaths due to AIDS-related illnesses.[5] In 2021, there were an estimated 1.5 million new HIV infections, with 38.4 million people living with HIV at the end of 2021.[6] Gay men, bisexual men, other queer men, and men who have sex with men who may not identify as gay or bisexual (hereafter referred to as GBM), are one of the five groups outlined by the World Health Organization as key populations for HIV, along with trans and gender diverse people, sex workers, people who inject drugs and people in prisons and other closed settings.[7] It is estimated that GBM have a 28 times greater risk of acquiring HIV than adult men in the general population.[8] In Australia, 71% of HIV diagnoses notified over the past 10 years have been attributed to sex between men, however the proportion of HIV diagnoses attributed to sex between men has declined from 76% in 2016 to 68 % in 2021.[9]

GBM are at increased risk of HIV due to intersecting biological, behavioural, societal factors. First, the per sex-act risk of HIV transmission has been estimated to be 18 times higher for receptive anal sex than for male-to-female transmission during vaginal sex.[10-12] While both insertive and receptive anal sex present transmission risk, risk for receptive partners during anal sex is heightened as a result of the rectal mucosa lacking the protective humoral immune barrier present in cervicovaginal secretions.[13] Rectal tissue is also more susceptible to abrasions through microtrauma associated with anal intercourse, which may facilitate transmission further.[14] Second, while cumulative HIV risk increases with a greater number of recent and lifetime partners,[15] concurrent sexual partners,[16] and condomless anal sex,[17, 18] risk is also indirectly associated with broader social factors and the context in which sex occurs. Substance use during sex,[19] digital technology[20] and place-based[20] environments where GBM meet partners, sexual networks,[21] and stigma associated with homosexuality (including criminalisation[22]) and HIV and its role in impeding access to education and prevention programmes, have all been identified as moderators of HIV acquisition risk for GBM.[23-25] Finally, high community-prevalence of HIV among GBM means that the chance that a sexual partner is living with HIV is greater compared to heterosexual people. The prevalence of HIV among GBM ranges from an estimated 5% in South-East Asia to 13% in Eastern and Southern Africa.[8] In Australia, it is estimated that 9.2% of GBM were living with HIV in 2021.[9]

The early years of the AIDS response among GBM were characterised by a focus on the promotion of condoms as a primary prevention method.[26] The global response now underscores the importance of evidenced-based combination prevention, the combination of behavioural strategies to reduce transmission,[27] structural approaches to facilitate HIV prevention,[28] as well as biomedical prevention methods, namely the timely diagnosis of HIV and treatment imitation (treatment as prevention, or TasP) and HIV pre-exposure prophylaxis (PrEP).[29] The introduction of a new class of drugs in 1995 which led to combination therapy for HIV, known as highly effective anti-retroviral treatment (HAART), meant HIV infection would no longer be considered a fatal infection, but a life-long, manageable chronic illness.[30] However, despite significant technological advancements in HIV treatment over the past four decades, there remains no HIV cure or vaccine.[31, 32] Following the uptake of HAART in many countries, evidence began to accumulate on the effect of early treatment initiation on reducing mother-to-child transmission of HIV.[33, 34] This soon led to a growing field of research into the effectiveness of HIV treatment initiation and viral suppression among people living with HIV in preventing HIV transmission more broadly, including in the context of sexual transmission.

As evidence for treatment as prevention was accumulating, a consensus statement released by peak HIV bodies, known as the Swiss Statement, was released in 2008, stating that a person with HIV on treatment and with a viral load of less than 40 copies/ml could be considered non-contagious.[35] In 2011, the first trial evidence of the impact of early ART initiation on HIV transmission in sero-different heterosexual partnerships found that early ART initiation was associated with a 96% reduction in HIV transmission to the partner without HIV.[36] Subsequent observational cohort studies of sero-different couples, both heterosexual couples and GBM, which followed participants for long periods of follow-up have contributed to the evidence that the risk of sexual transmission of HIV from virally supressed people to their partners is virtually zero.[37, 38] Since these larger observational studies the Swiss Statement has become broad medical consensus,[39] with more recent adoption of U=U (undetectable = untransmittable) campaigns by global and country-level HIV bodies.[40]

With the growing evidence of TasP, peak HIV bodies such as UNAIDS and the World Health Organization (WHO) released ambitious HIV elimination targets. The current UNAIDS 2025 targets include the 95-95-95 targets, which aim for 95% of people living with HIV knowing their status, 95% of those diagnosed with HIV on antiretroviral treatment, and 95% of those on treatment achieving an undetectable viral load,[41] equating to a total of 85.7% of all people living with HIV achieving viral suppression. In 2020, it was estimated that among all people living with HIV globally, 84% (95% confidence interval [CI]: 67%-98%) knew their status, 73% (CI: 56%-88%) of those diagnosed were accessing treatment and 66% (CI: 53%-79%) of those who had accessed treatment had supressed

viral loads, falling well short of targets.[42] Further, significant inequalities in the proportion of people living with HIV virally suppressed exist across key populations, as well as across the globe, ranging from 72% in the Western Pacific Region and 68% in the African Region, to 58% in the South-East Asia Region, and just 21% of people living in the Eastern Mediterranean Region.[42]

1.1.2 Pre-exposure prophylaxis (PrEP)

The concept of antiretroviral treatment medications taken by people without HIV to reduce their risk of HIV acquisition has been considered since the late 1990s,[43] and was based on data from early animal studies and observational studies of post-exposure prophylaxis (PEP; the use of antiretroviral drugs taken after potential HIV exposure), among healthcare workers with needlestick injuries.[44, 45] Pre-exposure prophylaxis refers to the use of medicines taken prior to exposure to the infection agent to reduce risk of acquiring an infection. HIV pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral medications taken prior to sexual activity, to prevent HIV acquisition in people without HIV. The first drugs to be considered for PrEP were tenofovir disoproxil fumurate (TDF) and emtricitabine (FTC). First approved for HIV treatment by the US CDC in 2001,[46] these drugs were chosen for PrEP studies because of their high potency, high tolerability and safety, and high levels of concentration in the genital tract.[47] Early animal trials on the use of oral TDF alone for the prevention of HIV were completed as early as in 2006, with data from rhesus monkeys suggesting some preventive effect against repeated simian HIV (SHIV) inoculation.[48, 49] A later study published in 2008 found that the use of daily, oral TDF and FTC in combination had high efficacy against repeated rectal exposure to SHIV among rhesus macaques, with all animals who received daily TDF/FTC protected from infection.[50]

The first evidence for the efficacy of TDF/FTC for the prevention of HIV in humans came from the iPrEX trial, a double-blind, randomised controlled trial of once-daily oral TDF/FTC, labelled under the brand name Truvada by Gilead Sciences.[51] Over a total of 3,324 person-years, 100 incident HIV infections were detected, with the per-protocol analysis finding an HIV risk reduction of 44% in the TDF/FTC arm compared to placebo. In a post-hoc analysis comparing HIV incidence among those with detectable study drug level during follow-up to those without a detectable level, the HIV risk reduction increased to 92% (CI: 40%-99%). The trial was extended to an open-label extension cohort study, where participants were offered daily oral PrEP and followed for 72 weeks. In this observational study, among participants with drug level concentrations indicative of high adherence (>4 pills per week), no new HIV infections were detected.[52]

Between 2010 and 2015, several other trials exploring the efficacy of Truvada were conducted and highlighted the strong correlation between adherence to PrEP and its efficacy[53] **(Figure 1.1)**. The PROUD study in the UK was an open-label, randomised controlled trial which randomly assigned 544 GBM to received daily TDF/FTC either immediately or after a deferral period of 1 year. PrEP was associated with an 86% reduction in HIV acquisition risk, representing a greater effect than in the earlier, placebo-controlled iPrEX study, suggesting a high adherence among participants receiving PrEP in a real-world clinical setting. These studies were followed by the IPERGAY study, a randomised, placebo-controlled trial which explored the efficacy of non-daily, or event-driven PrEP.[54] Participants were randomised to follow a so-called 2-1-1 regimen; a single dose of two PrEP pills between 2-24 hours before sex, with two additional single-pill doses taken 24 and 48 hours after the pre-sex dose. On-demand PrEP was associated with a relative HIV reduction of 97%,[54] the highest efficacy observed in a placebo-controlled PrEP trial.

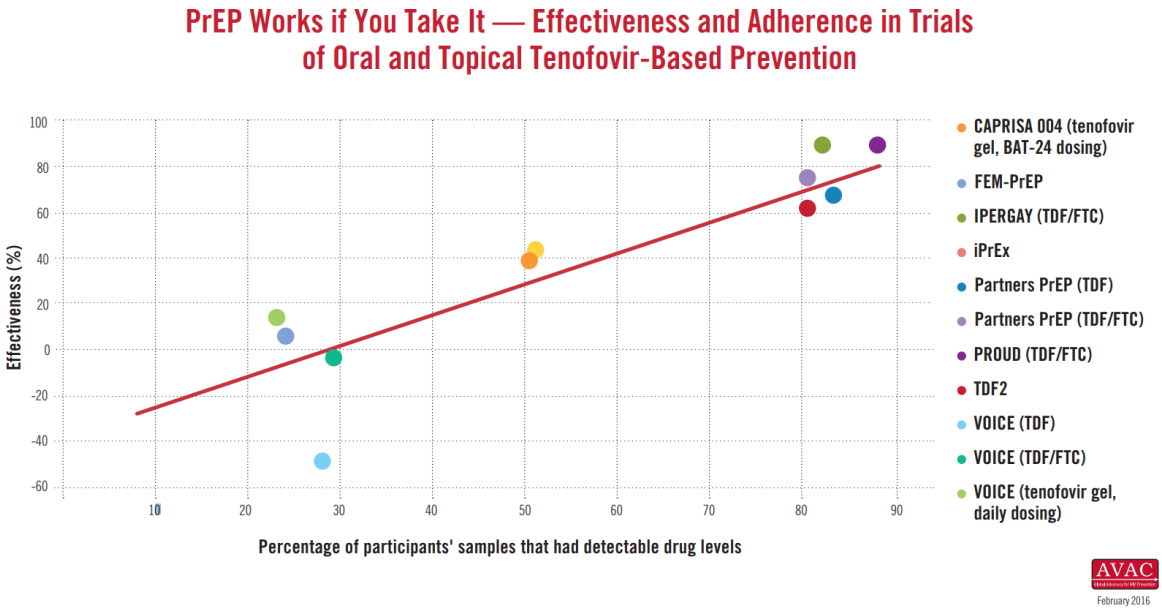

Figure 1.1: Efficacy of PrEP compared to adherence reported in trials of daily oral PrEP to 2016.

Source: *Pre-exposure prophylaxis (PrEP) by the Numbers* - AVAC
(https://www.avac.org/infographic/effectiveness-and-adherence-trials-oral-and-topical-tenofovir-based-prevention)

The growing body of evidence for the efficacy of PrEP led to global and national guidelines being released in multiple countries. As early as 2012, the WHO recommended that people in sero-different relationships and men who have sex with men at high risk of HIV be offered TDF-based daily oral PrEP as an additional prevention choice.[55] In September 2015, the WHO released updated guidelines on PrEP which included a recommendation that all people at substantial risk of HIV be offered TDF-based oral PrEP, with substantial risk provisionally defined as an HIV incidence rate among the population of 3.0/100 person-years or greater.[56] In response to the IPERGAY study results, the WHO updated their guidance in 2019 to include event-driven PrEP for use among men who have sex with men.

The advent of HIV PrEP revolutionised HIV prevention, reinvigorating global HIV elimination efforts. In 2016, the United Nations General Assembly Political Declaration on Ending AIDS by 2030 outlined a global target to achieve 3 million people at high risk of HIV having accessed PrEP by 2020. By the end of 2020 approximately 2.7 million people had initiated oral PrEP globally.[57]

Future PrEP modalities

New forms of non-daily or non-oral PrEP are available or in development. The first injectable, long-acting form of PrEP, a two-monthly injection of cabotegravir, sold under the brand name Apretude and developed by ViiV Healthcare, was approved in the US in December 2021 and in Australia in August 2022.[58] Two large double-blind, double-dummy, randomised controlled trials explored the efficacy of long-acting cabotegravir (CAB-LA) for PrEP among GBM and transgender women (HIV Prevention Trials Network [HPTN]-083) and among cisgender women (HPTN-084), respectively. The HPTN083 study enrolled 4,570 cisgender men and transgender women who have sex with men across Argentina, Brazil, Peru, South Africa, Thailand, the US and Vietnam. Participants were randomised to either 8-weekly injections of cabotegravir long-acting PrEP (CAB-LA) or daily TDF/FTC oral PrEP. A total of 52 HIV infections were diagnosed during study follow-up, 13 in the CAB-LA arm (annual incidence rate of 0.41%) and 39 infections in the TDF/FTC arm (annual incidence rate of 1.22%). The reduction in HIV incidence was 66% in the CAB-LA arm compared to the oral TDF/FTC arm, and the study was stopped early as CAB-LA was deemed to have met statistical criteria for superiority compared to TDF/FTC.[59] Following the results of the HPTN083 study, the WHO released guidelines on CAB-LA for HIV PrEP in July 2022, recommending CAB-LA be offered to populations at risk of HIV.[60]

Another form of PrEP currently under development is long-acting injectable lenacapavir, with an injection frequency of 6-monthly under consideration.[61] Different modalities of HIV PrEP may offer significant benefits to people at risk of HIV by overcoming issues of adherence, accessibility and discretion around use of HIV biomedical prevention. However, new forms of PrEP will require a range of considerations for effective implementation, including cost-effectiveness, acceptability to end-users, and differing efficacies. There will also be important implications for the required frequency of clinics visits for different PrEP modalities, the subsequent impact on clinic capacity, and identifying the optimal frequency for STI screening among people who use these new types of PrEP.

1.1.3 PrEP implementation in Australia

Approval and implementation studies

Tenofovir with emtricitabine (Truvada) was approved by the Australian Therapeutic Goods Administration (TGA) for use as HIV PrEP in 2016.[62] However, prior to regulatory approval in Australia, a small proportion of GBM were self-importing PrEP from overseas (approximately 3% of GBM in Melbourne reporting self-importing PrEP in 2014)[63] or accessing PrEP from small pilot studies in Melbourne and Sydney.[64, 65] The aims of these pilot studies were to explore the acceptability of PrEP among GBM in Australia, assess the impact of PrEP use on sexual behaviours and provide evidence for future considerations for national implementation.

From 2016, larger implementation studies were established, first in the states of Victoria and New South Wales (where an estimated 67% of Australia's GBM population reside), and then across each state and territory.[66-68] These studies were largely funded by jurisdictional governments, in part in response to considerable community lobbying and the fact that PrEP was not available as a subsidised medicine through Australia's universal health care system, known as Medicare. These studies enrolled over 20,000 GBM collectively and served as real-world HIV prevention studies, helping to develop best practice models of care[69] and PrEP delivery[70] for later PrEP availability through Medicare, and resulted in rapid scale up of PrEP coverage in major capital cities in Australia. Throughout this thesis, I draw on findings from the PrEPX Study, a large PrEP implementation study which recruited over 5,000 GBM and other people at risk of HIV from 26th July 2016, initially in the state of Victoria and later expanding into the states of South Australia and Tasmania[66] (see appendix C1 p 320).

Publicly funded PrEP

Data collected during real-world PrEP studies in Australia facilitated cost-effectiveness modelling which showed daily oral PrEP to be cost-effective if subsidised, and as such TDF/FTC was approved by Australia's Pharmaceutical Benefits Advisory Committee (PBAC) to be listed on the Pharmaceutical Benefits Scheme (PBS), Australia's subsidised medicines scheme. From April 1st 2018, PrEP was made available at a highly subsidised price for those eligible for Medicare (i.e. Australian citizens and permanent residents), and at this time many of the PrEP studies transitioned participants to accessing PrEP through the PBS. PBS-subsidised PrEP can be prescribed and dispensed in three-monthly supply, and through Medicare individuals are required to make co-payments each time PrEP is dispensed at a pharmacy. Medicare dispensing co-payments range from $7 for concession card holders to $40 per month. Since PBS listing, there have been more than 51,000 people dispensed PrEP from the PBS until June 2022, with the annual number of people dispensed PrEP plateauing at around 30,000 between 2020-2022.[71] In 2020, it was estimated that among GBM without HIV who were eligible for PrEP, 92.5% were aware of PrEP, and 57% had been prescribed PrEP in the previous six months.[72]

As PrEP is only accessible through the PBS for people who live in Australia and qualify for a Medicare card, people who are Medicare-ineligible, such as international students, migrant workers or other non-permanent residents, cannot access publicly-funded PrEP. Several community-driven initiatives in Australia offer PrEP to Medicare ineligible people for free through collaborations with international pharmacies and charities. However, many people who access these services are left out-of-pocket for clinical consultations and STI testing related to PrEP. Government and pharmaceutical company-funded clinics have also been set up to provide free PrEP and STI testing services for those ineligible for Medicare,[73, 74] however the number of people they can see is limited.

Australian PrEP guidelines

The Australian Society for Sexual Health, Viral Hepatitis and HIV Medicine (ASHM), the governing body for clinical HIV guidelines in Australia, first released clinical guidance for prescribing PrEP, the ASHM National PrEP Guidelines, in 2017.[75] Initially based largely on the US CDC's 2014 PrEP guidelines,[76] the guidelines have since been updated a number of times. Early ASHM PrEP guidelines were influenced by initial PrEP studies which included specific inclusion criteria to recruit the most at-risk individuals. For example, in the PrEPX Study, the following inclusion criteria were used;[66]

1. Is a regular sexual partner of an HIV-positive male partner with whom condoms were not consistently used in the past three months, and the HIV-positive partner is not on treatment and/or has detectable HIV viral load).
2. Reports at least one episode of receptive condomless anal intercourse with any casual HIV-positive male partner or a male partner of unknown HIV status
3. Has a diagnosis of rectal gonorrhoea, chlamydia and/or syphilis during the last three months
4. Reports more than one episode of anal intercourse in the last three months when proper condom use was not achieved (e.g. condom slipped off or broke)
5. Is uncircumcised and reports more than one episode of insertive condomless anal intercourse in the last three months where the serostatus of their partner was not known, or the partner was HIV positive and not on antiretroviral treatment.

The initial ASHM 2017 guidelines classified individuals' risk as high or low, based on estimates of HIV incidence among participants from an observational HIV study, the HIM study.[75] These guidelines recommended the PrEP be prescribed to those who both reported HIV-related risk behaviour in the past three months, and who anticipated they would have HIV risk in the following three months after commencing PrEP. Alongside the listing of PrEP on the PBS in 2018, the PBAC issued guidance on prescribing oral PrEP for people who meet eligibility for publicly-subsidised PrEP. As the approval and listing of PrEP on the PBS was based on cost-effectiveness modelling of preventing future HIV diagnoses and associated costs, PBAC guidance included eligibility for PrEP as "medium to high risk" of HIV.[77] However, in 2019, ASHM's National PrEP Guidelines were updated and included a more relaxed set of eligibility criteria, where individuals who do not report risk in the past three months should still be considered for PrEP, if they reported anticipated risk.[78] The 2021 ASHM guidelines[79] now recommended prescribing PrEP to anybody who asks for it, regardless of HIV risk, and includes a section on 'suitability for PrEP' to guide clinician-patient discussions. The guidelines cite reasons for relaxing eligibility criteria as the fact that many people do not feel comfortable disclosing risk to providers, and that PrEP is also associated with benefits other than HIV risk reduction, including reduced anxiety[80] and increased sexual satisfaction.[81]

1.1.4 Impact of PrEP on population-level HIV

While PrEP is safe and highly effective at reducing individual-level HIV acquisition risk among those who take it according to recommendations during periods of risk (prevention effective adherence),[82] the translation of these individual-level benefits to population-level declines in HIV is dependent on multiple factors. Models of care which inadequately support long-term adherence to PrEP, and

inequitable access and use of PrEP among certain populations, may hinder the impact of PrEP on population-level HIV.[83-85] During the early years of PrEP roll-out, there were also concerns that population-level declines in condom use may offset HIV prevention gains from uptake of PrEP. Multiple mathematical models have estimated the anticipated impact of PrEP implementation on population-level HIV rates.[86-88] Early modelling of HIV transmission among GBM in the US showed that provision of PrEP to 40% of all GBM who reported multiple partners in the previous 12 months, with individuals' adherence covering 40% of days, could prevent 9.5% of HIV infections over 5 years.[89] If this were scaled up to 80% coverage of GBM with multiple partners, and adherence covering 80% of days, the proportion of infections which could be prevented increases to 43%. An Australian modelling study which explored the impact of reaching UNIADS HIV care cascade targets among GBM in Australia, found that even if Australia achieved the 95-95-95 targets, already low rates of HIV transmission mean that only modest reductions in HIV incidence may be achievable through PrEP scale-up.[90]

Assessing the real-world impact of PrEP on HIV incidence at a population-level is made difficult by challenges associated with measuring impact when concurrent changes are occurring in other indicators related to primary prevention and TasP. Although many settings which have rolled out PrEP have seen declines in HIV notifications over time, especially among GBM, uptake in PrEP has occurred in parallel to improvements in HIV treatment uptake and time to viral suppression. For example, in Australia, the median time between diagnosis and treatment initiation among GBM newly diagnosed with HIV declined from 168 days in 2013 to just 15 days in 2019.[91] These reductions in time to viral suppression, and therefore reduced community-level viremia (the proportion of the population with detectable HIV viral load) has been associated with declines in HIV incidence among GBM, even prior to PrEP roll-out.[92]

The first real-world data which suggested PrEP uptake may be having an impact on population-level HIV incidence among GBM came from San Francisco, where PrEP use began to increase among GBM from 2013. HIV notifications in San Francisco declined steeply from 2013 to 2016, with 2016 being the lowest number of infections reported since the start of the pandemic.[93] Ecological analysis of prescriptions and diagnoses data in the US found an association between PrEP prescriptions and HIV diagnoses at a state-level in the US, with authors suggesting greater PrEP uptake was associated with declines in HIV in the subsequent year.[94] However, ecological analyses like this are limited by unmeasured confounders, and also are unable to account for changes in other indicators such as HIV testing.[95] An evaluation of PrEP implementation in Scotland found that new HIV diagnoses among GBM fell from 229 to 184 (19.7% risk reduction) between pre-PrEP implementation (July 2015 to June 2017) and post-PrEP implementation (July 2017 to June 2019). During the same period, HIV

incidence among GBM attending sexual health clinics in Scotland fell from 5.1/100py to 3.3/100py (incidence rate ratio = 0.57).[96]

The first Australian data to suggest PrEP implementation was having an impact on population-level HIV was from the state of New South Wales, where the EPIC-NSW study enrolled over 9,000 participants. In the twelve months following study implementation and PrEP roll-out, new HIV infections among GBM in NSW declined by 25%, compared to the twelve months pre-PrEP implementation.[97] In Victoria, the number of newly acquired HIV notifications among GBM declined by 30% in the three years following the start of the PrEPX Study, compared to the three years prior to study enrolment.[98] In 2018, the first year of public subsidy for PrEP (following rapid scale up through PrEP implementation studies), the number of HIV diagnoses attributable to male-to-male sex in Australia dropped to 677, an 18-year low.[99] Since then, HIV diagnoses among GBM have declined further; in 2021, the number of HIV notifications among GBM declined to 377, although this drop may, in part, be due to declines in testing[100] and changes in sexual partnering due to physical distancing regulations during the COVID-19 pandemic.[101]

Reductions in HIV diagnoses among GBM following the introduction of TasP and roll-out of PrEP in some countries are considerable achievements. There is currently no evidence that individual or population-level changes in behaviour following PrEP implementation significantly counteracts the HIV preventive effect of PrEP. In the era of PrEP, we must contextualise the growing epidemic of other STIs and our response with the significant reductions in HIV diagnoses and substantial positive impact of PrEP on the sexual health and general wellbeing of GBM.[102]

1.2 The HIV and STI syndemics

1.2.1 The role of core groups in STI transmission

The role of 'core groups' in the transmission of STIs has been a critical theoretical concept of STI epidemiology for over four decades,[103] however how core groups are defined and factors moderating their influence have expanded over time.[104] People which bare the largest burden of STI transmission, 'core groups', may include people with repeat infections and people with a high number of partners.[105] However, STI transmission can also be concentrated geographically, with 'core areas' or 'risk spaces' being reflective of neighbourhood sociocultural factors, location of sexual health services and local partner selection.[105] Finally, changes in the size and location of core

groups and core areas for STI transmission occur over time, with changes in population composition and access to health care, as well as changes in behaviour and sexual mixing. Conceptual frameworks for STI transmission have expanded to include multiple network-related concepts, including concurrent partners, the duration and timing of partners, preferential attachment, sexual mixing, sexual positioning practices,[106, 107] HIV sero-sorting,[108] and PrEP-sorting.[109] Throughout this thesis, I draw upon these concepts in the context of core groups of GBM at risk of STIs and changes in sexual networks following the implementation of HIV PrEP in Australia

1.2.2 Epidemiology of non-HIV STIs among gay and bisexual men

Sexually transmissible infections (STIs) are a major cause of morbidity globally, with approximately 370 million diagnoses of curable STIs occurring each year, more than 1 million per day.[110] Similar to HIV, GBM have a greater incidence of STI diagnoses compared to heterosexuals in almost all settings around the world.[111, 112] The most common bacterial STIs among GBM globally are *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea) and *Treponema pallidum* (syphilis), all of which are curable. Common viral STIs, including human papilloma virus (HPV) and herpes simplex virus (HSV), are incurable yet manageable with medication. While bacterial STIs have a higher incidence among GBM, the prevalence is far greater for HPV and HSV, given they are life-long infections.[113-115]

The syndemic relationship between HIV and STIs is driven by similar behavioural risk factors, sexual networks, and the fact that HIV infection is more likely to occur if an STI is present, and vice versa.[116] Infection with a bacterial STI among people living with HIV who are not on HIV treatment has been shown to increase the amount of virus present in the genital tract, increasing the potential for onward HIV transmission.[117] People without HIV who are infected with STIs which cause sores or chancres, such as HSV or syphilis, are at increased risk of HIV acquisition.[118] While it is true that an individual's risk of HIV is increased if they are infected with an STI, there is currently no evidence globally that reducing STI prevalence at a population-level leads to decreased HIV transmission.[119]

Globally, infection rates of chlamydia and gonorrhoea are increasing among GBM.[120, 121] In Australia, gonorrhoea notifications have continued to rise, almost tripling from 13,947 in 2012 to 34,765 in 2019, with 73% of gonorrhoea infections in 2019 among men.[9] Analysis of GBM attending sexual health services estimated that gonorrhoea incidence increased from 12.4/100py to 24.6/100py from 2010 to 2017 among those returnging for repeat testing.[120] Similar increases in chlamydia notifications have been observed, however the proportion of all cases which are among men is lower (49% in 2019)[9]. Increasing notifications of syphilis among GBM have been reported in the

US[122] and Europe.[123] In Australia, there has also been an increasing trend in syphilis over the past two decades. Analysis of nearly 100 years of syphilis diagnoses from the Melbourne Sexual Health Centre, a large, publicly funded sexual health clinic in Melbourne, Victoria, found that following peaks during the 1920' and 1940's, syphilis diagnoses fell to almost zero by the early 1990's.[75] Rates of syphilis then began to rise among men in the early 2000's, and have continued to increase since.[75] A recent systematic review and meta-analysis of 275 studies estimated the global prevalence of syphilis among GBM, from 2000 to 2020, at 7.5% (95%CI: 7.0-8.0), with prevalence of syphilis ranging from 1.9% (1.0-3.1) in Australia, to 10.6% (8.5-12.9) in Latin America.[124]

The synergistic relationship between HIV and STIs among GBM is most notable for syphilis. In many countries, incidence of syphilis has been higher among GBM with HIV[125] compared to GBM without HIV. Reasons for the increased rate of syphilis among GBM with HIV include increased likelihood of serosorting among GBM with HIV (resulting in relatively closed sexual networks that facilitate reinfections)[126, 127] and decreased use of condoms among GBM using HAART.[128] It has also been suggested that HIV treatment may inadvertently increase the risk of syphilis acquisition by altering innate and acquired immune responses to *treponema pallidum.*[129]

While bacterial STIs share several commonalities with HIV in respect to socio-behavioural and ecological risk factors, there are key differences in the pathophysiological drivers of bacterial STIs and HIV. Among GBM, chlamydia and gonorrhoea are commonly diagnosed at three anatomical sites; in the rectum, the throat or pharynx, and the urethra. The incidence of infection at each anatomical site differs due to different likelihoods of transmission during specific sex acts and varying length of infection at each site in the absence of treatment. Our previous analysis of STIs among GBM participating in the PrEPX study (appendix C1, p 320) found that the rate of rectal STIs (chlamydia and gonorrhoea) was 56.8/100py, compared to 23.7/100py for pharyngeal and 19.3/100py for urogenital infections, respectively. For gonorrhoea, pharyngeal infections were more common than urogenital infections, whereas for chlamydia urogenital infections were more common **(Table 1.1).**

Modelling work suggests that oral sex plays a large part in gonorrhoea transmission among GBM,[130] with saliva being used for lubricant during anal sex by many GBM.[131-133] A number of specific behaviours have been shown to further increase the risk of bacterial STI transmission, including sharing of dildos and sex toys, fisting, fingering and rimming.[134, 135] Syphilis can be transmitted during multiple stages of infection, for example during exposure to chancres during primary syphilis, via

Table 1.1. Incidence of Sexually Transmissible Infections During Follow-up Among Participants of the PrEPX Study

	No. of Infections	Incidence Rate per 100 Person-Years (95% CI)
All STIS	2928	91.9 (88.7-95.3)
Chlamydia	1434	45.0 (42.7-47.4)
Rectal	1091	34.3 (32.3-36.3)
Urethral	381	12.0 (10.8-13.2)
Pharyngeal	127	4.0 (3.3-4.7)
Gonorrhoea	1242	39.0 (36.9-41.2)
Rectal	719	22.6 (21.0-24.3)
Urethral	233	7.3 (6.4-8.3)
Pharyngeal	629	19.7 (18.3-21.3)
Syphilis	252	8.0 (7.1-9.0)
Site		
Rectal infections	1810	56.8 (53.4-60.4)
Urethral infections	614	19.3 (17.4-21.3)
Pharyngeal infections	756	23.7 (22.0-25.6)
Age group, y		
18-24 (n = 307)	161	86.5 (74.6-101.5)
25-29 (n = 634)	554	103.3 (94.9-112.1)
30-34 (n = 620)	733	107.1 (99.8-115.3)
35-39 (n = 482)	495	83.4 (76.4-91.2)
40-44 (n = 356)	354	81.9 (73.8-90.9)
45-49 (n = 437)	486	88.7 (81.2-97.1)
≥50 (n = 145)	145	70.8 (60.2-83.4)

skin-to-skin contact during secondary syphilis, or via seminal fluid during either infectious stage.[136] Understanding the differential risks of STI transmission among GBM by pathogen, anatomical site and specific behaviours is important for informing future prevention strategies which aim to interrupt transmission during specific sexual acts. For example, in Chapter 8 were explore a hypothetical antimicrobial lubricant for use during anal sex to prevent the transmission of gonorrhoea.

1.2.3 Factors driving increasing trends in STIs among GBM

While HIV and other STIs have many epidemiological similarities, over the past 10 years trends in HIV and bacterial STIs among GBM have been diverging in many settings, with HIV beginning to fall but STIs continuing to rise.[137] Several behavioural and social factors have been hypothesised as driving the observed increasing trends in STI incidence among GBM over the past three decades. Condom use among GBM had been declining in many settings prior to the introduction of PrEP in the 2010's. A systematic review of studies on behavioural trends among GBM in Europe, the US and Australia between 1990 – 2013 found that increasing trends in condomless anal sex, including condomless anal sex with a partner of different HIV status.[138]

The introduction of internet-based geosocial networking platforms, such as Grindr, led to changes in the way people met sex partners.[139] GBM who meet partners online are more likely to engage in condomless sex, have more casual sex partners and have higher rates of substance use.[140, 141] Increased detection of STIs may also be occurring due to increases in testing,[142] as well as advances in testing modalities, including highly sensitive nucleic-acid amplification testing (NAAT) which become standard in Australia for chlamydia and gonorrhoea in 2014.[143] Diversifying sexual networks, including those characterised by varying incidence and prevalence of STIs, may also be influencing STI transmission trends. Reductions in serosorting as a risk-reduction strategy (choosing sexual partners with the same HIV status) among GBM have occurred alongside greater awareness of HIV treatment as prevention (TasP or U=U) and increased use PrEP.[144, 145]

1.2.4 Impact of PrEP on sexual behaviour

While clinical trials exploring the efficacy of PrEP were being conducted, discussions around the concept of 'risk compensation' began to take place.[146] Risk compensation occurs in the context of reduced perceived risk that leads to reductions in a particular preventive behaviour;[147] in the context

of PrEP this occurs when people taking PrEP reduce or cease using condoms because of the protection against HIV that PrEP conveys. However, it is important to understand that the risk of an individual acquiring HIV in the context of TasP and effective PrEP use remains extremely low, even in the absence of condoms. Changes in behaviour may however have implications for other infections for which TasP and PrEP have no protective effect, such as bacterial STIs (see section 1.2.4).

Risk compensation in the context of HIV has been proposed since the 1990's, when it was suggested that the advent of an HIV vaccine may actually lead to a worsening of the HIV epidemic, given anticipated behavioural risk compensation among GBM.[148] Similar concerns were raised with the introduction of HAART for HIV, however a systematic review of 58 studies found that among GBM with HIV the use of ART was not associated with an overall decrease in condom use.[149] However, included studies were published to April 2012, prior to growing trust in TasP and community-driven movements such as U=U.[40, 150] Behavioural change stemming from PrEP use may reduce the population-level and individual-level benefits of HIV PrEP in a number of ways. Declines in condom use which occur alongside poor PrEP adherence may lead to increased individual-level risk, while population-level benefits may be counteracted if condomless sex becoming normative continues into periods where people are not using PrEP, or if PrEP implementation impacts condom use among GBM not using PrEP.

Individual-level behaviour change

An early systematic review of PrEP studies found no conclusive evidence for risk compensation in the form of behavioural change among PrEP users.[82] However, a key limitation of this review was the inclusion of blinded studies, where participants are likely to be hesitant to increase risk behaviours when being unsure if they were taking a study drug or a placebo. Data from prospective open-label studies, in which participants were aware they were receiving PrEP, offer more realistic insights into the potential for PrEP to lead to population-level behaviour change. In 2018, we published a systematic review and meta-analysis of open-label, non-blinded, PrEP studies among GBM. Across studies, there was evidence for a change in behaviour following PrEP uptake, including a decline in the proportion of GBM reporting consistent condom use, an increase in the proportion reporting partners who were living with HIV, and an increase in the number of recent condomless sex partners. PrEP uptake also appeared to influence rates of other STIs (see Section 1.2.4).

In the PrEPX study in Victoria, we observed substantial declines in condom use with casual partners among participants over the first 12 months of follow-up. The proportion of participants starting

PrEP for the first time at study enrolment who reported consistent condom use fell from 32.2% in the six months prior to enrolment to 14.0% at 12 months follow-up. The proportion reporting never using condoms increased from 5.1% at baseline to 19.8% at 12 months follow-up **(Figure 1.2)**.

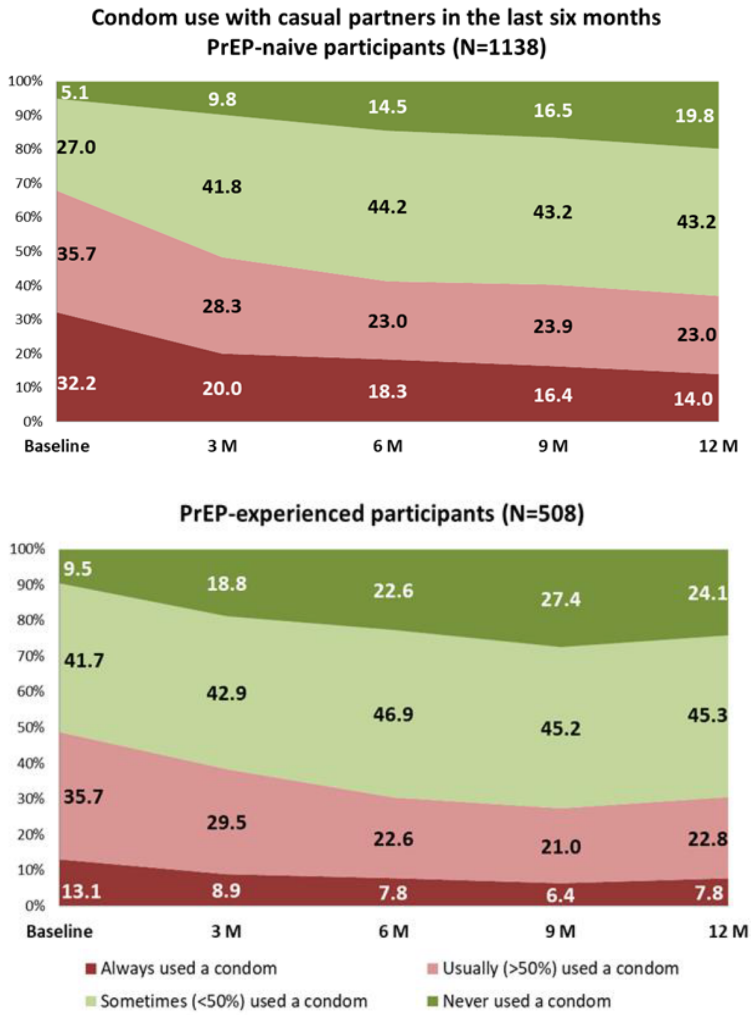

Figure 1.2: Proportion of PrEPX participants reporting frequency of condom use with casual sex partners in the last 6 months, from baseline to month 12, by whether participants reported using PrEP at enrolment

*Reference: **Traeger M** et al. Longitudinal changes in condom use with casual partners among gay and bisexual men using HIV pre-exposure prophylaxis. 10th IAS Conference on HIV Science, Mexico City, Mexico. 21-24 July 2019. [Appendix E1 p 391]*

Population-level behaviour change

In addition to individual-level changes in sexual behaviours, population-level changes have been observed in countries which have implemented PrEP at scale, including in Australia. Data from the

Gay Community Periodic Surveys (GCPS; an annual national behavioural survey of GBM across Australia) found that between 2013 and 2017, GBM reporting consistent condom use in the past six months fell from 46% to 31%, as PrEP use increased from 5% to 16%.[151] The most recent GCPS data from Melbourne found that in 2022, just 12.9% of GBM reported using condoms consistently with casual partners in the past six months. However, although consistent condom use has fallen dramatically, so called 'net-prevention-coverage', the proportion of GBM reporting either consistent condom use, PrEP use, or being virally supressed, increased from 68.1% to 74.9% from 2014-2019.[152]

Uptake of PrEP may also lead to changes in sexual networks among GBM. Serosorting, where individuals have sex with other people of the same HIV status, has been used as a risk-reduction method by GBM for decades.[153] However, PrEP implementation has led to declines in serosorting among GBM,[154] as PrEP users report being more comfortable having sex with partners living with HIV.[144] International data also show that PrEP users are more likely to have sex with other PrEP users, compared to non-PrEP users.[155-157]

1.2.5 Impact of PrEP on the epidemiology of non-HIV STIs

While there is strong evidence that PrEP use is associated with changes in sexual behaviour at both the individual and community level, the population-level impact of PrEP on the transmission of non-HIV STIs is more contentious. Understanding the impact of PrEP implementation on STI transmission and detection is challenged by significant selection biases (those who start PrEP are already at high risk of STIs), detection biases (PrEP users are tested for STIs more frequently than non-PrEP users and compared to pre-PrEP use), and the simultaneous changes in behaviour, sexual networks and testing associated with PrEP implementation.[158, 159]

An early meta-analysis which compared STI incidence rates between cohorts of GBM using PrEP and cohorts of GBM not using PrEP found much higher rates of STIs among PrEP users, with authors reporting that PrEP users were 23.5 times more likely to acquire gonorrhoea, 11.2 times more likely to acquire chlamydia, and 44.6 times more likely to acquire syphilis.[160] However, concerns were raised[161] about the causal relationship from this analysis as PrEP users have a high baseline risk for STIs. As mentioned previously, a systematic review and meta-analysis in 2016 explored the impact of PrEP on behaviour and STIs and found no change in STI risk once starting PrEP. However this review included blinded trial data,[82] and participants in blinded trials not being aware if they were receiving study drug or not is likely to have influenced the lack of change in reported sexual behaviour.

Our 2018 meta-analysis[162] also explored change in STI positivity among GBM from prior to PrEP use to after initiating PrEP. With the inclusion of later open-label studies (overcoming the weakness in the previous review), we found an increase in the odds of being diagnosed with an STI of 24% after starting PrEP **(Figure 1.3)**. The increase was greater for rectal STIs (odds ratio=1.39 [CI: 1.03-1.87]), and for studies which were published from 2016 onwards (odds ratio=1.47 [CI: 1.05-2.05]). The findings of a greater increase in STI positivity in more recent studies suggest that there may have been an increasing trust in the HIV-protective effect of PrEP, leading to normalisation of condomless anal sex over time.

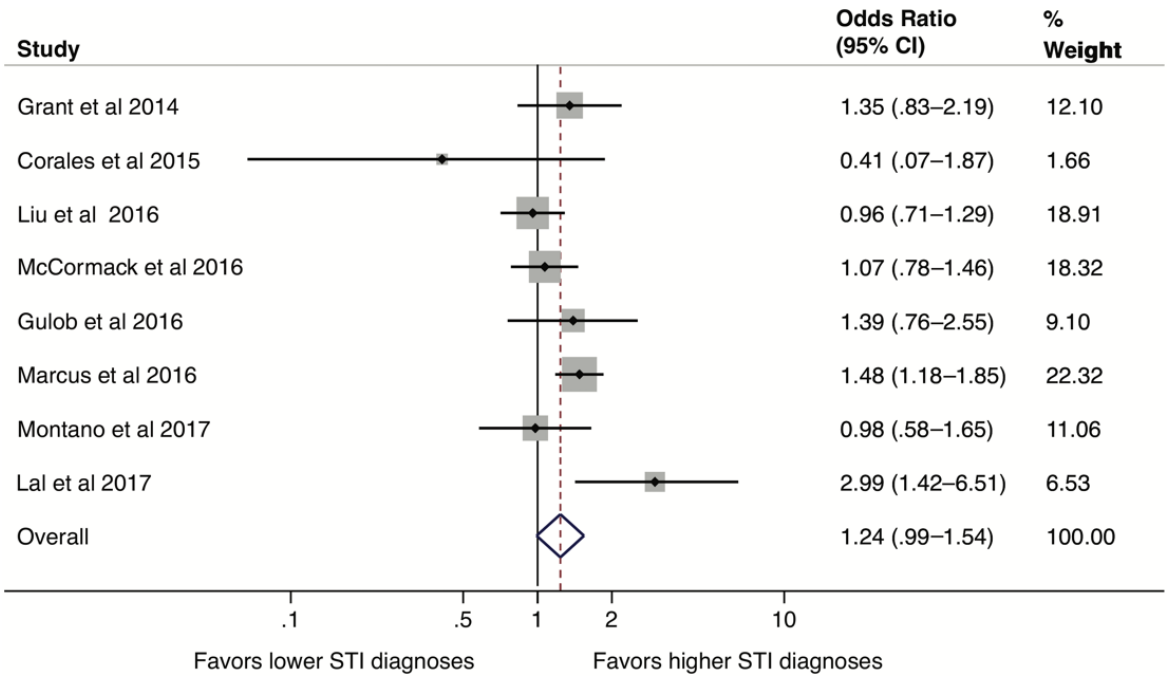

Figure 1.3: Meta-analysis of impact of PrEP use on STI positivity among gay and bisexual men enrolled in open-label PrEP trials.

Reference[162]: Traeger MW et al. Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex with Men: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018;67(5):676-86.

A major limitation of many of the early PrEP trials in exploring the changes in STI risk following PrEP use was that most lacked adequate follow-up time prior to study enrolment to calculate individual-level STI incidence prior to people initiating PrEP. Further, many of these studies involved PrEP protocols which included the provision of safe-sex counselling and condoms to participants, which may have led to underestimates in the magnitude of risk compensation associated with PrEP use which would occur through real-world implementation outside of a study environment. Using data from a pre-existing sentinel surveillance system (see Chapter 2) which covered a high proportion of clinics involved in the PrEPX study in Victoria, we were able to overcome previous studies' lack of pre-PrEP comparison data by retrospectively linking participants' STI testing data from study clinics prior to their enrolment in the study. A secondary analysis of 1,378 PrEPX participants found that overall STI incidence increased from 69.5 per 100 person-years in the 12 months prior to enrolment to 98.4 per 100 person-years during study follow-up, representing a 41% increase (appendix C1, p 320).[67] Among those initiating PrEP for the first time at enrolment, the increase was 71%. However, the PrEPX protocol[66] (and Australian PrEP guidelines[79]) recommended three-monthly STI testing alongside PrEP prescribing, and after adjusting for the increase in STI testing rate from pre to during study follow-up, the increase in STI incidence among those starting PrEP for the first time was attenuated to 21%.

We also found that STIs were highly concentrated among a subgroup of GBM who were diagnosed with multiple STIs during follow-up; 25% of participants were diagnosed with multiple infections during study following, with these participants accounting for 76% of all infections diagnosed **(Figure 1.4)**. In regression analysis exploring covariates associated with incident STIs during follow-up, we found that after multivariable adjustment, frequency of condom use with casual partners was not significantly associated with STI diagnosis (hazard ratio for never using condoms compared to always using condoms with casual partners: 1.31 [CI: 0.88 – 1.97]). However, number of anal sex partners and frequency of group sex in the past six months were strong indicators of STI risk, both showing dose-response relationships with increased risk.

Another analysis of data from the EPIC-NSW study in New South Wales explored STI positivity among participants in the 12 months prior to PrEP initiation to during the first 24 months of PrEP follow-up.[163] In this study, authors report that there were already increasing trends in STI positivity in the years prior to study enrolment, at that STI positivity remained stable during PrEP use.

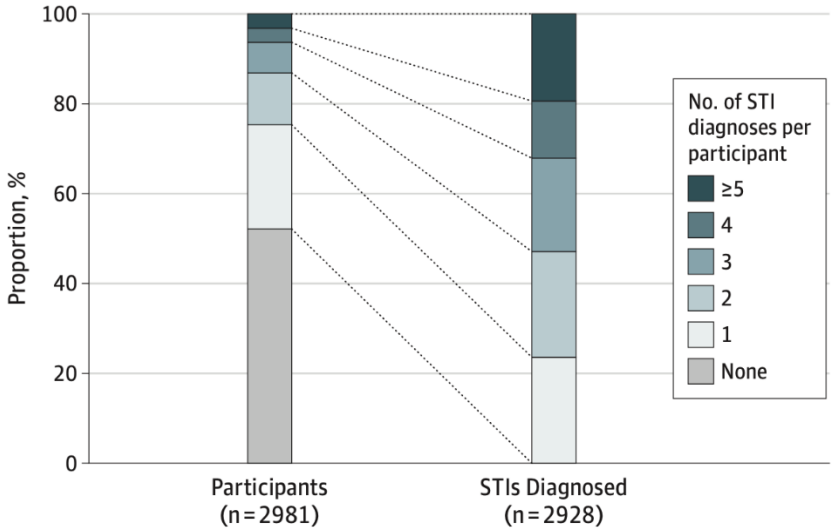

Figure 1.4: Distribution of STI diagnoses among participants of the PrEPX Victoria implementation study by number of infections per participant during follow-up.

Reference[67]: Traeger MW at al. Association of HIV Preexposure Prophylaxis with Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection. JAMA. 2019;321(14):1380-90. [Appendix C1, p 320]

These data were the first large cohort data to show an association between PrEP use and STI risk, while taking into account changes in testing frequency and pre-existing trends, respectively. However, participants in these studies likely reflected early adopters of PrEP, who may have higher pre-existing risk profiles and not be representative of the wider population of GBM who would later take up PrEP. Interpreting population-level increases in STI incidence or positivity among GBM in the context of PrEP implementation studies is difficult given the complex interplay between individual-level behaviours and sexual networks and relative STI risk.[164] Our findings of high rates of repeated infections and strong association between group sex and STI risk suggest that STI risk among PrEP users is likely associated with specific sexual networks potentially driving repeat STI infections.

The long-term impact of PrEP implementation on STI incidence among GBM has been widely debated, with some suggesting that high frequency screening associated with PrEP use may drive down STI incidence through early detection and treatment of asymptomatic infections.[165] An early modelling study of GBM in the US found that accompanying PrEP scale up with 40% coverage of bi-annual STI screening would lead to 42% of gonorrhoea and 40% of chlamydia infections being averted over 10 years due to more timely detection and treatment.[165] An Australian modelling study found that higher frequency of testing associated with wider PrEP uptake alone would likely not be enough to curtail the growing syphilis epidemic among the wider GBM population.[166] In Chapters 2

and 3 of this thesis, I explore long-terms trends in STI testing and corresponding incidence rates during periods of wide PrEP uptake post-implementation studies in Australia.

1.2.6 Hepatitis C among gay and bisexual men

Alongside HIV and bacterial STIs, GBM are also at increased risk of hepatitis C.[167] Globally, hepatitis C virus (HCV) is mostly transmitted through sharing of injecting equipment.[168] While hepatitis C is less commonly transmitted through sex, certain sexual behaviours increase the risk of transmission.[169] Prior to the 2010's, treatment of hepatitis C involved the use of interferon medication, with 24-28 week regimens having significant side effects and were only up to 65% effective.[170, 171] In 2012, new treatments known has direct acting antivirals (DAAs) became available, which involve taking a daily pill for 8-12 weeks with few side effects, and have a more than 95% cure rate.[172] In March 2016, DAAs were publicly subsidised in Australia leading to rapid scale up of DAA treatments which included scale up among people with HIV through integrated care models linked to a micro-elimination of HIV-hepatitis C coinfection strategy.[173]

Among GBM, hepatitis C has historically been concentrated among GBM with HIV, with higher transmission in this population associated with sexual networks, intersecting sexual and drug use behaviours, and specific contexts in which sex occurs.[174, 175] A common setting associated with sexual transmission of HCV is group sex, which may compound HCV risk factors such as serosorting based on HIV status, condomless anal sex, and sexual practices which may cause trauma to the mucosa and increase rectal bleeding.[176, 177] However, over the past decade, there has been an increasing trend of hepatitis C diagnosed among GBM without HIV.[178] While some countries observed such trends prior to PrEP rollout, hepatitis C among GBM without HIV has been linked to PrEP use in many settings.[179-182]

Given the concern for hepatitis C transmission among GBM without HIV, many PrEP trials included hepatitis C testing protocols. Data from early-adopters of PrEP in the Netherland showed both high baseline HCV prevalence[183] and prospective HCV risk.[180] However, this study enrolled a small number of participants and had a stringent enrolment criteria based on reported risk behaviours, given the recruitment limit. Data from the PrEPX study in Victoria showed that GBM enrolled in the study had a relatively low incidence of hepatitis C, with an incidence rate of 0.3/100 person-years[184] (appendix C5 p 351). Hepatitis C incidence was also low among GBM taking PrEP in the EPIC-NSW study.[185] A national analysis of hepatitis C incidence among GBM in Australia using sentinel surveillance data showed that hepatitis C incidence has rapidly declined since the availability of direct-acting antiviral

medications (DAAs) from 2016. The analysis also highlighted that rates of hepatitis C among GBM with evidence of PrEP use has slightly declined since 2016[186] (appendix C6, p 357). In this thesis, a systematic review and meta-analysis which explores hepatitis C incidence among GBM using PrEP is presented in Chapter 5, indicating hepatitis C risk among GBM using PrEP varies by setting, behaviours and DAA availability.

1.3 STI control in the era of PrEP

1.3.1 Importance of STI control

While many bacterial STIs are asymptomatic among GBM, especially rectal chlamydia and gonorrhoea,[187] there are a number of concerns regarding the increasing rates of STIs among GBM, including antimicrobial resistant strains[188] and potentially harmful sequelae among both GBM and other populations.[189] In the HIV PrEP era, novel prevention and surveillance strategies are needed to inform and refine responses to increasing transmission of STIs and the threats they pose.

Harmful sequelae and transmission in other populations

Although rare, chlamydia infection among men can cause urinary tract infections, damage sperm DNA, and lead to acute epididymitis, urethritis and prostatitis,[190] and possibly be a contributing factor to infertility among some men with idiopathic infertility.[191] Gonorrhoea is more likely to lead to symptomatic infections when in the urethra. Data from the PrEPX study show that approximately 83% of urethral infections of gonorrhoea among men are symptomatic[192] (see appendix C3). Gonorrhoea is also more likely to lead to adverse outcomes such as scarring in the sperm duct, and can impair sperm motility and viability.[193] Untreated syphilis can lead to serious tertiary complications years after infection including cardiovascular and neurological disease.[194] Syphilis infection is also linked to increased HIV transmission[117] and acquisition risk.[118]

Increased rates of bacterial STIs among women pose serious public health threats. For example, infection during pregnancy can lead to a range of adverse birth outcomes including stillbirth and neonatal death.[195] After many years of no cases, congenital syphilis cases have increased in Australia since 2017.[196, 197] Similarly, since the early 2010's, gonorrhoea has been increasing among heterosexuals in Australia,[198] with the number of gonorrhoea cases among females notified in

Victoria increasing from 291 in 2010 to 1673 in 2019, a 475% increase.[199] Spatial analysis of gonorrhoea notifications in Victoria also shows that while cases of gonorrhoea among GBM are concentrated in inner-urban areas, cases among heterosexual populations are more dispersed in outer-suburban areas.[200] Similar geographical trends have been observed for syphilis.[201] The drivers of increased transmission of syphilis and gonorrhoea among heterosexual populations are not completely understood, and while it may represent separate epidemics from those among GBM, genomic analysis of syphilis[202] and gonorrhoea[202] in Australia shows that GBM are represented in lineages and transmission clusters associated with heterosexual transmission, suggesting that bisexual men and other men who have sex with men and women (MSMW) may serve as a bridging population between the two groups. Hence, a public health response which reduces STI transmission among GBM may have wider impact among other populations, reducing the burden of harmful sequelae.

Antimicrobial resistance

The ability of a disease-causing microbe to survive exposure to specific antimicrobial drugs facilitates antimicrobial resistance (AMR). A study published in 2022 by the a global collaborative work group on AMR estimated that, in 2019, there were almost 1.3 million deaths attributable to bacterial AMR.[203] While antibiotic-resistant bacterial STIs are not typically associated with death, there is a risk that untreatable STIs may lead to serious sequalae. Since 2010, cases of multi-drug-resistant gonorrhoea have been identified in seven countries, including Australia.[204] In 2016, the first global failure to cure pharyngeal gonorrhoea with dual therapy (ceftriaxone and azithromycin) was reported in the UK. In its resistance threats 2019 report, the US CDC listed drug-resistant gonorrhoea on its Urgent Threats list, and *Mycoplasma genitalium* on its watch-list.[204] Australia has had an official strategy on AMR since 2015,[205] with the latest strategy, *Australia's National Antimicrobial Resistance Strategy – 2020 and Beyond*, released in 2020.[206] The Australian strategy largely aligns with the WHO's *Global Action Plan on AMR.*[207] Key objectives of the strategies include, among others, prevention and control of infections and the spread of resistance, appropriate usage of antimicrobials and antimicrobial stewardship, and integrated surveillance and response to resistance.

There is evidence that wider uptake of PrEP, and the increased screening, detection and treatment of STIs associated with PrEP use, may be driving higher rates of antibiotic consumption among GBM.[208, 209] Rates of antibiotic resistance for *Mycoplasma genitalium* among GBM using PrEP is also high,[210] with modelling work suggesting that frequent testing associated with PrEP use and

treatment of asymptomatic infections may be driving this increased resistance.[211] Further, current and anticipated future use of antibiotics for STI prophylaxis in GBM may have the potential to drive antimicrobial resistance further (see section 1.3.3).

1.3.2 STI screening and control strategies

Given the high asymptomatic rate of bacterial STIs among GBM, screening for STIs in the absence of symptoms has been a key pillar of STI control among GBM.[212] When PrEP was introduced through implementation studies in Australia in 2016, specific PrEP guidelines recommended three-monthly comprehensive STI testing at each PrEP visit.[75] At this time, general Australian STI testing guidelines recommended that sexually-active GBM be screened at least annually, and up to four times per year for GBM with HIV and GBM without HIV reporting specific risk behaviours (*e.g.* multiple casual partners, condomless anal sex). General testing guidelines for GBM were updated in 2019 to recommend that all sexually active GBM be tested for bacterial STIs every three months, and for hepatitis C annually, regardless of HIV status, reported risk behaviours or PrEP use.[213]

While there is some evidence that achieving high rates of chlamydia screening among females may lead to population-level declines in adverse outcomes such as pelvic inflammatory disease,[214] there is no real-world data to show that high rates of screening among GBM will lead to declines in STI prevalence or incidence, [215] although modelling work suggests that it may be possible.[165] However, models which have explored the impact of PrEP-associated testing on STI incidence have largely assumed persistent PrEP use and high adherence to testing protocols. In reality, PrEP discontinuation among GBM is high in many settings,[216] and data presented in this thesis shows that testing among GBM ever prescribed PrEP in Australia is well below the recommended three-monthly frequency (see Chapter 4).

In the context of limited capacity to test all GBM at high frequencies, strategies which differentiate screening among individuals at different levels of risk may have greater impact. For example, a US modelling study found that greater reductions in syphilis incidence among GBM would be achieved through increased screening frequency among people with a prior syphilis diagnosis, compared to increased coverage of annual screening among all GBM.[217] Epidemiological data, such as that generated in this thesis, can inform testing guidelines and improve efficiency of screening protocols. In Chapter 8, I include an in-depth discussion on the evidence of different screening strategies among GBM, including risk-guided screening, population-level screening and opt-out screening, and

how strategies should be guided by contemporary understandings of STI transmission and differential risk across subpopulations.

An additional tool for controlling the spread of STIs is partner notification, where people diagnosed with an STI inform their recent partners either directly or through a health care provider or public health department that they may have been exposed to an STI. Online services also exist where people diagnosed with an STI can anonymously let their partners know that they should seek an STI screen.[218] A survey of Australian GBM found that 70% of respondants were more likely to contact a partner if such an online service was available to them.[219] However, data from the Netherlands showed that among partners of GBM diagnosed with HIV, gonorrhea or syphilis, approximately 64% of partners potentially at risk of an STI were unnotifiable due to anonymity, i.e., a name, phone number or address was not available.[220]

1.3.3 Biomedical STI prevention strategies

Antibiotic prophylaxis

The use of antibiotics to prevent STIs has been explored as both pre- and post-exposure prophylaxis. Doxycycline is a moderate-spectrum tetracycline antibiotic, which is generally well tolerated and rapidly absorbed after oral administration.[221] Doxycycline is routinely used as first line treatment for chlamydia, and second line treatment for syphilis.[222, 223] Three major studies have explored the efficacy of doxycycline in preventing bacterial STIs among GBM. A small, open-label pilot study of 30 GBM with HIV who had previously been diagnosed with repeat syphilis infection were randomised to receive 100mg of doxycycline daily as STI pre-exposure prophylaxis, with a control arm receiving standard of care. During 48 weeks of follow-up, participants in the doxycycline arm were 73% less likely to be diagnosed with a bacterial STI at any study visit.[224] A larger open-label extension of 232 participants of the French IPERGAY PrEP study, explored the efficacy of 200mg doxycycline taken within 72 hours of sex, as STI post-exposure prophylaxis (PEP). Over a median of 8.3 months, doxycycline PEP use was associated with a relative reduction of 70% and 73% for chlamydia and syphilis, respectively. However, the reduction in gonorrhoea was not significant.[225] Finally, a large open-label study in the US of 501 GBM and transgender women, either living with HIV and or using PrEP, randomised participants 2:1 to receive 200mg doxycycline to be taken within 24 hours of condomless sex. In this study, which was stopped early due to high efficacy, doxycycline PEP reduced chlamydia by 74-88%, syphilis by 77-87%, and gonorrhoea by 55-57%.[226] In each of these studies, adherence to doxycycline was high in the intervention arms.

There are however several concerns about the widespread use of doxycycline for STI prophylaxis.[227] First, prolonged use of antibiotics may negatively impact the gut microbiome.[228] While the exact impact of prolonged doxycycline use on adverse outcomes related to changes in the microbiome are not well understood, dysbiosis of gut bacteria has been linked to inflammatory bowel disease, obesity, and poor mental health.[229, 230] Second, there is concern that widespread use of doxycycline among people at ongoing risk for STIs, including GBM, may drive antibiotic resistance in STIs such as gonorrhoea and *Mycoplasma genitalium.*[231] Third, use of doxycycline prophylaxis may drive resistance in other infections for which doxycycline is relied on for treatment, including skin infections such as *Staphylococcus aureus*.[232]

Although concerns around resistance and impact on gut health are warranted, there is growing evidence that use of doxycycline as prophylaxis is already occurring in the community without formal guidelines; in this context it is possible that current practices (e.g. patterns of dosing, adherence) may facilitate antimicrobial resistance. While not yet recommended for use in Australia, a survey of PrEP users attending the Melbourne Sexual Health Centre found that in 2019, 9.9% reported using antibiotics as STI prophylaxis in the past month.[233] These reflect survey data from the UK where 9% of GBM using PrEP also reported previously using STI prophylaxis.[234] There are a number of ongoing studies exploring implementation of doxycycline prophylaxis, including a large, multi-centre open-label study in Australia which aims to explore a range of secondary outcomes related to doxycycline PrEP/PEP implementation, including adherence, change in behaviour, impact on gut microbiome, and antibiotic resistance.[235] Further real-world data is needed to help guide the effective implementation of doxycycline prophylaxis to ensure future policy and clinical guidelines include strategies to maximise impact yet minimise unnecessary or over-prescribing, with ongoing monitoring for resistance crucial.

Vaccines

There is also ongoing research into the development of vaccines for a number of STIs,[236] with a particular global focus on gonorrhoea vaccines.[237] A retrospective case-control study of patients attending sexual health clinics in New Zealand found that vaccines for meningococcal disease may provide some protection against gonorrhoea. People who were vaccinated with the outer membrane vesicle meningococcal group B vaccine (MeNZB) were 31% less likely to be cases (people diagnosed with gonorrhoea) than controls (people with a positive chlamydia test only).[238] Current RCTs are aiming to estimate the efficacy of such vaccines against gonorrhoea,[239] and while some efficacy is expected, little is known about long-term protection. However, a recent modelling study

found that a vaccine with even modest (50%) efficacy for a period of 2 years, with a targeted immunisation strategy, could lead to the prevalence of gonorrhoea among GBM being rapidly and substantially reduced.[240]

The advent of novel biomedical interventions may provide new ways to prevent STIs. However, as with the success of HIV combination prevention, curtailing the rise in bacterial STIs among GBM will likely require multiple strategies. For interventions which aim to interrupt STI transmission, such as test and treat strategies and biomedical prevention strategies, effective and efficient targeting of these interventions toward those with greater rates of diagnosis, will likely lead to improved impact on population-level transmission. Strategies which aim to reduce harmful sequelae and prevent growing antimicrobial resistance will require ongoing, time-sensitive epidemiological surveillance. Further, it is important to consider that different strategies, each which have a different impact on patient-burden and on pleasure, will likely be more acceptable to different subgroups of GBM. In Chapters 6 of this thesis, I explore variation in attitudes towards STI prevention among GBM, and in Chapter 7 explore the impact of a hypothetical gel-based biomedical intervention for reducing gonrrhoea transmission among GBM in Australia.

1.4 Thesis rationale and aims

The body of work contained in this thesis aims to better understand the epidemiology of STIs among gay and bisexual men in Australia following widespread PrEP availability, specifically focusing on the bacterial STIs of chlamydia, gonorrhoea and syphilis, as well as sexually transmitted hepatitis C. The specific aims are to:

1. Assess the long-term trends in bacterial STIs following PrEP implementation in Australia.
2. Enhance understanding of the sexual and health seeking behaviours and attitudes of gay and bisexual men taking PrEP.
3. Inform clinical and public health strategies to help guide Australia's response to STIs among gay and bisexual men.

1.5 Thesis outline

This thesis comprises 9 chapters, of which 6 present published or submitted work. The following provides an overview of the methods and aims of chapters 2 to 9.

Chapter 2 is a methods-focused chapter which outlines the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) surveillance system. ACCESS routinely extracts clinical and pathology data from over 100 clinical and laboratory services in Australia and provides a data platform for surveillance and epidemiological research related to HIV and STIs among key populations. ACCESS is the primary data source for empirical studies presented in Chapters 3, 4 and 6, contributes data to studies included in the meta-analysis presented in Chapter 5, and provides parameterising data for the mathematical model presented in Chapter 7.

Chapters 3 and 4 are longitudinal analyses of ACCESS data among GBM in Australia which span periods of PrEP implementation. **Chapter 3** explores STI trends among PrEP users over the first four years of PrEP implementation in Australia (2016-2019), describing incidence of chlamydia, gonorrhoea and syphilis. **Chapter 4** then takes a more detailed look at syphilis, expanded to include a decade of data (2012-2021), and compares trends in syphilis incidence and testing among PrEP users and non-PrEP users, including GBM with HIV.

Chapter 5 is a systematic review and meta-analysis which looks at hepatitis C incidence among GBM using PrEP, and the first review to explore the difference in hepatitis C incidence among PrEP users by country-level availability of hepatitis C DAA treatments. This meta-analysis includes data from three Australian studies, including the PrEPX study and other studies that utilise data from the ACCESS surveillance system.

Chapter 6 utilises survey data collected from participants in the PrEPX study who were enrolled through ACCESS clinics. Using latent class analysis, this chapter identifies four key groups of GBM using PrEP classified according to their different attitudes towards STIs and STI prevention, and explores associations between class membership and recent STI diagnosis. Findings have salient implications for the targeting of new STI interventions among GBM using PrEP.

Chapter 7 is a mathematical model which explores the population-level impact of a hypothetical antimicrobial intervention on gonorrhoea incidence among GBM in Victoria, Australia. Calibrated to ACCESS data and behavioural data from the PrEPX study, the model finds that even an intervention which has modest efficacy at reducing gonorrhoea risk during the time of sex (*e.g.* an antimicrobial lubricant which reduces gonorrhoea risk by 50%) could have population-level benefits if uptake is adequate among GBM.

Chapter 8 is a research synthesis and commentary article commissioned for a special issue for the journal Sexual Health in July 2022. Focused on STI Prevention in the 2020's, this chapter describes the importance of risk identification for STI control and explores new and emerging risk populations. Citing data generated from studies reported in earlier chapters, the article describes increasingly diversifying STI risk, including in the context of PrEP use. Tying together themes discussed throughout the thesis, Chapter 8 also discusses important considerations for the future STI control among GBM, including the benefits and harms of risk-based screening, and novel methods for targeting new STI interventions towards those most at risk.

Chapter 9 is a discussion chapter summarising the key findings of the thesis, and their implications for public health.

Chapter 2

The ACCESS surveillance system

The ACCESS surveillance system collects data from a large network of sentinel clinics that see high caseloads of people at risk of STIs and blood borne viruses in Australia, alongside laboratory data from participating private and public laboratories. ACCESS is the primary data source for analyses presented in Chapters 3 and 4, provided the evaluation data platform for the PrEPX Study which is described in Chapter 6, provided key data for parametrising the mathematical model in Chapter 8, and was the primary data source for three studies included in the meta-analysis presented in Chapter 5. During my PhD, I was a key member of the core ACCESS Study team and was responsible for the ongoing management of ACCESS surveillance data. I contributed to site recruitment and liaising with site investigators, data extraction, and working with the GRHANITE (software used to anonymise and extract ACCESS data from participating sites) data extraction team from the University of Melbourne. I also developed the code and processes used to interpret hepatitis C pathology data, and the code to identify PrEP users in the ACCESS database, which allowed for the monitoring of STI outcomes among PrEP users across Australia.

This chapter describes the history, scope and methodology of the ACCESS surveillance system, and its use as research infrastructure across clinical trials, cohort studies and public health evaluation programs. Two ACCESS protocol papers are included as Appendices D1 (p 366) & D2 (p 378).

2.1 Surveillance of HIV and STIs in Australia

In Australia, chlamydia, gonorrhoea, and syphilis (alongside HIV since 1983) are notifiable conditions,[241] meaning that diagnosing clinicians or laboratories must notify positive results to jurisdictional health departments by law. In addition to national regulation, each state and territory in Australia has separate surveillance reporting requirements, especially for syphilis. HIV and STI notifications data in Australia are used to monitor trends over time in the number of diagnoses, aggregated by the basic characteristics of people diagnosed, with regular jurisdictional reports and annual national reports typically made publicly available.[121] While national notification data sets have a complete coverage of diagnoses, they are limited in their ability to account for changes in trends in testing when reporting on cases detected, as only diagnoses and not negative tests are recorded. Further, additional epidemiological data such as PrEP use, gender of partner and symptomatic status is limited. So-called 'enhanced surveillance' for diagnoses of HIV, gonorrhoea and syphilis are undertaken in some jurisdictions, in which diagnosing clinicians or health department workers complete additional demographic and behavioural data collected for each notified case. Through the collection and linkage of epidemiological and laboratory data, enhanced surveillance allows for monitoring of notification rates among particular subgroups and a deeper understanding of routes of transmission, which can be used to inform public health response. For example, in Australia HIV notifications are classified based on likely route of acquisition, including male-to-male sex, heterosexual sex, sharing of injecting drug equipment or mother-to-child transmission. While the manual collection of epidemiological data during enhanced surveillance provides useful insights into epidemiology and transmission dynamics, it is often expensive and time consuming.

Sentinel surveillance is method of surveillance which involves closer monitoring a specific disease through a network of doctors, clinics or laboratories, selected to best represent a particular population where disease is more likely to occur.[242] While sentinel surveillance does not capture all diagnoses across a population, it is typically able to provide more detailed data to help monitor outcomes like trends in testing among key groups, with negative tests also usually captured. When all tests are included in a sentinel surveillance system, denominator data allows for the calculation of rates of testing, positivity, and incidence over time. Sentinel systems can also act as an early detection mechanism for emerging disease trends and new outbreaks.

2.2 The ACCESS sentinel network and coverage

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance for Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) has been monitoring Australia's response to STIs and BBVs for over a decade.[243] ACCESS is a collaboration between Burnet Institute, the Kirby Institute, and the National Reference Laboratories (NRL). ACCESS was Australia's first national sentinel surveillance program for monitoring blood borne viruses and STIs, and closely informed the only other such system which was established to specifically monitor outcomes among populations of Aboriginal and Torres Strait Islander people.[244] ACCESS collaborates with and extracts data from more than 100 specialised clinical services and diagnostic laboratories to monitor Australia's response to STIs. ACCESS was initially established in 2008 at a network of clinics in Victoria, to monitor trends in chlamydia testing and diagnoses.[245] ACCESS was then expanded to monitor HIV and chlamydia in Victoria and New South Wales. Through the receipt of ongoing national funding in 2016, ACCESS expanded to include clinics and laboratories in multiple Australian states and territories, with the overarching aim of providing data to monitor specific HIV, viral hepatitis and STI indicators against targets outlined in disease-specific national strategies.[246, 247] Following further funding of a large observational study that aimed to measure the impact of HIV viral suppression on HIV incidence,[248] ACCESS expanded to recruit the majority of publicly-funded sexual health clinics in NSW, and other key tertiary and primary care clinics in other jurisdictions. ACCESS also receives funding from the health departments of multiple state and territory governments for specific state-level HIV and STI reporting.

As of July 2022, 121 services were collaborating on the ACCESS project, including sexual health clinics, general practices, community health care centres, drug and alcohol services, hospital clinics and public and private laboratories. The majority of ACCESS clinics are in NSW and Victoria, which are Australia's most populous states, and where an estimated two-thirds of Australia's GBM reside[248] **(Figure 2.1)**.

2.3 Innovative data extraction and linkage

The ACCESS surveillance system works by utilising the data extraction software known as GHRANITE.[249] GHRANITE was developed by the University of Melbourne is used for a number of clinical, epidemiological and surveillance projects nationally. GHRANITE can be configured to specific clinical patient management software platforms and is installed on clinic servers. GHRANITE

automatically and routinely performs data extractions, usually after hours, meaning minimal input is required from clinical services once installed. GHRANITE de-identifies patient-identifying data (e.g., first and last name, date of birth, Medicare number, mobile phone number) into a non-reversable hash-code and assigns this unique code to patient records before extracting patient data (demographics, pathology reports and electronic prescriptions) and sending it to the Burnet Institute. Individuals' data can then be linked using a probabilistic linkage algorithm to identify repeat episodes of care for individual patients within and across services using the hash-code. Validation of this linkage method in a large gold-standard subset of ACCESS data including 86,538 medical records found that sensitivity of the linkage keys ranged from 94% to 95% and estimated specificity ranged from 91% to 99%, depending on data fields available to create linkage hashes.[250] By using this method, ACCESS can link deidentified patient records accurately both over time and across services **(Figure 2.2)**.

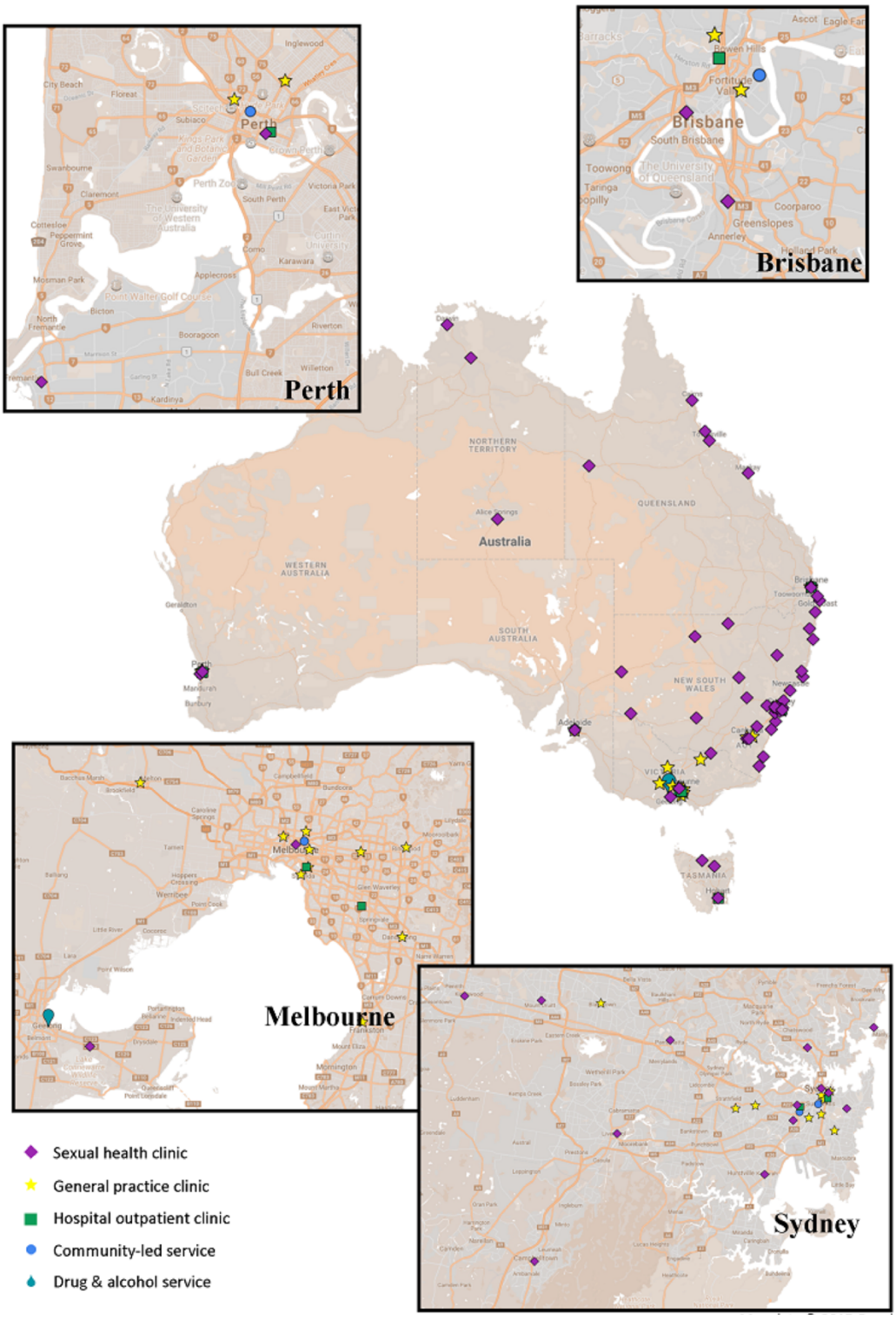

Figure 2.1: Health services participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance network as of March 2018

Reference: Callander D et al. Monitoring the Control of Sexually Transmissible Infections and Blood-Borne Viruses: Protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). [Appendix D1 p 366]

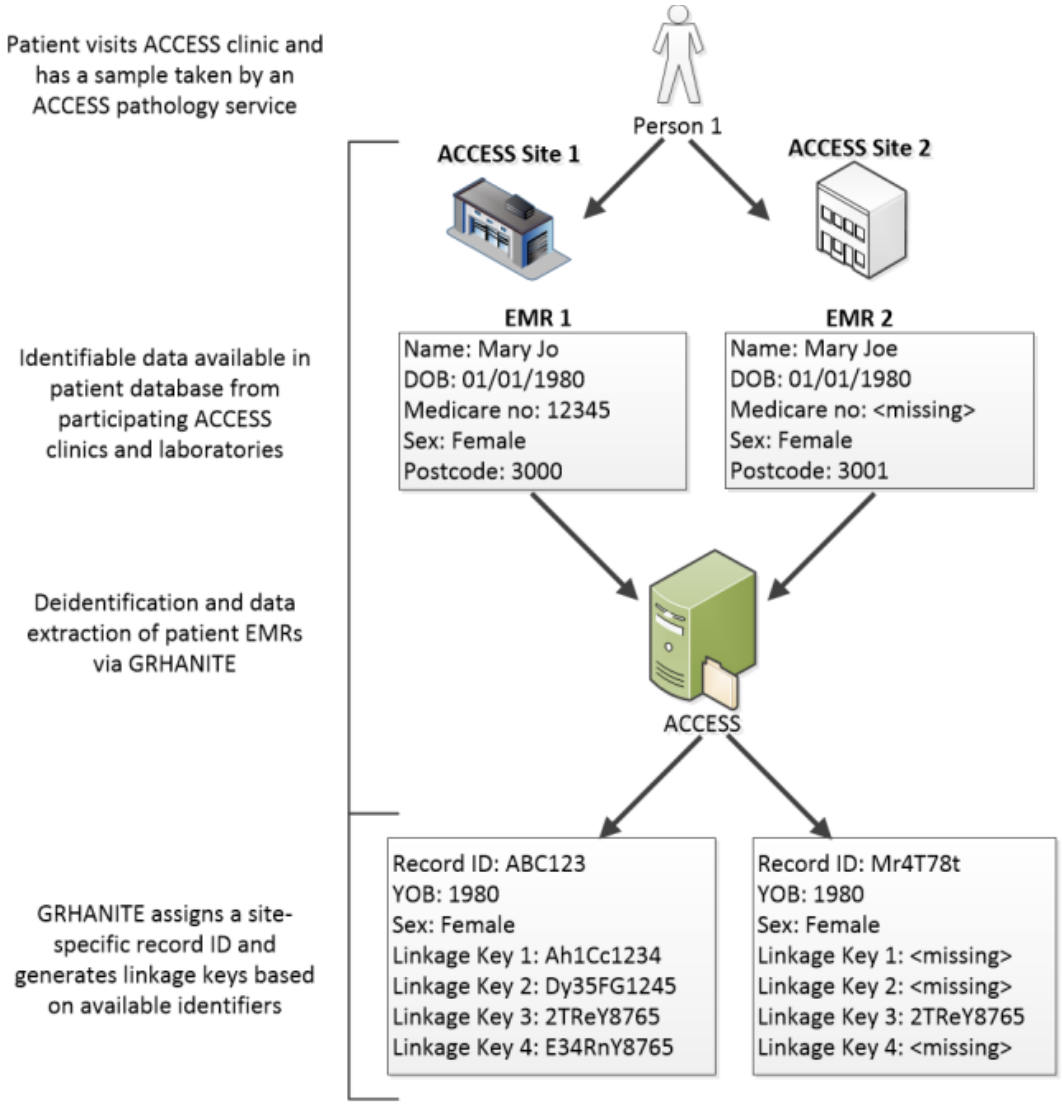

Figure 2.2: Data extraction in the ACCESS surveillance system using GHRANITE to deidentify electronic medical records and create linkage keys.

Reference[67]: Nguyen L et al. Privacy-preserving record linkage of deidentified records within a public health surveillance system: Evaluation study. Journal of Medical Internet Research. JAMA. 2020; 22(6):e16767. [Appendix D2 p 378]

2.4 Data management and disease interpretation

Raw patient data extracted from services participating in ACCESS go through a series of cleaning, mapping and interpretation stages prior to being available for public health surveillance and research. First, data fields from multiple patient management systems across all clinics are mapped to corresponding data tables. Next, data are split into diseases. A key strength of ACCESS is its ability to capture laboratory pathology results stored within patient management system. While data on which tests are ordered and performed are often stored as "atomised" data within patient management systems (*e.g.* binary data which indicate if a test has been ordered or not), the most useful information is stored within laboratory reports, usually in html or rich text format. Using a range of parsing methods, including natural language processing, all pathology reports extracted by ACCESS are parsed for key information, including:

- date of specimen collection
- anatomical site of specimen (e.g. urethra, pharynx, rectum, cervix)
- specimen collection method (e.g. swab, first-pass urine, midstream urine, blood)
- pathogen
- test type (e.g. PCR, antibody, culture)
- test assay
- quantitative result or qualitative result (e.g. positive, negative, indeterminate)
- result units (IU, copies/mL)

Data then go through a series of interpretation algorithms, which take results of different tests and determine instances of new infections. These algorithms are typically aligned with national case definitions for new confirmed or probable cases of diseases of interest. For example, for hepatitis C, a positive antibody or RNA test following a previous negative antibody test is assumed to be a new case of primary hepatitis C infection. For syphilis, an algorithm which utilises pathology data, including serology (treponemal and non-treponemal tests) and PCR tests, is used to identify new cases of infectious syphilis (primary, secondary or early latent), in alignment with the national definition of a notifiable case (See Chapter 4).

Individual-level, line-listed data, containing all pathology results at ACCESS clinics is available for HIV, hepatitis B, hepatitis C, chlamydia, gonorrhoea, syphilis and *mycoplasma genitalium*. Further, all clinical consultation types and dates, recorded electronic prescriptions for key medicines and drugs of interest, and relevant clinical diagnoses captured in patient management systems are available and linked to disease data. To determine a prescription for HIV PrEP, tenofovir prescriptions are

flagged in the ACCESS database. Prescriptions among people with an HIV positive test result are assumed to be for HIV treatment and separated from PrEP prescriptions. Prescriptions for less than 28 days are assumed to be for HIV PEP.

2.5 Using ACCESS as research infrastructure

Alongside its primary role as a national sentinel surveillance system, ACCESS contributes data to a wide range of research, including clinical trials and implementation studies. The routine extraction of ACCESS data and ability to perform privacy-protected linkage of patient records provides a clinical network and infrastructure for studies being undertaken in situ at ACCESS clinics; this includes the ability to evaluate "natural experiments", such as the introduction of PrEP. The routine and semi-automated processes of ACCESS data extraction allow for ongoing, longitudinal monitoring of individuals accessing sexual health care across Australia. Specifically, it allows for monitoring STIs and evaluating public health interventions in a real-world context, where clinical interactions are not affected by specific research protocols. ACCESS provided data for the PrEPX[66] and EPIC-NSW implementation studies and formed the main data source for study evaluations.

Chapter 3

Real-world trends in bacterial STIs among gay and bisexual men using PrEP following nation-wide PrEP implementation in Australia

In Chapter 1, I described the implementation of PrEP in Australia, from early pilot studies in 2014, to larger implementation studies from 2016, through to listing of PrEP on Australia's universal health care scheme in 2018. I reported on studies that highlighted the strengths of using the ACCESS surveillance system to evaluate STI outcomes among participants accessing PrEP through implementation studies, namely the PrEPX study in Victoria and the EPIC-NSW study in New South Wales. By comparing STI incidence prior to and post-enrolment, these studies generated the first empirical STI incidence data for GBM prior to and after they commenced using PrEP, and helped better understand the impact of PrEP on STI transmissions. However, as outlined, these studies enrolled GBM on the basis of specific risk-based criteria, and participants were early adopters of PrEP who may not be reflective of all GBM in Australia, including those who later accessed PrEP through public subsidy. Further, these studies were limited to 12-24 months of follow-up. Since PrEP was listed as a subsidised medicine on the PBS in 2018, prescribing guidelines changed to allow for the prescribing of PrEP to a larger population of people.

Chapter 3 describes an analysis of national data from the ACCESS system and spans an observation period which includes the years of the implementation studies and the years following PBS-listing of PrEP. Using the ACCESS system, we believe this analysis captured approximately 70% of all PrEP users in Australia to 2019, represents the largest cohort of PrEP users from which trends in STI incidence have been estimated globally, and is the only analysis which explores real-world trends in STIs in the context of widespread availability and uptake of highly-subsidised PrEP for an extended period of time. We also explore the distribution of STIs in relation to repeated infections among GBM.

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This chapter is included in the original ***The Lancet Infectious Diseases*** format in Appendix B1 (p 271)

Chapter 3

Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis in Australia following nation-wide pre-exposure prophylaxis implementation: an analysis of sentinel surveillance data

Authors

Michael W. Traeger[1,2], Prof Rebecca Guy[3], Jason Asselin[1], Prital Patel[3], Allison Carter[3,4,5], Edwina Wright[1,6,7], Prof Andrew Grulich[3], Hamish McManus[3], Prof Christopher K. Fairley[8,9], Eric P.F. Chow[8,9,10], Anna McNulty[11,12], Robert Finlayson[13], Charlotte Bell[14], Louise Owen[15], Lewis Marshall[16,17,18], Darren Russell[19,20], Darryl O'Donnell[21], Prof Basil Donovan[3,11], Prof Margaret E. Hellard*[1,6,7], Prof Mark A. Stoové*[1,2],
on behalf of the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS)

*co-senior authors

Author affiliations

1. Burnet Institute, Melbourne, Australia;
2. School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia;
3. Kirby Institute, UNSW Sydney, Sydney, Australia;
4. Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada
5. Australian Human Rights Institute, UNSW Sydney, Sydney, Australia;
6. Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Australia;
7. Peter Doherty Institute, Melbourne Australia;
8. Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia;
9. Central Clinical School, Monash University, Melbourne, Australia
10. Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia
11. Sydney Sexual Health Centre, Sydney, Australia;
12. School of Population Health, UNSW Sydney, Sydney , Australia
13. Taylor Square Private Clinic, Sydney, Australia;
14. Adelaide Sexual Health Centre, Adelaide, Australia;
15. Tasmanian Sexual Health Service, Hobart, Australia;
16. Sexual Health Service, Fremantle Hospital, Fremantle, Australia
17. University of Notre Dame Australia, Fremantle, Australia
18. University of Western Australia, Perth, Australia
19. Cairns Sexual Health Centre, Cairns, Australia
20. James Cook University, Cairns, Australia
21. Australian Federation of AIDS Organisations, Sydney, Australia

3.1 Summary

Background

Although data from large implementation trials suggest that sexually transmissible infection (STI) risk increases among gay and bisexual men who initiate HIV pre-exposure prophylaxis (PrEP), there are few data on the trends in population-level STI incidence in the years following widespread PrEP implementation. We aimed to describe trends in bacterial STI incidence among gay and bisexual men using PrEP across Australia in the context of broad PrEP availability through Australia's subsidised medicines scheme.

Methods

We analysed linked clinical data from HIV-negative gay and bisexual men aged 16 years or older who had been prescribed PrEP across a sentinel surveillance clinical network, including 37 clinics in Australia, between Jan 1, 2016, and Dec 31, 2019. Patients were included if they had STI testing at least twice during the observation period. Repeat testing methods were used to calculate chlamydia, gonorrhoea, syphilis, and any STI incidence rates during individuals' periods of PrEP use. Incidence rate ratios (IRRs) for estimated change in incidence per half calendar year (6-month) period were calculated using negative binomial regression. Secondary analyses compared STI incidence rates across individuals initiating PrEP in each year from 2016 to 2019, as well as by length of time using PrEP (per each additional 6 months of PrEP use).

Findings

22 730 men were included in the analyses. During the observation period, 11 351 chlamydia infections were diagnosed in 6630 (30·1%) of 22 034 men over 25 991·2 person-years of PrEP use (incidence rate 43·7 cases [95% CI 42·9–44·5] per 100 person-years). Chlamydia incidence decreased from 48·7 cases per 100 person-years in July–December, 2016, to 42·0 cases per 100 person-years in July–December, 2019 (IRR for estimated change per 6-month period 0·98 [95% CI 0·97–0·99]; p=0·0031). 9391 gonorrhoea infections were diagnosed in 5885 (26·9%) of 21 845 men over 24 858·7 person-years of PrEP use (incidence rate 37·8 cases [95% CI 37·0–38·5] per 100 person-years). Gonorrhoea incidence decreased from 45·5 cases per 100 person-years in July–December, 2016, to 37·2 cases per 100 person-years in July–December, 2019 (IRR 0·97 [95% CI 0·96–0·98]; p<0·0001). Declines in chlamydia and gonorrhoea incidence were most prominent in the first 18 months of observation and incidence was stable thereafter. 2062 syphilis infections were diagnosed in 1488 (7·7%) of 19 262 men over 21 978·9 person-years of PrEP use (incidence rate 9·4 cases [95% CI 9·0–

9·8] per 100 person-years). Syphilis incidence increased from 6·2 cases per 100 person-years in July–December, 2016, to 9·8 cases per 100 person-years in July–December, 2019 (IRR 1·08 [95% CI 1·05–1·10]; p<0·0001).

Interpretation

Chlamydia and gonorrhoea incidence among gay and bisexual men using PrEP were highest in the early months of PrEP implementation in Australia and stabilised at slightly lower rates thereafter following wider PrEP uptake. Lower prospective STI risk among people initiating PrEP in later years contributed to the observed trends in STI incidence. Widespread PrEP implementation can contribute to increased STI screening and detection.

3.2 Research in Context

Evidence before this study

We searched PubMed for studies published in English between Jan 1, 2010, and June 30, 2021, using the terms “pre-exposure prophylaxis”, “men who have sex with men”, “gay and bisexual men”, and “sexually transmitted infections”. Multiple meta-analyses of clinical trials and cohort studies reported that gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) had high incidences of bacterial sexually transmissible infections (STIs), and some large cohort studies reported increases in incidence of bacterial STIs among gay and bisexual men after PrEP initiation. However, most studies have been linked to implementation and demonstration projects, which generally reflect early periods of PrEP implementation, and few studies have reported population-level trends in bacterial STI incidence associated with high population-based uptake of PrEP. Furthermore, most studies have reported trends in STI positivity rather than incidence. Multiple mathematical modelling studies, which have relied on parameters generated from these early demonstration studies, have projected the effect of widespread PrEP uptake and subsequent increases in STI testing on population-level STI incidence, with varying conclusions. At the time of this study, no empirical data were available on real-world trends in STI incidence over long periods of PrEP use and in the context of widespread country-level access to PrEP, at both the individual and population levels.

Added value of this study

To our knowledge, this study includes the largest cohort of gay and bisexual men using PrEP with the largest total person-years of follow-up from which STI incidence rate estimates and trends have been reported internationally. We analysed linked data from the Australian Collaboration for

Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) system—a large, national network of sentinel clinics that monitor Australia's response to blood-borne viruses and STIs. The automated extraction of clinical data through the ACCESS system enabled the capture of data showing trends in clinical outcomes in the context of widespread availability and highly government subsidised PrEP in Australia. We estimate that the ACCESS clinical network captures 70% of gay and bisexual who have received government-subsidised PrEP in Australia through 2019. In our analysis, 22 730 men were prescribed PrEP and were observed between Jan 1, 2016, and Dec 31, 2019; outcome-specific analyses captured between 21 978 and 25 991 person-years of PrEP use. During the observation period, 44% of men who had been prescribed PrEP were diagnosed with any STI. We observed moderate declines in population-level incidence of chlamydia and gonorrhoea in the first 18 months of PrEP implementation as PrEP was scaled up rapidly, followed by a stabilisation in incidence thereafter. Incidence of syphilis increased across the observation period.

Implications of all the available evidence

Our analysis shows that, in the context of highly subsidised and broad access to PrEP in Australia, STI testing rates were high among gay and bisexual men who had been prescribed PrEP, and chlamydia and gonorrhoea incidence stabilised in this population in the years following widespread PrEP uptake. These data represent real-world, population-level incidence estimates of bacterial STIs following high and prolonged uptake of PrEP among gay and bisexual men, and reinforce that gay and bisexual men using PrEP are a priority population for bacterial STIs. These data suggest that concerns around exponentially increasing rates of STI transmission following wide-scale PrEP implementation have not materialised in Australia.

3.3 Introduction

Reductions in HIV diagnoses among populations of gay and bisexual men and other men who have sex with men have been observed following the implementation of HIV pre-exposure prophylaxis (PrEP) programmes in multiple countries, including Australia.[97] Implementation of PrEP has also led to considerable increases in testing for sexually transmissible infections (STIs) among gay and bisexual men, because PrEP prescribing guidelines recommend comprehensive screening for STIs at PrEP prescribing visits. Guidelines generally recommend either 3-monthly or 6-monthly screening on the basis of people receiving PrEP having a high baseline risk for STIs and an increased likelihood of condomless sex.[162]

In Australia, PrEP was initially made available through large implementation studies, which collectively enrolled more than 20,000 participants from early 2016, most notably in the states of Victoria and New South Wales,[163] where an estimated 67% of Australia's population of gay and bisexual men reside.[248] Data from a large, linked sentinel surveillance system allowed for the direct measurement of STI incidence among participants in these implementation studies. A previous analysis of gay and bisexual men enrolled in the PrEPX study in Victoria found that, after controlling for increases in rates of testing, STI incidence increased by 21% (95% CI: 6–39) following PrEP initiation compared with the incidence 12 months before PrEP initiation. A relatively small proportion of men using PrEP, who had repeat infections, accounted for more than three-quarters of the burden of STI diagnoses.[67] Another analysis of gay and bisexual men enrolled in the EPIC-NSW study in New South Wales found similarly high rates of STI incidence during PrEP use, but found some attenuation in the already increasing trends in incidence of some STIs observed before the implementation of PrEP.[163]

These previous studies aimed to measure the effect of PrEP implementation on STI transmission among populations of gay and bisexual men, but interpreting the contribution of various factors, including changing testing rates, behavioural changes, and potential changes in sexual networks following PrEP implementation, is complex. Furthermore, uptake of PrEP and other biomedical prevention strategies, such as treatment as prevention, are occurring in the context of pre-existing increasing trends in STI notifications. As previous studies have only explored STI incidence in the initial periods of PrEP implementation, analysis of long-term, population-level, surveillance data on STI incidence outside of implementation and demonstration projects might help explain how PrEP uptake and the associated increase in STI testing is influencing trends in STI incidence.

PrEP was made widely available through primary care in Australia in April, 2018 at a highly subsidised price, via the Pharmaceutical Benefits Scheme, to be prescribed at visits once every 3 months alongside comprehensive HIV and STI testing. Previous modelling studies on the effect of high rates of STI screening with PrEP use on population-level gonorrhoea and chlamydia incidence among gay and bisexual men have shown varied results,[165, 251] with one study suggesting that 3-monthly STI testing among men using PrEP would not be enough to reduce gonorrhoea prevalence among gay and bisexual men. However, an Australian modelling study suggested that increased PrEP coverage might result in declines in new syphilis cases through increased STI testing.[166]

Increasing notifications of STIs among gay and bisexual men in Australia and internationally, especially in the context of more widespread PrEP use, suggests increasing transmission of STIs. However, notification data are influenced by changes in testing rates and might miss some nuances

only captured by incidence trend estimates. Furthermore, PrEP uptake in Australia has been gradual, and the changing composition of the population using PrEP over time, especially between those enrolled in early implementation studies and those who accessed PrEP when it was more widely available, might influence incidence trend estimates.

We aimed to estimate population-level incidence rates of bacterial STIs among gay and bisexual men using PrEP in Australia in the context of broad PrEP availability through Australia's subsidised medicines scheme. We also aimed to explore the association between length of time taking PrEP and individual-level STI incidence, how STI risk differs among gay and bisexual men initiating PrEP at different times, and how these factors influence overall trend estimates.

3.4 Methods

Study design and participants

We analysed routinely collected surveillance data from a large network of sentinel clinics across Australia. 37 clinics (19 sexual health clinics [including multiclinic and outreach services] and 18 general practice clinics) participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) system were included in the study. The ACCESS protocol has been previously published.[243] Briefly, retrospective patient data (demographics, pathology reports, and electronic prescriptions) were deidentified and extracted from patient management systems of participating services using the specialised data extraction software suite GHRANITE. Participants' data were linked within and across services using a highly sensitive linkage algorithm which utilised probabilistic and deidentifying linkage keys generated from patient identifiers created before data were extracted.[250]

HIV-negative cisgender and transgender gay and bisexual men aged 16 years or older who had attended an ACCESS service and had been prescribed PrEP during the observation period from Jan 1, 2016, to Dec 31, 2019, were eligible for inclusion in the analyses. Patients were included if they had STI testing at least twice during the observation period, as we used repeat testing methods to estimate STI incidence.[252]

Ethics approval was provided by the human research ethics committees at Alfred Hospital (248/17), Central Australia (CA-19-3355), Northern Territory Department of Health and Menzies School of Health (08/47), University of Tasmania (H0016971), Aboriginal Health and Medical Research Council (1099/15), AIDS Council of New South Wales (2015/14), Victorian AIDS Council and Thorne Harbour

Health (VAC REP 15/003), Western Australian Aboriginal Health Ethics Committee (885), and St Vincent's Hospital (08/051). As our study analysed deidentified data collected under the auspices of public health surveillance, individual patient consent was not required. Individuals were able to opt out of the surveillance system at will.

Procedures

Data were extracted up to June 30, 2021, to reduce the effects of right censoring bias on inflating incidence estimates in the final 6 months of the observation period.[253] Our analysis was censored before 2020 because restrictions were implemented following the COVID-19 pandemic that greatly influenced PrEP use and sexual behaviour among Australian gay and bisexual men,[101, 254] which made it difficult to compare trends during this period.

Individuals' person-time at risk began at the date of their first PrEP prescription if they had an STI test on the same date (or within the previous 7 days), or from their first STI test after PrEP prescription. Individuals contributed person-time until they were censored at: their last STI test during the observation period, or Dec 31, 2019, whichever occurred first. Individuals who did not receive another PrEP prescription within 4 months of a previous PrEP prescription were considered to have ceased PrEP use and were censored at 4 months after their last PrEP prescription (4 months was chosen on the basis of the distribution of days between PrEP prescriptions; appendix A1.5, p 215). These participants were able to be re-entered into the analysis if they received a subsequent PrEP prescription, with person-time recommencing at their subsequent STI test after the prescription.

Statistical analysis

For all STI tests conducted among participants within the observation period, we calculated the median and 90th percentile number of days since the participant's previous test. Overall incidence rates per 100 person-years during the observation period were calculated for chlamydia, gonorrhoea, infectious (primary, secondary, or early [<2 years] latent) syphilis, and any STI. Results were disaggregated by anatomical site (rectal, pharyngeal, or urogenital) and age group fixed at cohort entry (approximating median split <35 years *vs* ≥35 years). For the any STI outcome, we calculated the number and proportion of participants diagnosed with none, one to four, and five or more STIs during follow-up, and the attributable proportion of all STIs diagnosed among each group.

For trend analyses, incidence rates per 100 person-years were calculated and plotted for each half calendar year (6-month) period from July, 2016, to December, 2019, and were calculated as the number of incident infections divided by the total person-time accumulated. A series of negative binomial regression models (one for each respective STI outcome) with robust variance estimators clustered by individual were used to test for trends across the study period. In each model, time—a continuous variable representing half calendar years from July–December, 2016, to July–December, 2019— was included as the single independent variable. Incidence rate ratios (IRRs) represent the estimated change in incidence rate per each half calendar year (6 months) across the study period. Tests of non-linearity were performed for each trend analysis; where non-linearity was detected, piecewise negative binomial regression was used to examine trends in two periods, split at the median value of half calendar years (before January–June, 2018, *vs* from January–June, 2018, onwards; appendix A1.12, p 221). Additional sensitivity analyses were performed, namely including clinic as a random effect in mixed-effects negative binomial regression models (appendix A1.16, p 228) and using 6 months (rather than 4 months) since previous PrEP prescription as the cut-off time for censorship (appendix A1.15, p 226).

To describe STI risk among gay and bisexual men initiating PrEP in different years, we performed a secondary analysis of incidence trends, where time was measured in days since participants' PrEP initiation, rather than calendar time. We calculated incidence rates for each STI outcome in 6-monthly intervals of PrEP use since PrEP initiation, and overall incidence rates for each group by year of PrEP initiation (i.e., participants initiating PrEP in 2016, 2017, 2018, and 2019). Multivariable negative binomial regression was used to compare STI incidence among participants initiating PrEP in different years, and to calculate the association between time on PrEP (per 6-month increase) and STI incidence, adjusted for year of PrEP initiation. In these models, independent covariates were time on PrEP (continuous, 6-month intervals) and year of PrEP initiation (categorical). Separate negative binomial regression models were used to test for associations between time on PrEP and STI incidence for each group by year of PrEP initiation (those initiating PrEP in 2019 were excluded as at least 12 months of follow-up were needed to test for trend). Additional information on statistical methodology is provided in the appendix A1.1 (p 210). All analyses were performed using Stata (version 15.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3.5 Results

22,730 men were included in the analyses **(Table 3.1)**. A total of 160,778 chlamydia tests, 155,861 gonorrhoea tests, and 120,875 syphilis tests were done during the observation period. The median time between tests was 84 days (IQR 55–104) for chlamydia tests, 84 days (5–104) for gonorrhoea tests, and 90 days (70–108) for syphilis tests (appendix A1.6, p 216).

Table 3.1. Characteristics of PrEP users included in STI incidence analyses (N=22,703)

	n (%)
Age at PrEP initiation, years (mean, SD) (median, IQR)	36.4 (11.0) 34 (28 – 43)
Age group	
16-29	7,155 (31.5%)
30-39	7,923 (34.9%)
40-49	4,494 (19.8%)
50+	3158 (13.9%)
Year initiated PrEP	
2016	6,494 (28.6)
2017	5,789 (25.5)
2018	6,027 (26.5)
2019	4,420 (19.4)
Clinic type at PrEP initiation	
General practice	13,601 (59.8)
Sexual Health Clinic	9,129 (40.2)
Clinic state at PrEP initiation	
New South Wales	11633 (51.2%)
Victoria	6701 (29.5%)
Queensland	1247 (5.5%)
South Australia	1245 (5.5%)
ACT	825 (3.6%)
Western Australia	805 (3.5%)
Tasmania	262 (1.2%)
Northern Territory	12 (0.1%)

Data are n (%) unless otherwise stated. PrEP=HIV pre-exposure prophylaxis.

During the observation period, 11,351 chlamydia infections were diagnosed in 6,630 (30.1%) of 22,034 men over 25,991.2 person-years of PrEP use **(Table 3.2)**. The overall incidence rate of chlamydia was 43.7 cases (95% CI 42.9–44.5) per 100 person-years **(Table 3.3)**. 9,391 gonorrhoea infections were diagnosed in 5,885 (26.9%) of 21,845 men over 24,858.7 person-years of PrEP use **(Table 3.2)**. The overall incidence rate of gonorrhoea was 37.8 cases (95% CI 37.0–38.5) per 100 person-years **(Table 3.3)**. 2,062 syphilis infections were diagnosed in 1,488 (7.7%) of 19,262 men over 21,978.9 person-years of PrEP use **(Table 3.2)**. The overall incidence rate of syphilis was 9.4 cases (95% CI 9.0–9.8) per 100 person-years **(Table 3.3)**.

Table 3.2. Follow-up time and number of diagnoses by participant

	Chlamydia	Gonorrhoea	Syphilis	Any STI
Person-years at risk				
Total	25,991.2	24,858.7	21,978.9	23399.8
Mean (SD)	1.17 (0.95)	1.14 (0.93)	1.14 (0.94)	1.27 (0.99)
Diagnoses				
Total	11,351	9,391	2,062	20,116
Individuals diagnosed, n (%)	6,630 (30.1)	5,885 (26.9)	1,488 (7.7)	8,223 (44.5)
Among those ≥1 STI, median diagnoses (IQR)	1 (1 - 2)	1 (1 - 2)	1 (1 -1)	2 (1 - 3)

Data are n or n (%) unless otherwise stated. STI=sexually transmissible infection. *Any STI analysis only includes participants who had at least two tests for each infection (chlamydia, gonorrhoea, and syphilis).

Among the 18,483 individuals who contributed to the any STI outcome determination, there were 20,116 diagnoses of any STI over 23,399.8 person-years (mean follow-up 1.27 years [SD 0.99]; **Table 3.2**); participants who initiated PrEP in 2016 were followed-up for a mean of 2.3 years (SD 1.2; median 2.4 years, IQR 1.0–3.2). 8,223 (44.5%) of 18,483 men were diagnosed with any STI during the observation period; the median number of STI diagnoses per individual was two (IQR 1–3) and 1,049 (5·7%) men were diagnosed with five or more STIs, which accounted for 7,256 (36.1%) of 20,116 infections diagnosed **(Figure 3.1)**.

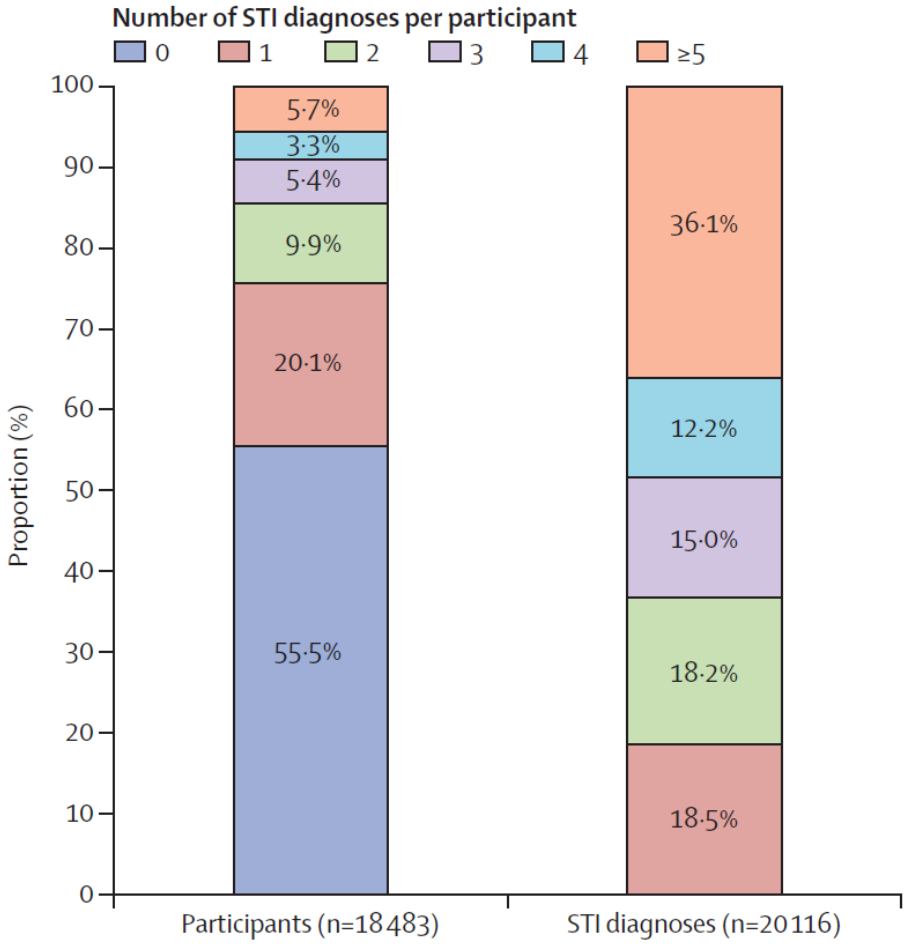

Figure 3.1: Number of STI diagnoses per participant during PrEP use and distribution of all STI diagnoses

PrEP=HIV pre-exposure prophylaxis. STI=sexually transmissible infection.

Table 3.3: Incidence rate and trends estimates among all PrEP users between 2016-2019 from primary analysis

		Study period				Trend Jul-Dec 2016 – Jul-Dec 2019	
		N	Person-years	Diagnoses	IR (95% CI) / 100py	IRR[a] (95% CI)	p-value
Chlamydia	Overall	22034	25991.2	11351	43.7 (42.9 - 44.5)	.98 (.97 - .99)[c]	0.0031
	Rectal	21121	25251.0	8449	33.5 (32.8 - 34.2)	.99 (.98 - .99)[c]	0.049
	Urogenital	21001	25064.9	3116	12.4 (12.0 - 12.9)	.99 (.97 - 1.01)	0.22
	Oropharyngeal	19921	24153.7	982	4.1 (3.8 - 4.3)	.96 (.93 - 1.00)	0.030
	Under 35	12103	12753.0	6372	50.0 (48.8 - 51.2)	.99 (.98 - 1.01)[c]	0.44
	Over 35	9931	13238.2	4979	37.6 (36.6 - 38.7)	.97 (.96 - .99)	.00027
Gonorrhoea	Overall	21845	24858.7	9391	37.8 (37.0 - 38.5)	.97 (.96 - .98)[c]	<0.0001
	Rectal	20984	24184.2	5420	22.4 (21.8 - 23.0)	.98 (.96 - .99)[c]	0.0030
	Urogenital	19467	22909.4	1569	6.8 (6.5 - 7.2)	.97 (.94 - 1.00)	0.079
	Oropharyngeal	21261	24399.7	5126	21.0 (20.4 - 21.6)	.97 (.96 - .99)[c]	0.0015
	Under 35	11958	12305.8	5691	46.2 (45.1 - 47.5)	.98 (.97 - 1.00)[c]	0.045
	Over 35	9887	12552.9	3700	29.5 (28.5 - 30.4)	.96 (.94 - .98)	<0.0001
Syphilis	Overall	19262	21978.9	2062	9.4 (9.0 - 9.8)	1.08 (1.05 - 1.10)[c]	<0.0001
	Under 35	10544	10897.1	1008	9.3 (8.7 - 9.8)	1.09 (1.05 - 1.13)[c]	<0.0001
	Over 35	8718	11081.8	1054	9.5 (9.0 - 10.1)	1.06 (1.03 - 1.10)[c]	0.00041
Any STI[b]	Overall	18483	23399.8	20116	86.0 (84.8 - 87.2)	.99 (.99 - 1.00)	0.17
	Under 35	10173	11642.2	11612	99.7 (97.9 - 101.6)	1.00 (.99 - 1.01)	0.91
	Over 35	8310	11757.5	8504	72.3 (70.8 - 73.9)	.99 (.97 - 1.00)	0.036

IR=Incidence Rate
IRR=Incidence Rate Ratio,
Calendar time analysis
[a]Average change per calendar half-year, half-year included as continuous variable in negative binomial model
[b]Any STI analysis only includes individuals with at least 2 tests for each infection (chlamydia, gonorrhoea and syphilis)
[c] Non-linearity detected, piecewise negative binomial regression performed (reported in Appendix A1.12 p 221)

Chlamydia incidence decreased from 48.7 cases per 100 person-years in July–December, 2016, to 42.0 cases per 100 person-years in July–December, 2019 (IRR 0.98, 95% CI 0.97–0.99; p=0.0031; **Figure 3.2**). However, the decline was non-linear, with the greatest decline during the first 18 months of observation; chlamydia incidence reached 42.7 cases per 100 person-years in July–December, 2017, and remained relatively stable thereafter. Gonorrhoea incidence decreased from 45.5 cases per 100 person-years in July–December, 2016, to 37.2 cases per 100 person-years in July–December, 2019 (IRR 0.97, 95% CI 0.96–0.98; p<0·0001). Similar to chlamydia, the decline was non-linear, with the greatest decline during the first 18 months of observation; gonorrhoea incidence fell to 38.7 cases per 100 person-years in July–December, 2018, and remained relatively stable thereafter. Infectious syphilis incidence increased during the observation period, from 6.2 cases per 100 person-years in July–December, 2016, to 9.8 cases per 100 person-years in July–December, 2019 (IRR 1.08, 95% CI 1.05–1.10; p<0·0001); the increase in syphilis incidence was greatest during the first 18 months of observation (1.25, 1.08–1.49; p<0.0001; **Figure 3.2, Table 3.3**).

In secondary analysis of incidence trends measured in days since PrEP initiation, chlamydia incidence did not change with increased time on PrEP (IRR for estimated change per 6 months of PrEP use 1.01, 95% CI 1.00–1.02; p=0.098). After adjusting for year of PrEP initiation, time on PrEP was not associated with chlamydia incidence (adjusted IRR 0.99, 0.98–1.00; p=0.14; **Figure 3.3**, **Table 3.3**). Gonorrhoea incidence did not change with increased time on PrEP (IRR 1.00, 0.99–1.01; p=0.99). After adjusting for year of PrEP initiation, longer time on PrEP (each additional 6 months) was associated with a slight decrease in gonorrhoea incidence (adjusted IRR 0.98, 0.97–0.99; p=0.0016). Each additional 6 months of PrEP use was associated with a modest increase in syphilis incidence (IRR 1.08, 1.06–1.11; p<0.0001). After adjusting for year of PrEP initiation, longer time on PrEP was still associated with an increase in syphilis incidence (adjusted IRR 1.08, 1.05–1.11; p<0.0001; **Figure 3.3**).

Table 3.4: Negative binomial regression models for association between STI incidence with year of PrEP initiation and time on PrEP from secondary analyses

		Year initiated PrEP [c]	Diagnoses	Person-years	IR / 100py (95% CI)	**Unadjusted IRR (95% CI)**	**p-value**	**aIRR (95% CI)**	**p-value**
Chlamydia	Year	2016	5749	126.9	45.3 (44.2 - 46.5)	-ref-		-ref-	
		2017	3089	72.4	42.7 (41.2 - 44.2)	.94 (.89 - .99)	0.031	.93 (.88 - .99)	0.016
		2018	1921	50.5	38.0 (36.4 - 39.8)	.84 (.79 - .89)	<0.0001	.83 (.78 - .88)	<0.0001
		2019	652	16.9	38.5 (35.6 - 41.6)	.85 (.78 - .93)	0.00021	.83 (.76 - .91)	<0.0001
	Time on PrEP (6m)[a]					1.01 (1.00 - 1.02)	0.098	.99 (.98 - 1.00)	0.14
Gonorrhoea		2016	4693	119.4	39.3 (38.2 - 40.4)	-ref-		-ref-	
		2017	2592	71.4	36.3 (34.9 - 37.7)	.92 (.86 - .98)	0.011	.90 (.85 - .96)	0.0020
		2018	1667	50.8	32.8 (31.3 - 34.5)	.83 (.78 - .89)	<0.0001	.80 (.75 - .86)	<0.0001
		2019	562	16.9	33.2 (30.6 - 36.1)	.84 (.77 - .93)	0.0052	.80 (.72 - .89)	<0.0001
	Time on PrEP (6m)[a]					1.00 (.99 - 1.01)	0.99	.98 (.97 - .99)	0.0016
Syphilis		2016	1080	105.1	10.3 (9.7 - 10.9)	-ref-		-ref-	
		2017	572	61.1	9.4 (8.6 - 10.2)	.91 (.78 - 1.06)	0.23	.98 (.84 - 1.14)	0.80
		2018	360	42.3	8.5 (7.7 - 9.4)	.83 (.71 - .97)	0.016	.94 (.81 - 1.11)	0.48
		2019	104	13.1	7.9 (6.5 - 9.6)	.77 (.62 - .96)	0.020	.93 (.74 - 1.17)	0.53
	Time on PrEP (6m)[a]					1.08 (1.06 - 1.11)	<0.0001	1.08 (1.05 - 1.11)	<0.0001
Any STI[b]		2016	8722	94.6	92.2 (90.3 - 94.2)	-ref-		-ref-	
		2017	4087	50.4	81.1 (78.6 - 83.6)	.88 (.83 - .93)	<0.0001	.88 (.83 - .93)	<0.0001
		2018	2345	32.2	72.7 (69.8 - 75.7)	.79 (.74 - .84)	<0.0001	.80 (.75 - .85)	<0.0001
		2019	708	9.8	72.6 (67.4 - 78.1)	.79 (.72 - .86)	<0.0001	.80 (.73 - .87)	<0.0001
	Time on PrEP (6m)*					1.03 (1.02 - 1.04)	<0.0001	1.00 (.99 - 1.02)	0.34

IR=Incidence Rate; IRR=Incidence Rate Ratio. [a] Average change per six months of PrEP use, included as continuous variable in negative binomial model. [b] Any STI analysis only includes individuals with at least 2 tests for each infection (chlamydia, gonorrhoea and syphilis) [c] For individuals initiating PrEP in 2016, 2017, 2018 and 2019, analyses included 42 months, 30 months, 18 months, and 6 months of PrEP use, respectively.

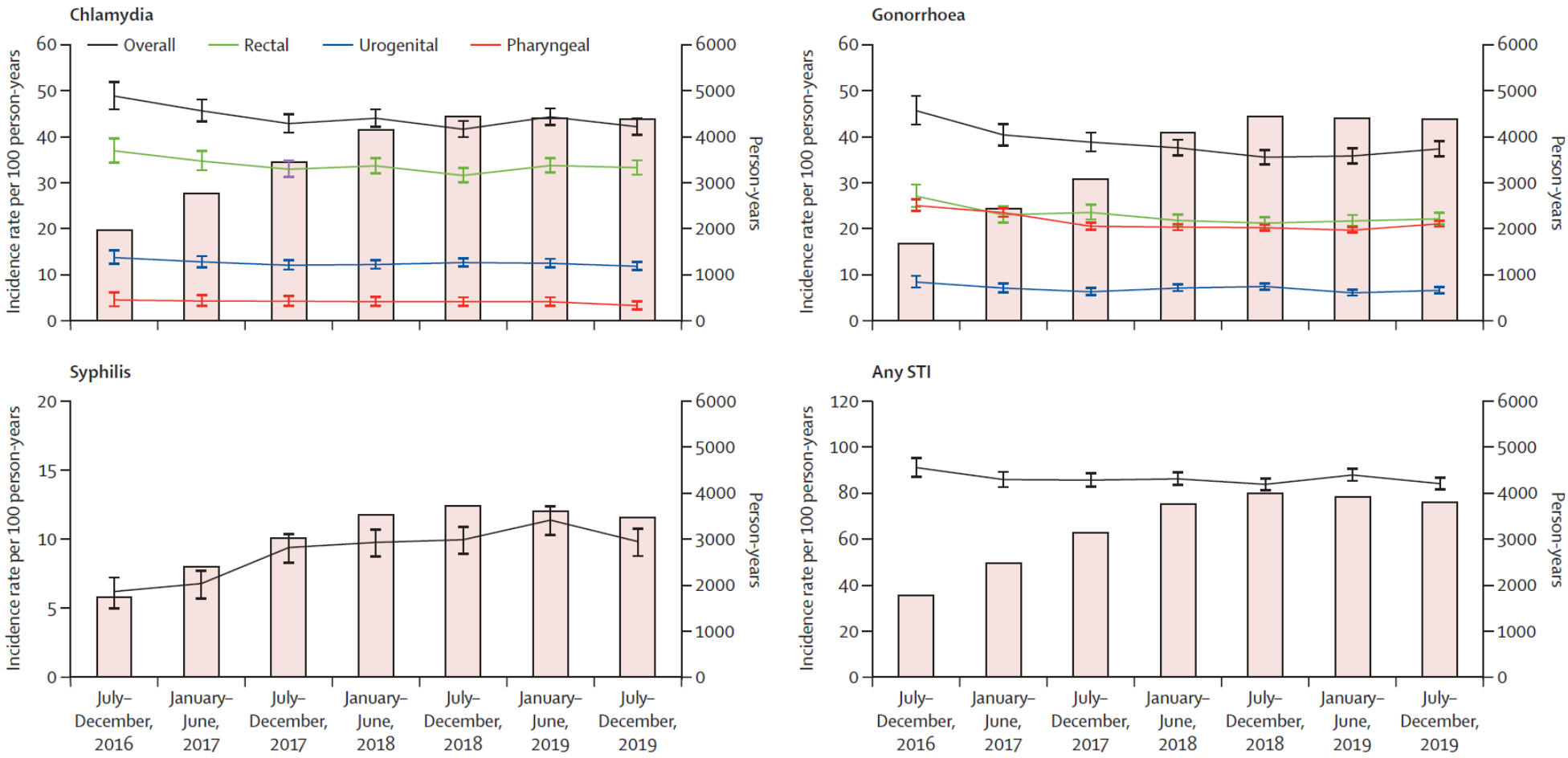

Figure 3.2: STI incidence rates by calendar half year, from July–December, 2016, to July–December, 2019

Error bars represent 95% CIs. Bars represent person-years of follow-up accrued in each period (right axis). Trends disaggregated by age group are shown in the appendix A1.9 (p 218). STI=sexually transmissible infection.

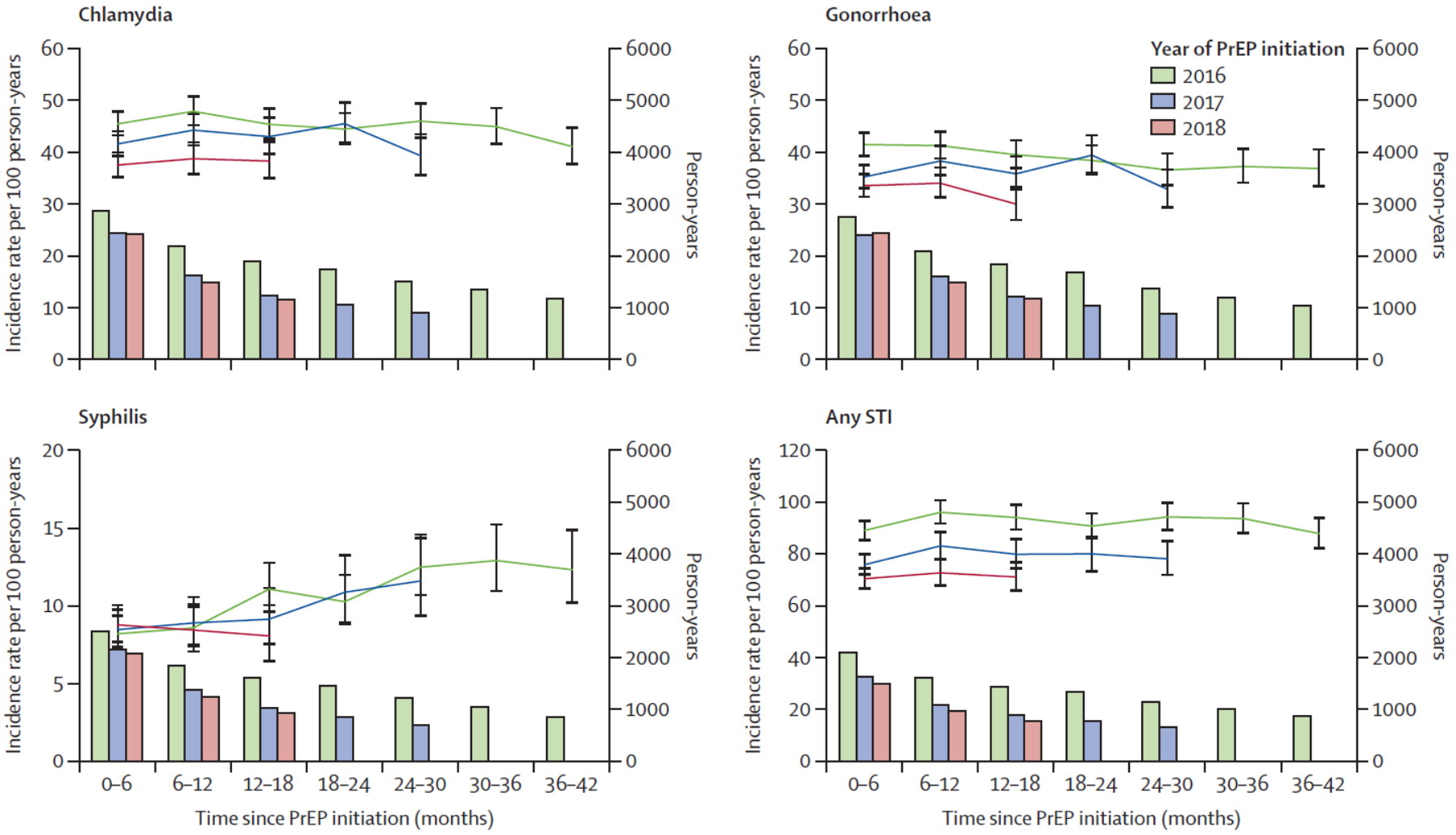

Figure 3.3: 6-monthly STI incidence rates, by time since PrEP initiation and by year of PrEP initiation

Error bars represent 95% CIs. Bars represent person-years of follow-up accrued in each period (right axis).
Incidence trends aggregated for all gay and bisexual men using PrEP are shown in the appendix A1.10 (p 219). STI=sexually transmissible infection. PrEP=HIV pre-exposure prophylaxis.

In the secondary analysis of incidence trends disaggregated by year of PrEP initiation, time on PrEP was only associated with a decrease in gonorrhoea incidence in participants who initiated PrEP in 2016, and an increase in syphilis incidence among those who initiated PrEP in 2016 and 2017 (appendix A1.13, p 224). Extending the censorship cutoff for PrEP use to 6 months since the previous prescription led to slightly decreased overall incidence rate estimates for each outcome (appendix A1.14, p225); however, the trends were similar to those in the primary analysis.

3.6 Discussion

To our knowledge, this is the largest cohort of gay and bisexual men using PrEP in which STI incidence rate estimates have been reported internationally. The large sample size in this study provided high precision in our estimates and statistical power to detect relatively small changes over time; significant trends should be interpreted with this in mind. Our analysis suggests that chlamydia and gonorrhoea incidence were high among gay and bisexual men using PrEP, particularly in the early months of nationwide PrEP implementation. Chlamydia and gonorrhoea incidence slightly declined in the years following broad access to PrEP in Australia, and seemed to stabilise later on in the study period. By contrast with chlamydia and gonorrhoea, syphilis incidence continued to increase among gay and bisexual men using PrEP during the study period. Approximately half (8,223 [44.5%] of 18,483) of all participants using PrEP were diagnosed with any STI during the study period, and 5.7% of participants were diagnosed with five or more STIs, which accounted for more than one-third of all infections diagnosed. These data represent real-world, population-level incidence estimates of bacterial STIs following high and prolonged uptake of PrEP among gay and bisexual men and reinforce that gay and bisexual men using PrEP are a priority population for bacterial STIs.

There are several possible reasons for the observed trends showing a decline then stabilisation in the incidence of chlamydia and gonorrhoea. Changes in the cohort population over time, driven by the observed lower prospective STI risk of people initiating PrEP in later years, are likely to have influenced the incidence trends. The criteria for prescribing PrEP evolved during our observation period, with early PrEP demonstration studies requiring specific risk-based criteria to be met for enrolment, and less stringent criteria used for prescribing following the listing of PrEP on the Pharmaceutical Benefits Scheme in 2018. It is also possible that the high testing frequency among people using PrEP in Australia is affecting STI transmission through greater detection and shorter infection duration. The median time between tests for all STIs in our cohort closely reflected the

recommended 3-monthly interval for STI testing among people using PrEP,[75] with 90% of all chlamydia and gonorrhoea tests occurring within 162 days of the previous test and 90% of all syphilis tests occurring within 174 days of the previous test. However, the effects of maintaining high STI testing rates on the incidence of STIs among people using PrEP are complex and multifaceted. Increased screening for STIs leads to greater likelihood of detecting an infection earlier, and therefore increases the rate of diagnosis and treatment of asymptomatic STIs among people using PrEP. More timely detection and treatment of bacterial STIs shortens the duration of infection, reducing the number of onward transmissions. However, shorter duration of infection, in turn, means individuals become susceptible to new infections faster.

In addition to the effects of increased testing, PrEP roll-out is likely to have contributed to substantial changes in both the size and constituents of sexual networks among gay and bisexual men. Data suggest that gay and bisexual men using PrEP are more likely to have condomless sex with other people using PrEP compared with gay and bisexual men not using PrEP.[144] Given the relatively small number of people using PrEP in Australia in 2016, high rates of chlamydia and gonorrhoea in the first year of PrEP roll-out might reflect a high rate of homogenous mixing within relatively small sexual networks of early adopters of PrEP who had a high baseline risk for STIs. As PrEP use expanded in 2017 and 2018, sexual networks are likely to have also expanded, leading to more disassortative mixing between early adopters of PrEP with higher risk and individuals with lower risk who initiated PrEP in later years, leading to a diffusion of STIs among a wider network. This heterogeneous mixing between early adopters and later adopters of PrEP might partly explain the observed chlamydia and gonorrhoea incidence declines in gay and bisexual men using PrEP, and the declines in gonorrhoea incidence among participants who initiated PrEP in 2016 in our subgroup analysis by time on PrEP.

The divergent steady increase in syphilis incidence might also have emerged as a result of changing sexual networks, in this case due to the increasing likelihood of HIV serodiscordant sex. Routinely collected biobehavioural data from gay and bisexual men in Australia show decreases in serosorting among both HIV-negative gay and bisexual men and gay and bisexual men living with HIV during our study period.[154] Increases in serodiscordant sex might have had a greater effect on syphilis transmission, given that syphilis diagnoses in Australia were much higher among gay and bisexual men living with HIV than among HIV-negative gay and bisexual men during our study period. An Australian survey conducted in 2018 showed that 48% of gay and bisexual men using PrEP reported being comfortable having condomless sex with gay and bisexual men living with HIV who had an undetectable viral load, compared with only 6% of gay and bisexual men not using PrEP. However, 78% of gay and bisexual men using PrEP reported being comfortable having condomless sex with

other people using PrEP.[144] These data suggest that, among gay and bisexual men using PrEP, comfort in having condomless sex with gay and bisexual men living with HIV might have evolved slower than comfort in having condomless sex with other gay and bisexual men using PrEP, potentially explaining the gradual increase in syphilis incidence among gay and bisexual men using PrEP in the years after PrEP implementation, compared with relatively stable trends in chlamydia and gonorrhoea incidence. Separate analysis of data from the ACCESS network suggests that there has been an increase in syphilis incidence among gay and bisexual men living with HIV from 2017 onwards.[255]

In addition to high-frequency STI testing, other interventions are required to drive down gonorrhoea and chlamydia incidence and to curtail the rise in syphilis incidence among gay and bisexual men using PrEP. As with previously reported data from gay and bisexual men using PrEP in Victoria, Australia,[67] our data suggest that STI diagnoses remain highly skewed, with about 6% of individuals accounting for more than one-third (36%) of all STIs diagnoses. Gay and bisexual men who have repeat and concurrent STIs might be prime candidates for novel biomedical prevention strategies. There is growing interest in Australia in the use of doxycycline prophylaxis for the prevention of STIs, with a study published in 2019 showing that 9·9% (95% CI 8·1–11·8) of people using PrEP attending a large sexual health centre in Melbourne reported using doxycycline prophylaxis in the previous month.[233] Daily and event-driven doxycycline use have been shown to reduce rates of chlamydia and syphilis incidence,[224, 225] and although it is not currently approved or recommended for STI prophylaxis in Australia, doctors can prescribe doxycycline off-label. A large study of doxycycline for the prevention of syphilis is ongoing in Australia.[231] In addition, there are future prospects for vaccines for bacterial STIs, including an ongoing randomised controlled trial of a meningococcal B vaccine (Bexsero) for gonorrhoea prevention.[239] In addition to novel biomedical prevention strategies, new models of partner notification (including community-led or peer-led models) and testing (self-testing or home-based testing) might be highly acceptable among people using PrEP and be effective in reducing STI transmission.

Our findings have implications for other countries currently implementing or planning to implement PrEP programmes at scale. These data show that incorporating a PrEP programme into existing clinical services and achieving high (3-monthly) STI testing rates can be accomplished. In this context, PrEP implementation reduces HIV diagnoses,[97] leading to cost-benefits in the long-term, and our analyses suggest that concerns around exponentially increasing rates of STI transmission following wide-scale PrEP implementation have not materialised in gay and bisexual men in Australia. Instances of stigma and hesitancy among practitioners to prescribe PrEP to individuals due to fear of increased STI acquisition risk, especially in the United States,[256] are likely to have hindered progress

towards achieving optimal PrEP coverage. Our analysis adds to the body of evidence showing that comprehensive and frequent STI screening of gay and bisexual men using PrEP might have benefits for STI transmission at the population level. Other benefits of PrEP use, including reduced HIV-related anxiety and increased pleasure should also be considered.[257]

Our analysis has a number of notable strengths, including the high PrEP coverage and large national cohort size. We estimate that our analyses captured approximately 70% of the 32 831 people dispensed publicly-funded PrEP in Australia between 2016 and 2019.[258] Other strengths of this study include long periods of follow-up with frequent testing, and data linkage between ACCESS clinics, which allowed us to follow individuals who transferred care between clinics involved in ACCESS and reduced loss to follow-up.

Several limitations of our analysis should be noted. First, individuals attending the ACCESS network might not be representative of all gay and bisexual men using PrEP across Australia. However, the included clinical services specialise in the care of gay and bisexual men and are responsible for a large share of HIV treatment,[91] and we captured a large proportion of gay and bisexual men using PrEP in Australia. Second, individuals might have accessed PrEP or STI testing, and therefore been diagnosed with an STI, at a service outside of the ACCESS network. However, given the short intervals between the tests included in this analysis (median 84–90 days), the effect of external testing is likely to have been minimal; individuals were censored from this analysis if they did not return for PrEP within 4 months of the previous prescription. Third, for individuals attending general practice clinics, we relied on an algorithm of rectal swab testing among male patients to infer status of gay and bisexual men, which might have misclassified some patients. Fourth, we were not able to definitively define periods of PrEP use, but rather inferred PrEP use on the basis of the date of the most recent prescription. It is possible that some gay and bisexual men received their PrEP prescription but did not initiate PrEP, or were using PrEP intermittently. By including participants in our analyses until 4 months after their previous PrEP prescription, we believe we have captured a period of follow-up that is likely to reflect STI risk during PrEP use. Routinely collected biobehavioural surveillance data suggest that event-driven PrEP use was low among Australian gay and bisexual men during our study period, with less than 10% of men using PrEP reporting non-daily use in 2019 and even fewer in earlier years.[259] Fifth, as the majority of these data were extracted from general practice clinics providing routine PrEP care, and as behavioural data is not routinely collected at these clinics, we were not able to include individual-level behavioural data or data on symptoms in our analyses. Finally, as only clinical testing data were extracted, and not data on STI treatments prescribed to participants, it could not be ensured that every STI was treated effectively and that all positive diagnoses were incident infections. However, the clinics included in this study

are highly experienced in managing STIs, and followed standard STI treatment guidelines. Australian STI testing guidelines for gay and bisexual men using PrEP did not change during the study period.

3.7 Conclusions

In this analysis of gay and bisexual men using PrEP in Australia, chlamydia and gonorrhoea incidence were highest during the first 18 months of PrEP implementation, and stabilised at slightly reduced incidence thereafter. The observed trends in STI incidence were influenced by lower prospective STI risk among gay and bisexual men initiating PrEP in later years after nationwide implementation, as well as slight declines in individual rates of some STIs following prolonged PrEP use and frequent STI testing. Although frequent testing of people using PrEP might be beneficial for population-level incidence of some STIs, changes in sexual networks of gay and bisexual men might be contributing to elevated STI incidence among some gay and bisexual men who use PrEP, and additional interventions aimed at interrupting transmission might be required to reduce STI transmission.

3.8 Article information

Contributors

MWT conceived the analysis. MWT, RG, and MAS contributed substantially to study conception, study design, and analysis and interpretation of the data. MWT, JA, and PP curated the data. MWT did the formal data analysis. HM provided methodological support. RG, JA, AC, BD, MEH, and MAS coordinated the ACCESS study and were responsible for acquisition of funding. EJW, MEH, and MAS provided academic supervision. CKF, EPFC, AM, RF, CB, LO, LM, and DR are ACCESS clinic investigators and contributed to data acquisition. MWT, JA, and MAS had full access to all the data in the study and verified the data. MWT led the manuscript preparation. All authors read and revised the manuscript critically for important intellectual content and approved the final version of the manuscript for publication.

Declaration of interests

MWT reports speakers' honoraria and investigator-initiated research grants from Gilead Sciences. RG reports research support funding from Gilead Sciences. CB reports honoraria from Gilead

Sciences. EJW is the chair of the COVID-19 Taskforce of the Australasian Society of HIV, Viral Hepatitis, and Sexual Health Medicine, and reports investigator-initiated research funding from ViiV Healthcare, and consulting and travel fees from Gilead Sciences. AG reports research grants from Sequris and ViiV Healthcare, receipt of study drug from GlaxoSmithKline, and personal fees from Merck Sharp and Dohme. MEH reports investigator-initiated research grants from Gilead Sciences and Abbvie. MAS reports investigator-initiated research grants from Gilead Sciences and Abbvie and consulting fees from Gilead Sciences. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data included in this study cannot be shared publicly because of the sensitive nature of participant data anonymously extracted from participating clinical services. Access to deidentified data is available via the Burnet Institute, Melbourne, VIC, Australia, with approval from the Alfred Hospital Human Research Ethics Committee for researchers who meet the criteria for access to confidential data. The ACCESS study protocol has been published previously.

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Chapter 4

Syphilis testing, incidence and reinfection among gay and bisexual men with and without HIV in Australia over a decade spanning HIV PrEP implementation

In Chapter 3, I used the ACCESS surveillance system to create the world's largest longitudinally-linked retrospective cohort of PrEP users. This large cohort allowed us to explore trends in chlamydia, gonorrhoea and syphilis among PrEP users and led to key understandings of the long-term epidemiology of bacterial STIs among PrEP users in Australia. However, while restricting the analysis to PrEP users allowed us to explore trends among a highly engaged cohort of GBM with high rates of testing, it did not explore trends among GBM who are not PrEP users or GBM with HIV. While we found that incidence rates of chlamydia and gonorrhoea were stable among PrEP users, we found that syphilis incidence increased among PrEP users. Despite stable incidence rates among PrEP users, the sexual networks in which these infections are transmitted are not restricted to PrEP users, but include all GBM. As such, in Chapter 4 we describe an analysis of data from the ACCESS surveillance network which was expanded to include all GBM. Given the historically higher rates of syphilis among GBM with HIV in Australia, we also included a longer, ten-year observation period, to explore longer-term trends in syphilis between GBM with and without HIV.

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Syphilis testing, incidence, and reinfection among gay and bisexual men with and without HIV in Australia over a decade spanning HIV PrEP implementation: an analysis of sentinel surveillance data

Authors

Michael W. Traeger[1,2,3], Rebecca Guy[1], Caroline Taunton[1,5], Eric P.F. Chow[7,8,9], Jason Asselin[1], Allison Carter[4,10,11], Mark Bloch[4,12], Christopher K. Fairley[7,8], Anna McNulty[12,14], Vincent Cornelisse[4,8,15], Phillip Reed[15], Louise Owen[16,17], Nathan Ryder[4,18], David Templeton[4,19,20], Darryl O'Donnell[21], Basil Donovan[4,13], Margaret E. Hellard*[1,2,22,23], Mark A. Stoové*[1,2,24], *on behalf of the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS)*

*co-senior authors

Author affiliations

1. Burnet Institute, Melbourne, Australia
2. School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
3. Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, United States
4. The Kirby Institute, UNSW Sydney, Sydney, Australia
5. Research School of Population Health, Australian National University, Canberra, Australia
6. Torres and Cape Hospital and Health Service, Cairns, Australia.
7. Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia
8. Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia
9. Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia
10. Australian Human Rights Institute, UNSW Sydney, Sydney, Australia
11. Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada
12. Holdsworth House Medical Practice, Sydney, Australia
13. Sydney Sexual Health Centre, Sydney, Australia
14. School of Population Health, UNSW Sydney, Sydney, Australia
15. Kirketon Road Centre, Sydney, Australia
16. Statewide Sexual Health Service, Tasmania, Australia
17. School of Medicine, University of Tasmania, Hobart, Australia
18. Hunter New England Sexual Health, New Castle, Australia
19. Department of Sexual Health Medicine, Sydney Local Health District, Sydney, NSW, Australia
20. Discipline of Medicine, Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia.
21. Australian Federation of AIDS Organisations, Sydney, Australia
22. Department of Infectious Diseases, Alfred Health
23. Doherty Institute and School of Population and Global Health, University of Melbourne, Melbourne Australia
24. School of Psychology and Public Health, La Trobe University, Melbourne, Australia

4.1 Abstract

Importance

Gay and bisexual men (GBM) remain overrepresented in syphilis notifications in Australia. Changes in condom use and sero-sorting associated with HIV pre-exposure prophylaxis and treatment as prevention may be driving syphilis transmission.

Objective

To describe trends in syphilis testing and incidence among GBM in Australia over a decade spanning widespread implementation of HIV PrEP, and explore risk-factors associated with syphilis diagnosis.

Design, Setting, Participants

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) is a large national network of sexual health and general practice clinics providing STI testing and care. Between January 1, 2012 and December 31, 2021 121,013 GBM visited a participating ACCESS clinic at least twice and 77,577 GBM had at least two syphilis test events, and were included in testing rate and incidence analyses, respectively.

Exposures

Trend analyses for syphilis testing and incidence were disaggregated by HIV status and PrEP use (determined by presence of a PrEP prescription at an ACCESS clinic from 2012-2021). Secondary analyses explored associations between demographics, recent PrEP use and history of bacterial STIs and syphilis infection.

Main outcomes and Measures

The primary outcome was incidence of infectious syphilis (primary, secondary or early latent). Annual incidence rates were calculated for each subgroup and incidence rate ratios described average changes in syphilis incidence from 2012-2019. In secondary analyses, hazard ratios described demographic and clinical risk factors for syphilis diagnosis.

Results

Among 121,013 GBM (mean age, 35.9 [SD, 12.1]) with at least two clinic visits, 7.8% were living with HIV at baseline and 28.8% were prescribed PrEP during the study period. The overall rate of syphilis testing was 102.4/100py; testing was highest among GBM with HIV (162.5/100py). Syphilis testing increased from 69.1/100py in 2012 to 131.7/100py in 2019 ($p<0.001$); most of the increase was

driven by increases among PrEP users. Among 77,577 GBM included in incidence analyses, the median time between syphilis tests was 119 days. Overall, there were 13,858 syphilis infections over 343,287py of follow-up (incidence rate=4.0/100py). Syphilis incidence was highest among GBM with HIV (8.0/100py), followed by HIV negative ever-PrEP users (4.2/100py) and HIV-negative never-PrEP users (1.9/100py). From 2012-2019, syphilis incidence increased among ever-PrEP users from 1.6/100py to 6.1/100py (p<0.001), and fluctuated between 6.3/100py and 8.6/100py among GBM with HIV. In multivariable Cox regression, ever being previously diagnosed with syphilis (adjusted Hazard Ratio [HR]=2.63, 95%CI=2.45-2.82) was the strongest predictor of syphilis risk, followed by recent (<12m) syphilis diagnosis (aHR=2.04, 95%CI=1.89-2.20), living with HIV (aHR=2.07, 95%CI=1.94-2.23) and recently (<12m) prescribed PrEP (aHR=1.91, 95%CI=1.77-2.06).

Conclusions and Relevance

Syphilis trends between GBM with HIV and GBM with evidence of PrEP use have been converging over the past decade in Australia, and rates of syphilis testing were below recommended screening guidelines for GBM. Previous syphilis infection was the strongest predictor of subsequent infection, highlighting the importance for future STI guidelines to include prior STI diagnosis as an indication for new targeted strategies (e.g. doxycycline prophylaxis).

4.2 Introduction

Despite a substantial decline in cases during the second half of the twentieth century with the introduction of penicillin-based treatments,[260] infectious syphilis remains a sexually transmissible infection (STI) of public health importance.[261-263] Untreated syphilis can lead to serious tertiary complications years after infection including cardiovascular and neurological disease,[194] and infection during pregnancy can lead to a range of adverse birth outcomes including stillbirth and neonatal death.[195] Syphilis infection has also been shown to increase the risk of onward transmission of HIV by increasing viral load among people with HIV,[117] and increasing acquisition risk through immunological impairment and the weakening of the epithelium associated with lesions during primary syphilis.[118]

Similar to other high income countries, gay and bisexual men (GBM) have the highest rate of syphilis compared to other population groups in Australia, and represent the majority of cases reported among men.[264] The diagnosis rate of syphilis among men in Australia has increased each year over

the past decade, from 9.1 per 100,000 men in 2010 to 39.9 in 2019.[264, 265] While syphilis incidence has historically been greater among GBM with HIV compared to GBM without HIV,[264, 266] recent analysis of data from more than 22,000 GBM using HIV pre-exposure prophylaxis (PrEP) in Australia highlighted increasing syphilis incidence among this population from 2016 to 2019, despite relatively stable rates of chlamydia and gonorrhoea.[267] Drivers of increasing STI notifications among GBM over the past decade are likely multifactorial and may include increased detection through greater rates of screening,[142] or increased transmission associated with changes in the way people meet sexual partners (such as through geosocial networking apps),[139] and population-level declines in condom use.[151] Reductions in serosorting (choosing sexual partners with the same HIV status) as a risk-reduction strategy among GBM have occurred alongside greater awareness of HIV treatment as prevention (TasP or U=U) and increased use of PrEP,[144, 145] which has been widely available in Australia since 2016,[67, 97] and may be contributing to increased STI transmission.

Recent analyses also suggest that the syphilis epidemic is becoming more generalised in Australia, with notification data from the state of Victoria showing increasing syphilis diagnoses among heterosexual men and women, especially in outer metropolitan areas which are geographically distinct from areas of high syphilis transmission among GBM.[201] Further, after virtual elimination in the early 2000's, congenital syphilis has re-emerged in Australia, with 40 cases reported between 2016-2020, compared to 19 between 2011-2015.[264] The drivers of increased syphilis transmission among heterosexual populations are not completely understood, and while genomic analysis of syphilis in Australia suggests that the syphilis epidemic is driven by multiple lineages, rather than one distinct outbreak, GBM were present in all lineages, including those mostly associated with heterosexual people.[268] Similar trends have been shown for gonorrhoea,[202] suggesting that bisexual men, and other men who have sex with men and women (MSMW), may serve as a bridging population between the two groups. Hence, a public health response which reduces syphilis transmission among GBM may also have wider impact for other populations.

Passive surveillance of syphilis notifications provides limited insights into transmission incidence trends in the absence of concurrent rates of testing, and often lacks the key clinical and demographic information needed to guide responses. To support the public health response to increasing rates of syphilis and help understand the drivers of syphilis transmission among GBM during a period of widespread uptake of PrEP, we analysed a decade of sentinel surveillance data from a large network of general practice and sexual health clinics across Australia. We aimed to describe epidemiological trends in infectious syphilis testing and incidence among GBM with and

without HIV in the years spanning nationwide PrEP implementation, and to explore demographic and clinical risk factors associated with infectious syphilis post-PrEP availability.

4.3 Methods

Study design and participants

Data were extracted from a network of 27 clinical services (6 sexual health services [including multi-clinic and outreach services] and 21 general practice clinics) participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS). ACCESS aims to achieve a high coverage of priority populations for HIV and other STIs in Australia, including GBM, to monitor the national response to STIs. The ACCESS protocol has been previously published.[243] Briefly, retrospective patient data (demographics, pathology reports and electronic prescriptions) were de-identified and extracted from electronic medical records of participating services using specialised data extraction software called GHRANITE™. Individuals' data are linked within and across services using a highly sensitive linkage algorithm which utilises probabilistic and de-identifying linkage keys generated from patient identifiers created prior to data being extracted.[250]

For this analysis, GBM aged 16 years and over attending an ACCESS service during the observation period were eligible for inclusion. The period of observation for this study was 1st January 2012 to 31st December 2021. Gay or bisexual status was inferred from reported gender of sexual partners or from a previously validated algorithm based on history of a rectal swab for chlamydia or gonorrhoea.[269]

Statistical analyses

Trends in syphilis testing

We calculated the annual rate of syphilis testing per 100 person-years from 2012-2021. For testing rate analyses, individuals were included if they had at least two clinic visits during the observation period. Individuals began contributing person time at their first recorded visit at a participating clinic after January 1st 2012, and were censored on 31st December 2021 or at their last recorded visit, whichever came first. Testing rate was calculated as the number of syphilis tests divided by the amount of person-time accrued between clinic visits in each calendar year multiplied by 100. All syphilis pathology results dated within seven days were considered part of the same test event.

Trends in syphilis incidence

New cases of infectious syphilis were defined using a previously validated algorithm of laboratory testing data (serological treponemal and non-treponemal tests, and syphilis PCR tests) which aligned with the national case definition for a new infectious syphilis (including primary, secondary, or early [<2 years] latent) diagnosis (appendix A2.6, p 235). The algorithm was developed and validated using laboratory tests and recorded clinical diagnoses among GBM attending two ACCESS clinics included in this analysis and over the same observation period (2012-2021). The algorithm has a reported sensitivity of 84.3% and specificity of 99.8%, which were consistent over the observation period.[270]

We calculated the annual incidence rate of infectious syphilis per 100 person-years from 2012-2021. Participants were included in incidence analyses if they were tested for syphilis at least twice during the observation period, as we used repeat testing methods to estimate incidence.[252] Individuals contributed person-time from their first recorded negative syphilis test after January 1 2012, and were censored at their last recorded test or 31st December 2021, whichever came first. Date of infection was defined as the midpoint between date of positive test event and date of previous negative test. Incidence rate was calculated as the number of syphilis diagnoses divided by the amount of person-time accrued between test events in each calendar year multiplied by 100.

To explore trends in repeated diagnoses of syphilis within individuals, we calculated a subgroup incidence analysis restricted to individuals with a diagnosis of syphilis during the observation period (2012-2021) and at least one subsequent syphilis test. In this analysis, individuals contributed person-time from their first recorded syphilis diagnosis during the observation period and were censored at their last syphilis test event or December 31st 2021.

Subgroup and trends analyses

Annual rates of syphilis testing and incidence were disaggregated by age group, HIV status, and 'ever-PrEP' status. For trend analyses, PrEP use was static and the cohort was dichotomised into ever-PrEP users and never-PrEP users during the observation period. Individuals with a PrEP prescription were prospectively and retrospectively categorised as ever-PrEP users for the entire observation period, with people classified as never-PrEP users having no record of a PrEP prescription at an ACCESS clinic during the entire observation period. This was done to aid interpretation and comparison of trends between the two groups over the years of PrEP implementation. Further, without behavioural data we could not ensure that individuals were taking PrEP as prescribed or when people ceased using PrEP. HIV status was time-varying and individuals

were classified as living with HIV from the date of their recorded HIV diagnosis or first evidence of HIV positivity.

Negative binomial regression with robust variance estimators clustered by individual was used to test for trends in syphilis testing and incidence over time. In each model, time—a continuous variable representing calendar year from 2012 to 2019 — was included as a single independent variable. Trend analyses were restricted to years prior to the impact of COVID-19 and associated lockdown measures.[100, 254] Incidence rate ratios (IRRs) represent the estimated change in incidence rate per each calendar year and p-values<0.05 were considered significant evidence against the null hypothesis of no trend over time.

Predictors of syphilis incidence

A secondary analysis was performed using Cox proportional hazards regression models to explore clinical and demographic factors associated with syphilis infection during years of PrEP availability and prior to the impact of COVID-19 (1st January 2016 to 31st December 2019). We used the conditional risk set model to allow for multiple failures (syphilis diagnoses) per participant.[271] Aboriginal or Torres Strait Islander was included as a time-fixed covariate. Time-varying covariates included age group (16-29, 30-39, 40-49, 50+ years); HIV status; ever previously prescribed PrEP (at an ACCESS clinics since data availability); recently prescribed PrEP; ever previously diagnosed with syphilis; recently diagnosed with syphilis; ever previously diagnosed with chlamydia; recently diagnosed with chlamydia; ever previously diagnosed with gonorrhoea; recently diagnosed with gonorrhoea; ever previously diagnosed with rectal chlamydia and/or gonorrhoea; and recently diagnosed with rectal chlamydia/gonorrhoea. Recent PrEP or STI diagnosis exposures were for the previous 12 months and at an ACCESS clinic. In the conditional risk set model, time-varying covariates which were related to recent events (e.g. recent PrEP prescription, recent STI diagnosis) were coded as 1 from the date of the event to 12 months post-event, and as 0 from 12 months post-event onwards, or as 0 for all person-time for people who did not experience the event.

Covariates found to be independently associated with syphilis infection (P<0.10) were included in a multivariable Cox model. The proportional hazards assumption of the multivariable Cox model was tested using Schoenfeld residuals,[272] with individual covariate and global tests showing no evidence for rejection of the null hypothesis of proportional hazards at the *P* value of less than 0.05 significance level. The multivariable model was assessed for multicollinearity by computing correlation coefficients and tolerance for model covariates, with evidence of multicollinearity defined as correlation of >0.5 or tolerance of <0.2.[273] All analyses were performed using STATA (version 15.1).

Ethics

Ethics approval for ACCESS was provided by the Human Research Ethics Committees at Alfred Hospital (248/17), Central Australia (CA-19-3355), Northern Territory Department of Health and Menzies School of Health (08/47), University of Tasmania (H0016971), Aboriginal Health and Medical Research Council (1099/15), ACON (2015/14), Victorian AIDS Council / Thorne Harbour Health (VAC REP 15/003), Western Australian Aboriginal Health Ethics Committee (885), and St. Vincent's Hospital (08/051). As our study analyses de-identified data collected under the auspices of public health surveillance, individual patient consent was not required. Individuals were able to opt-out of the surveillance system if they wish.

Role of the funding source

ACCESS funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

4.4 Results

Syphilis testing rate

A total of 121,013 GBM visited an ACCESS clinic at least twice between 2012 and 2021 and were included in testing rate analyses. The mean age was 39.9 years (SD, 12.1), 9,441 (7.8%) were living with HIV at their first visit, and 34,847 (28.8%) were prescribed PrEP at least once during the observation period **(Table 4.1)**. There were a total of 587,967 syphilis tests conducted over 574,151 person-years (py) of follow-up. The overall syphilis testing rate during the observation period was 102.4/100 person-years, with the testing rate increasing from 69.1/100py in 2012 to 131.7/100py in 2019 ($p<0.001$). The testing rate dropped in 2020 (the first year of COVID-19 restrictions) to 109.8/100py and then increased to 133.0/100py in 2021.

During the observation period, the overall testing rate was highest among GBM with HIV (162.5/100py), followed by HIV-negative ever-PrEP users (144.7/100py), and lowest among HIV-negative never-PrEP users (55.5/100py). From 2012-2019, syphilis testing rate increased among never-PrEP users from 42.9/100py to 71.5/100py ($p<0.001$), and decreased among HIV-positive GBM from 176.3/100py to 166.2/100py ($P<0.001$) **(Figure 4.1)**. Syphilis testing rate among ever-PrEP users

increased prior to PrEP introduction in 2016 (from 67.9/100py in 2012 to 97.8/100py in 2015), then increased to 178.0/100py by 2017, and remained high to 2019, then slightly dropped to 149.3/100py in 2020.

Syphilis testing rates increased over the observation period across all age groups and was highest among age groups 30-39 and 40-49 years **(Figure 4.1)**. Among never-PrEP users and HIV-positive individuals, testing rate decreased with increasing age, however among ever-PrEP users, testing rate increased with increasing age (appendix A2.2, p 232).

Syphilis incidence rate

In total, 75,577 individuals were tested at least twice for syphilis between 2012 and 2021 and were included in incidence analyses. The mean age was 35.5 years (SD, 12.1), 8,909 (11.8%) were living with HIV at their first visit, and 26,925 (35.6%) were prescribed PrEP at least once during the observation period (**Table 4.1).** The median time between syphilis test events in the incidence analysis was 119 days, and decreased from 140 in 2012 to 109 in 2019, then increased to 126 in 2021. Seventy-five percent of tests occurred within 215 days of a previous test.

There were a total of 13,858 syphilis infections diagnosed over 343,287py. The overall syphilis incidence rate during the observation period was 4.0/100py, with incidence increasing from 2.6/100py in 2012 to 5.2/100py in 2019 (p<0.001) **(Figure 4.1)**. Syphilis incidence dropped in 2020 to 4.6/100py and then increased to 5.9/100py in 2021.

During the observation period, overall syphilis incidence rate was highest among GBM living with HIV (8.0/100py), followed by HIV negative ever-PrEP users (4.2/100py) and HIV-negative never-PrEP users (1.9/100py). From 2012-2019, syphilis incidence increased among ever-PrEP users from 1.6/100py to 6.1/100py (p<0.001) **(Figure 4.1)**. Among GBM living with HIV, syphilis incidence fluctuated between 6.3/100py and 8.6/100py, with a modest increasing trend detected overall (IRR=1.03 [1.01-1.05]) from 2012-2019. There was also a modest increase in syphilis incidence among never-PrEP users over the observation period, from 1.6/100py in 2012 to 2.1/100py in 2019 (IRR=1.03 [1.00-1.06]; p=0.048).

Syphilis incidence rate increased over the observation period across all age groups, and was highest among age groups 30-39 and 40-49 years **(Figure 4.1)**. Among never-PrEP users and GBM living with HIV, incidence rate decreased with increasing age, however among ever-PrEP users, incidence was greatest among those aged 30-39 and 40-49 years (appendix A2.3, p 233).

Repeated syphilis incidence rate

8,909 GBM were diagnosed with syphilis at least once during the observation period and had at least one subsequent syphilis test, and were included in the subgroup analysis of repeated syphilis diagnosis. There were a total of 5,616 repeated syphilis diagnoses following individuals first-recorded syphilis diagnosis over a total of 32,360py. The overall rate of repeated syphilis diagnosis was 17.4/100py. The overall rate of repeated syphilis diagnosis was highest among GBM with HIV (18.5/100py) and HIV-negative ever-PrEP users (17.2/100py), with the rates between the two groups comparable between 2017-2021 **(Figure 4.2)**. Among never-PrEP users, the rate of repeated syphilis diagnosis was 14.5/100py and fluctuated between 12.2/100py and 22.3/100py over the observation period **(Figure 4.2)**. No trend was detected across 2012-2019 for repeated syphilis diagnosis among HIV-negative ever-PrEP (p=0.103) or never-PrEP (p=0.153) users, however, a modest decline among GBM with HIV was detected (IRR=0.96 [0.94-0.98]) **(Table 4.2)**.

Appendix A2.1 (p 231) contains additional data for testing and incidence rate analyses, including mean and median follow-up time and number of syphilis tests and diagnoses.

Risk factors for syphilis infection post-PrEP availability

In the secondary analyses restricted to 2016-2019 (post-widespread PrEP availability and before COVID-19 impact), a total of 61,672 GBM were included. Unadjusted and adjusted hazard ratios are presented in **Table 4.3**. In univariable analyses, the strongest predictors of syphilis diagnosis were recently diagnosed (past 12 months) with syphilis (HR=6.41, 95%CI=5.97-6.89), ever being previously diagnosed with syphilis (HR=4.78, 95%CI=4.49-5.08), and recent rectal STI (HR=3.61, 95%CI=3.41-3.83). Previous infection of other STIs were also associated with increased syphilis risk (Table 2). Living with HIV (HR=1.51, 95%CI=1.40-1.63), being of Aboriginal or Torres Strait Islander descent (HR=1.30, 95%CI=1.07-1.60), and being born outside of Australia (HR=1.13, 95%CI=1.04-1.22) were all associated with increased syphilis risk.

In the initial multivariable model, the covariates ever previously prescribed PrEP (tolerance = 0.115) and recently prescribed PrEP (tolerance = 0.116) were found to be multicollinear (correlation coefficient = 0.878). As such, only recently prescribed PrEP was retained in the final model. There was no evidence for multicollinearity across all other variables. In the final multivariable model, ever being previously diagnosed with syphilis (HR=2.63, 95%CI=2.45-2.82) was the strongest predictor of syphilis risk, followed by recent syphilis diagnosis (HR=2.04, 95%CI=1.89-2.20), living with HIV (HR=2.07, 95%CI=1.94-2.23) and recently prescribed PrEP (HR=1.91, 95%CI=1.77-2.06). After

multivariable adjustment, being of Aboriginal or Torres Strait Islander descent (HR=1.17, 95%CI=1.00-1.37), and being born outside of Australia (HR=1.09, 95%CI=1.02-1.17) were moderately associated with increased syphilis risk. Associations with other STI diagnosis and syphilis infection were also attenuated in multivariable analysis **(Table 4.3)**.

Table 4.1. Characteristics of gay and bisexual men included in syphilis testing and incidence rate analyses at cohort entry

	Included in testing analyses (had at least 2 clinic visits) N = 121,013 n (%)	Included in incidence analyses (had at least 2 syphilis tests) N = 77,577 n (%)
Age at cohort entry, mean (SD)	34.9 (12.1)	35.5 (12.1)
Age group at cohort entry		
16-29	51,397 (42.5)	29,833 (39.5)
30-39	32,241 (26.6)	21,242 (28.1)
40-49	20,427 (16.9)	13,467 (17.8)
50+	16,948 (14)	11,035 (14.6)
HIV status as cohort entry		
HIV-positive	9,441 (7.8)	8,909 (11.8)
HIV-negative	111,572 (92.2)	66,668 (88.2)
Prescribed PrEP during observation period		
Yes	34,847 (28.8)	26,925 (35.6)
No	86,166 (71.2)	48,652 (64.4)
Aboriginal or Torres Strait Islander		
Yes	2,451 (2.0)	1,108 (1.5)
No	93,684 (77.4)	58,900 (77.9)
Not stated / missing	24,878 (20.6)	15,569 (20.6)
Clinic type at cohort entry		
Sexual Health Clinic	68,405 (56.5)	34,863 (46.1)
General Practice	52,608 (43.5)	40,714 (53.9)
Year of entry (first visit or first syphilis test)		
2012	52,683 (43.5)	28,701 (38.0)
2013	7,686 (6.4)	5,159 (6.8)
2014	8,646 (7.1)	5,329 (7.1)
2015	8,967 (7.4)	6,292 (8.3)
2016	9,533 (7.9)	7,203 (9.5)
2017	9,360 (7.7)	6,872 (9.1)
2018	8,627 (7.1)	5,882 (7.8)
2019	7,428 (6.1)	4,865 (6.4)
2020	4,490 (3.7)	3,006 (4.0)
2021	3,593 (3.0)	2,268 (3.0)

Table 4.2. Rates of syphilis testing and incidence during the study period, and incidence rate ratios for changes in rates from 2012-2019

		Entire observation period (2012-2021)			Trends analysis* (2012-2019)	
		Person-years of follow-up	Number of events (tests or diagnoses)	Overall rate / 100 person-years	Incidence Rate Ratio (95% CI)	p-Value
Syphilis tests	All GBM	574,151	587,967	102.4 (102.1 - 102.7)	1.11 (1.11-1.12)	<0.001
	Never PrEP users	290,017	160,991	55.5 (55.2 - 55.8)	1.08 (1.07-1.08)	<0.001
	Ever PrEP users	195,476	282,889	144.7 (144.2 - 145.3)	1.18 (1.17-1.18)	<0.001
	HIV+ GBM	88,658	144,087	162.5 (161.7 - 163.4)	0.99 (0.99-0.99)	<0.001
Syphilis diagnoses	All GBM	343,287	13,858	4.0 (4.0 - 4.1)	1.10 (1.08-1.11)	<0.001
	Never PrEP users	138,008	2,607	1.9 (1.8 - 2.0)	1.03 (1.00-1.06)	0.048
	Ever PrEP users	136,165	5,756	4.2 (4.1 - 4.3)	1.23 (1.20-1.26)	<0.001
	HIV+ GBM	69,114	5,495	8.0 (7.7 - 8.2)	1.03 (1.01-1.05)	0.001
Repeated Syphilis diagnoses	All GBM	32,360	5,616	17.4 (16.9 - 17.8)	0.99 (0.97-1.01)	0.217
	Never PrEP users	5,376	777	14.5 (13.5 - 15.5)	0.96 (0.90-1.02)	0.153
	Ever PrEP users	11,966	2,063	17.2 (16.5 – 18.0)	1.04 (0.99-1.10)	0.103
	HIV+ GBM	15,018	2,776	18.5 (17.8 - 19.2)	0.96 (0.94-0.98)	0.001

* Incidence rate ratio from negative binomial regression model represents mean change in per one year increase from 2012-2019
CI = confidence interval

Table 4.3. Unadjusted and adjusted hazard ratios for factors associated with syphilis infection among GBM attending ACCESS clinics between 2016-2019

Covariate	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
Age group				
15-29	-reference-		- reference-	
30-39	0.96 (0.88 - 1.04)	0.34	0.98 (0.91 - 1.05)	0.589
40-49	0.87 (0.80 - 0.96)	0.004	0.97 (0.90 - 1.05)	0.448
50+	0.60 (0.54 - 0.66)	<0.001	0.83 (0.76 - 0.90)	<0.001
Aboriginal or Torres Strait Islander				
No	- reference-		- reference-	
Yes	1.30 (1.07 - 1.60)	0.01	1.17 (1.00 - 1.37)	0.048
Missing/not reported	0.81 (0.75 - 0.88)	<0.001	0.96 (0.90 - 1.03)	0.282
Born in Australia				
Yes	- reference-		- reference-	
No	1.13 (1.04 - 1.22)	0.005	1.09 (1.02 - 1.17)	0.014
Missing/not reported	0.76 (0.71 - 0.81)	<0.001	0.83 (0.78 - 0.88)	<0.001
Living with HIV	1.51 (1.40 - 1.63)	<0.001	2.00 (1.85 - 2.16)	<0.001
Previously prescribed PrEP (ever)*	1.58 (1.47 - 1.69)	<0.001	-	-
Recently prescribed PrEP (12 months)	1.74 (1.63 - 1.86)	<0.001	1.91 (1.77 - 2.06)	<0.001
Previous syphilis diagnosis (ever)	4.78 (4.49 - 5.08)	<0.001	2.63 (2.45 - 2.82)	<0.001
Recent syphilis diagnosis (12 months)	6.41 (5.97 - 6.89)	<0.001	2.04 (1.89 - 2.20)	<0.001
Previous CT diagnosis (ever)	2.65 (2.49 - 2.83)	<0.001	1.16 (1.06 - 1.26)	0.001
Recent CT diagnosis (12 months)	3.42 (3.23 - 3.63)	<0.001	1.57 (1.45 - 1.71)	<0.001
Previous CT diagnosis (ever)	2.61 (2.46 - 2.78)	<0.001	1.26 (1.18 - 1.36)	<0.001
Recent NG diagnosis (12 months)	3.22 (3.03 - 3.41)	<0.001	1.50 (1.40 - 1.61)	<0.001
Previous rectal STI diagnosis (ever)	2.93 (2.75 - 3.12)	<0.001	1.22 (1.11 - 1.33)	<0.001
Recent rectal STI diagnosis (12 months)	3.61 (3.41 - 3.83)	<0.001	1.13 (1.03 - 1.24)	0.012

*Omitted from multivariable model due to collinearity with *recently prescribed PrEP*

Rectal STI = Rectal chlamydia and/or rectal gonorrhoea

Observation for risk-factor analysis was restricted to 2016-2018 to include years where PrEP was available and prior to the impact of COVID-19

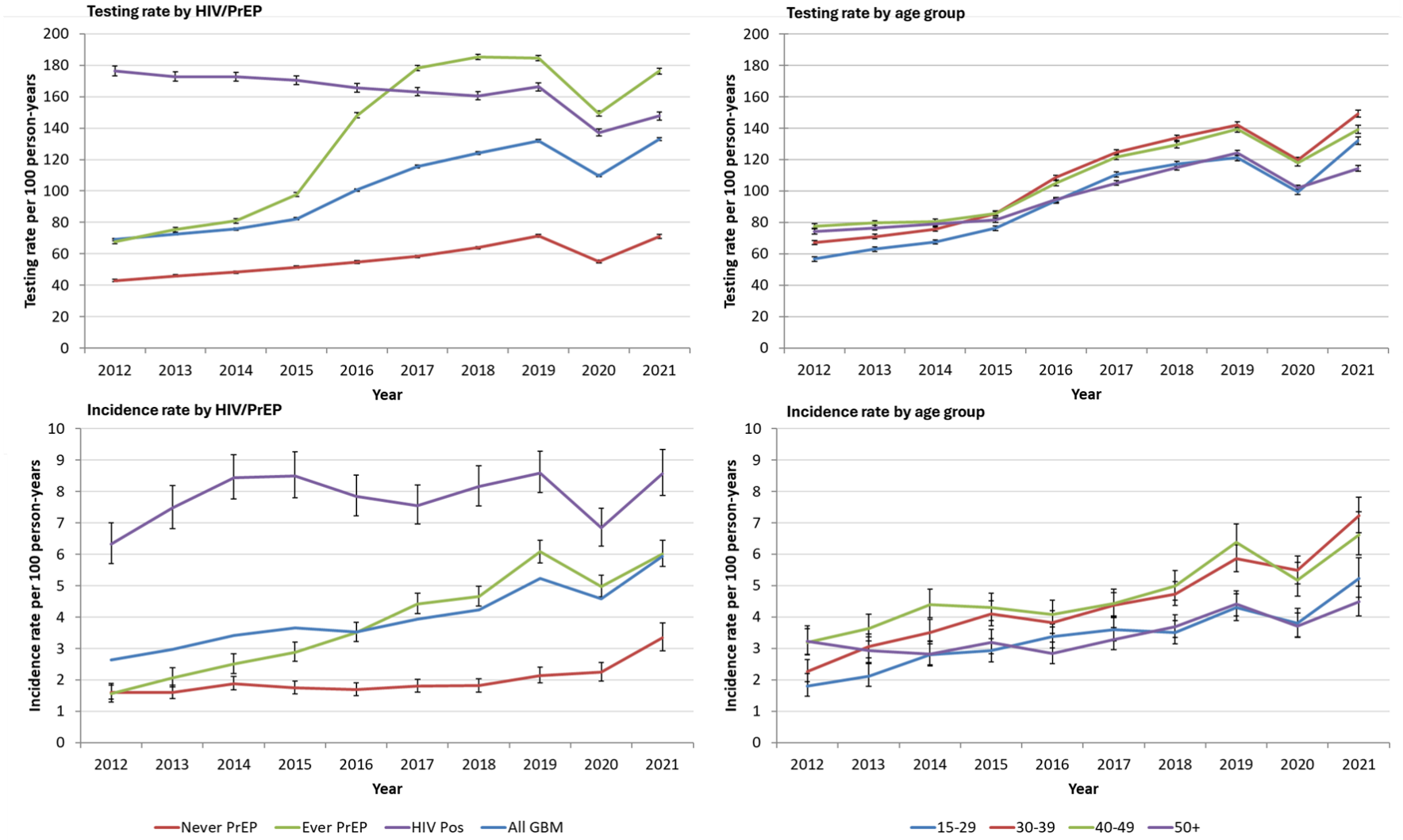

Figure 4.1. Annual rate per 100 person-years of syphilis testing and incidence among GBM attending ACCESS clinics from 2012-2012, by HIV status and ever-PrEP use status.

Appendices A2.2 (p 232) and A2.3 (p 233) contain numerical values for testing and incidence rates. Vertical bars represent 95% confidence intervals.

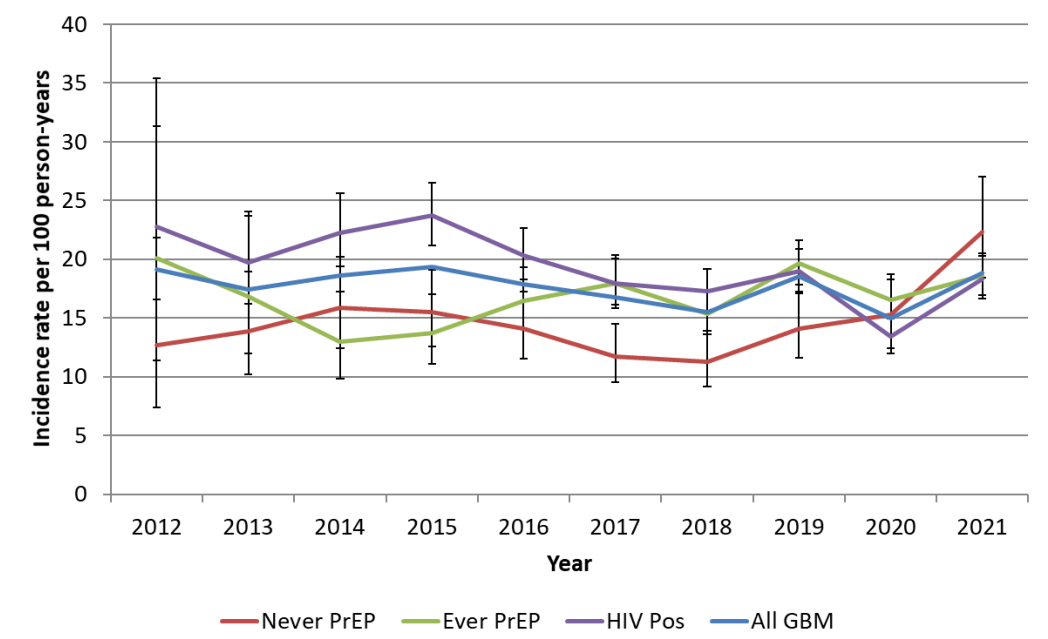

Figure 4.2. Annual rate per 100 person-years of repeated syphilis diagnoses among GBM with a previous diagnosis of syphilis infection attending ACCESS clinics from 2012-2012, by HIV status and ever-PrEP use status.

Vertical bars represent 95% confidence interval

4.5 Discussion

To our knowledge, this analysis represents the largest longitudinal cohort of syphilis incidence trends among GBM reported globally, and the largest population-level analysis of syphilis incidence among both GBM with and without HIV prior to and following widespread availability of PrEP. Across our national network of sentinel clinics, we observed increasing rates of syphilis infection among both HIV-negative GBM and GBM living with HIV, with the most notable increase among GBM with evidence of PrEP use. Increases in syphilis incidence were observed alongside modest increases in overall syphilis testing, however testing steadily declined among GBM with HIV, falling below the rate of testing among PrEP users from 2017 onwards. Among those with a recorded syphilis diagnosis across the network, the rate of repeated syphilis diagnosis was more than four times greater than the overall syphilis diagnosis rate, and was comparable between GBM with and without HIV. The historically high rates of syphilis infection among GBM with HIV has previously been attributed to repeat infections in relatively closed sexual network; our findings suggest diversifying sexual networks influenced by changing trends in both PrEP use and serosorting are now influencing syphilis infection rates among GBM without HIV.

Increasing rates of syphilis transmission among GBM without HIV have been reported internationally.[274, 275] Our analysis shows most of the increase in syphilis diagnoses among GBM in Australia is occurring among a subgroup of GBM who have used PrEP. While syphilis incidence in the ever-PrEP group did not surpass the incidence of GBM with HIV, our previous analysis of HIV-negative GBM with continuous PrEP use (i.e. individuals were censored after four months since their last PrEP prescription) in Australia found a syphilis incidence rate of 9.4/100py (CI: 9.0-9.8),[276] above the incidence rate of GBM with HIV in every year in this analysis. After multivariable adjustment, recent PrEP use (HR=1.91) and living with HIV (HR=2.00) had similar hazard ratios for syphilis infection. Taken together, these data suggest that GBM with HIV are no longer the single group most at risk of syphilis, and that incidence between GBM with HIV and PrEP users is converging.

Syphilis incidence was increasing among GBM classified as ever-PrEP users prior to PrEP availability in 2016. As we retrospectively classified individuals as ever-PrEP users, the higher and increasing incidence in this group likely reflects both pre-existing risk characteristics and the impact of PrEP use on STI risk. The early phases of PrEP roll-out in Australia was through implementation studies which involved specific risk-based inclusion criteria, including recent condomless sex and prior STI diagnosis.[66, 68] Our observed trends occurred alongside a decade-long trend of decreasing rates of consistent condom use with casual partners among GBM in Australia which also began prior to PrEP introduction,[152, 277] which were accelerated following PrEP roll-out in 2016.[151] While PrEP use has

been associated with individual-level changes in condom use and increased risk of a rectal STI diagnosis,[162] previous analyses of GBM enrolled in two large PrEP implementation studies in Australia found no significant change in syphilis incidence immediately following PrEP initiation and no change in the rate of change of syphilis positivity following PrEP initiation, respectively.[67, 163] Increasing rates of syphilis among all groups of GBM are likely a product of pre-existing longer-term trends being accelerated by changes in sexual networks and reductions in serosorting post-PrEP availability. Serial cross-sectional surveys from Melbourne show serosorting with casual partners declined from 67.5% in 2012 to 32.2% in 2021 among GBM with HIV.[278, 279] Similarly, the number of GBM disclosing their HIV status to casual partners has declined,[278] and more GBM report comfort relying on PrEP for condomless sex.[144]

Rates of syphilis reinfection were higher in each group across the entire observation period, not just in the period of widespread PrEP availability. Among GBM with no evidence of PrEP, the incidence of repeated syphilis diagnosis was almost 8-fold greater than for overall syphilis diagnosis. In regression analyses, previous diagnosis of syphilis was the strongest predictor of future syphilis infection, even after adjusting for HIV status and recent PrEP prescription. Further, the rate of repeated infection did not change over the observation period, and in fact declined among GBM with HIV. Declines in testing and reinfection among GBM with HIV are likely, in part, due to less frequent HIV monitoring testing over time, as guidelines on how often GBM with HIV should have viral load/CD4 tests changed during the observation period. However, taken together, these findings support the hypothesis that sexual networks play a key role in driving syphilis transmission, and that while these networks may be associated with serosorting among GBM with HIV in earlier years, and with reduced serosorting among PrEP users and GBM with HIV in the era of PrEP and U=U, networks likely also include HIV-negative GBM not using PrEP. Fully understanding the impact of sexual networks on syphilis transmission is made difficult by a lack of individual-level data on sexual mixing for detailed sexual network analysis.

Such networks of high rates of reinfection offer ideal opportunities to impact population-level incidence by interrupting transmission chains. While campaigns aimed at reducing risk behaviour or improving early symptom recognition have generally shown poor impact,[280] clinically-led prevention interventions to enhance testing, detection and treatment rates, as well as novel biomedical prevention strategies such as doxycycline post-exposure prophylaxis (PEP), which interrupt chains of transmission, may deliver greater population-level benefits. Doxycycline PEP has been shown to reduce the risk of syphilis by 87% and 77% among PrEP users and GBM with HIV in a clinical trial, respectively.[281] When balancing the potential impact of doxycycline PEP with serious concerns around adverse effects on gut health and the potential for community-level antimicrobial resistance

associated with widespread use,[282] it should be acknowledged that doxycycline as STI prophylaxis is acceptable to most GBM[283] and data from Melbourne show that some GBM are already using doxycycline prophylactically.[233] Future guidelines for doxycycline prophylaxis prescribing should include prior diagnosis as an indication for doxycycline prescribing, and not be limited to GBM using PrEP or living with HIV.

Our data show that frequency of syphilis testing among all groups of GBM is well below the currently recommended three-monthly screening for all sexually active GBM.[284] An Australian modelling study found that higher frequency of testing associated with wider PrEP uptake in isolation would likely not be enough to curtail the growing syphilis epidemic among the wider GBM population.[166] This model suggested that increasing testing frequency among those already being tested would have a greater impact on syphilis transmission than increasing testing coverage, a finding that has been echoed in modelling studies from North America.[217, 285] In the context of limited resources and clinic capacity to increase testing, data suggest that strategies which prioritise increased screening among people with a previous diagnosis may provide the greatest yield for diagnosing and interrupting transmission chains. Modelling work highlights that strategies which increase screening among GBM with a prior syphilis infection are among the most efficient at reducing population-level syphilis.[286] New models of self-testing, including novel rapid point-of-care tests which detect acute syphilis infection[287, 288] have great potential for enhancing overall rates of testing as well as supplementing clinic testing in specific subgroups who may benefit from more frequent screening.

Strengths and limitations

There are considerable strengths to this analysis. First, clinics participating in the ACCESS surveillance project have a significant coverage of GBM attending for STI testing in Australia. Although sexual orientation is not collected is national census data, a previous analysis which aimed to estimate the population of GBM in Australia by triangulating multiple data sources, including census data on same-gender-partnered households and six different surveys, estimated a population size of 132,203 GBM residing in Australia in 2016.[248] While our cohort reflects GBM attending over a 10-year period, approximating coverage using this population-size estimate, our syphilis incidence analysis captures in the order of 60-70% of all GBM residing in Australia. Second, the highly accurate data linkage between ACCESS clinics allowed us to longitudinally monitor individuals who transferred care between clinics participating in ACCESS and reduce loss to follow-up.

A number of limitations of our analysis should be noted. First, individuals might have been tested and diagnosed with syphilis at a clinical outside of the ACCESS network. However, given the short intervals between the tests included in this analysis (median 119 days), the effect of external testing is likely to have been minimal. Second, for individuals attending general practice clinics, in the absence of sexuality recorded on their electronic medical record, we relied on an algorithm of rectal swab testing among male patients to infer status of gay and bisexual men, which might have misclassified a small number of patients, although specificity for this algorithm was high (99%). Finally, as only clinical testing data were extracted, and not data on STI treatments prescribed to participants, it could not be ensured that every STI was treated effectively and that all positive diagnoses were incident infections. However, the clinics included in this study are highly experienced in managing STIs and followed standard STI treatment guidelines.

4.6 Conclusions

In this analysis of a large cohort of gay and bisexual men accessing syphilis testing in Australia, we found that syphilis trends between GBM with HIV and GBM with evidence of PrEP use have been converging over the past 10 years, and that the rate of testing for syphilis continues to fall below recommended screening guidelines. While GBM with HIV and with a history of PrEP use were more likely to be diagnosed with syphilis, previous syphilis infection was the strongest predictor of subsequent infection, and rates of reinfection were high regardless of HIV status and PrEP use. In the era of HIV PrEP, strategies to address increasing rates of syphilis, such as targeted screening and novel biomedical prevention strategies, should focus on interrupting transmission within sexual networks associated with high rates of reinfection. Future guidelines for doxycycline prophylaxis should include prior syphilis diagnosis as an indication for doxycycline prescribing.

4.7 Article information

Contributors

MWT, RG, CT and MAS conceived the study. MWT, RG, CT, VJC, EPFC, CKF, BD, MEH, MAS contributed substantially to interpretation of the data. MWT undertook the formal data analysis. MWT, JA and AC curated the data. RG, JA, AC, BD, MEH and MAS coordinate the ACCESS study and were responsible for funding acquisition. EPFC, MB, CKF, AM, PR, LO, NR, DJT are ACCESS clinic

investigators and contributed to data acquisition. MWT, JA and MAS had full access to all the data in the study and verified the data. MAS and MEH provided academic supervision to MWT. MWT lead the manuscript preparation.

All authors read and revised the manuscript critically for important intellectual content and approved the final version of the manuscript for publication.

Data sharing

De-identified individual participant data included in this study cannot be shared publicly because of the sensitive nature of participant data anonymously extracted from participating clinical services. Access to de-identified data is available via the Burnet Institute with approval from the Alfred Hospital Human Research Ethics Committee for researchers who meet the criteria for access to confidential data. The ACCESS study protocol have been published previously.

Declaration of interests:

M.W.T. reports speakers' honoraria and investigator-initiated research grants from Gilead Sciences.

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Chapter 5

Incidence and prevalence of hepatitis C among HIV-negative gay and bisexual men using PrEP: a systematic review and meta-analysis

In Chapters 3 and 4 I explored trends in bacterial STIs in the context of PrEP and produced data which offered contemporary insights into the interplay between PrEP implementation and STI incidence among GBM. Our group's work has also explored hepatitis C among PrEP users in Australia. In the PrEPX study in Melbourne, we found that hepatitis C incidence was comparatively low at 0.3/100 py (see appendix C5, p 351). Using ACCESS surveillance data, we also found consistently low rates of hepatitis C among PrEP users nationally during periods of PBS-listed PrEP (see appendix C6, p 351). These findings were not reflective of trends in other STIs among PrEP users in Australia, or of hepatitis C incidence among early PrEP users in other countries. We hypothesised that the low rates of hepatitis C observed among PrEP users in Australia were influenced by HIV-hepatitis C co-infection micro-elimination strategies among GBM with HIV in Australia which occurred just prior to and during the initial access to PrEP in 2016.[173] Chapter 5 presents a systematic review and meta-analysis which aims update the global evidence on hepatitis C among PrEP users, and to explore the difference in HCV rates among PrEP users relative to DAA availability in respective countries.

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Incidence and prevalence of hepatitis C virus among HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP): a systematic review and meta-analysis

Authors

Michael W. Traeger[1,2], Brendan L. Harney[1,2,3], Rachel Sacks-Davis[1,2,7], Daniela K. van Santen[1,2,4,5], Vincent J. Cornelisse[3,6,7], Edwina J. Wright[1,3], Margaret E. Hellard[1,3], Joseph S. Doyle*[1,3], Mark A. Stoové*[1,2]

*Co-senior

Author affiliations

[1] Burnet Institute, Melbourne, Australia

[2] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

[3] Department of Infectious Diseases, The Alfred and Monash University, Melbourne, Australia

[4] Department of Infectious Diseases, Research and Prevention, Public Health Service of Amsterdam, Amsterdam, the Netherlands

[5] Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

[6] Kirketon Road Centre, Sydney, Australia

[7] The Kirby Institute, UNSW Sydney, Australia

[8] Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

5.1 Summary

Background

Gay and bisexual men (GBM) using HIV pre-exposure prophylaxis (PrEP) are at increased risk for sexually transmissible infections. However, hepatitis C virus (HCV) risk among PrEP users is less clear. We explored HCV prevalence and incidence among cohorts of GBM using PrEP and sources of heterogeneity in HCV risk across PrEP populations.

Methods

We conducted a systematic review and meta-analysis of open-label PrEP studies published to April 2022 which reported HCV prevalence (antibody or RNA) at study baseline or HCV incidence during follow-up among HIV-negative GBM using PrEP. Pooled prevalence and incidence estimates were calculated using random-effects meta-analysis, and subgroup analyses were performed by study- and country-level characteristics, including availability of HCV direct-acting antiviral (DAA) therapy at the time of study enrolment. A narrative review explored reported behavioural outcomes.

Findings

Twenty-four studies were included; 11 studies provided a pooled HCV antibody prevalence of 0.96% (95% CI: 0.62-1.30) and a pooled HCV RNA prevalence of 0.38% (95% CI: 0.19-0.56). Among 19 studies, HCV incidence ranged from 0.0 to 2.93/100 person-years (py); the pooled estimate was 0.83/100py (95% CI: 0.56-1.09). HCV incidence was higher in 12 studies which began follow-up before broad DAA availability (1.29/100py) than in 8 studies which began follow-up after broad DAA availability (0.32/100py), and higher in studies in Europe compared to North America and Australia. Behavioural characteristics associated with HCV acquisition risk varied and were reported across drug use and sexual behaviour domains.

Interpretation

Early reports of high HCV incidence among PrEP-using cohorts likely reflect specific risk-based eligibility criteria of smaller PrEP studies and enrolment prior to DAA scale-up. More recent studies in settings where both DAAs and PrEP have been implemented at-scale report lower HCV incidence. PrEP-specific HCV testing guidelines should be guided by local epidemiological contexts and consider the cost-effectiveness of universal HCV screening among PrEP users at a time when HCV prevalence among PrEP users is declining.

5.2 Introduction

Global guidelines on hepatitis C treatment and prevention highlight gay and bisexual men and other men who have sex with men (GBM) as a priority population.[7] Among GBM globally, those living with HIV have been historically overrepresented in hepatitis C diagnoses,[289, 290] a result of intersecting behavioural and demographic risk factors[291] and driven further by specific and more concentrated sexual networks constituted of GBM living with HIV.[292] The availability of highly efficacious direct-acting antiviral (DAA) treatments for hepatitis C virus (HCV) in many countries from early 2014 has galvanised hepatitis C elimination efforts globally, lead to ambitious elimination targets.[293, 294] Widespread uptake of DAA treatment has been associated with rapid declines in population-level hepatitis C viremia and incidence among GBM living with HIV in multiple settings, including in Australia[173] and Europe.[295, 296] However, alongside the development and approval of DAA treatments for HCV, biomedical advances in HIV prevention, including treatment as prevention (TasP)[37] and HIV pre-exposure prophylaxis (PrEP),[297] have been associated with increases in condomless sex among GBM,[151, 162] as well as an increases in bacterial STIs.[67] While the impact of PrEP implementation on HCV transmission among HIV-negative GBM is less documented, the influence of PrEP on condom use and sexual networks, specifically increased rates of sero-different sex among GBM,[162] has raised concerns for the potential bridging of HCV transmission networks between GBM living with HIV and HIV-negative GBM.[298, 299]

While hepatitis C elimination strategies are underpinned by testing and treating populations at ongoing risk for hepatitis C,[173, 261] including GBM, national guidelines on how often PrEP users should be screened for HCV vary considerably, from every 3-12 months for all GBM using PrEP,[79, 213, 300] to only in the presence of ongoing risk factors (e.g. injection drug use),[301] with some countries, such as the UK, having no specific guidelines for HCV screening in PrEP users.[302] Early clinical studies which reported relatively high baseline risk of hepatitis C among GBM taking PrEP, were likely biased towards individuals with specific risk characteristics, as early PrEP demonstration studies often had specific risk-based enrolment criteria (e.g. recent condomless anal sex with casual partners or recent STI diagnosis)[303]. Participants in these studies may not reflect the level of risk observed among wider populations of PrEP users following widespread PrEP implementation or in the context of more widespread DAA availability.

Estimates of pooled hepatitis C incidence among GBM using PrEP have varied across reviews,[304, 305] and in the context of a declining hepatitis C incidence among GBM living with HIV following DAA implementation,[173, 186, 296] none have investigated heterogeneity in hepatitis C risk among PrEP users relative to DAA availability at the time of study. In this systematic review and meta-analysis of

hepatitis C among GBM using HIV PrEP, we aimed to provide updated estimates of hepatitis C incidence among PrEP users globally, examine rates of hepatitis C incidence among PrEP cohorts across study- and country-level characteristics, including the availability of DAA treatments for hepatitis C at the time of PrEP roll-out.

5.3 Methods

A protocol for this review was registered prospectively (PROSPERO registration number 2020 CRD42020179455).

Eligibility criteria

Studies were included if they reported data on hepatitis C prevalence or incidence among GBM using HIV PrEP, inclusive of daily or on-demand/event-driven PrEP. We included prospective observational cohort studies, open-label one-armed trials, and non-blinded randomised controlled trials (i.e. participants were aware they were using PrEP).

Outcomes

To be included, studies must have reported one of the below primary outcomes:

1. Hepatitis C antibody prevalence – point estimate of hepatitis C antibody positivity at PrEP initiation or study baseline
2. Hepatitis C RNA prevalence – point estimate of hepatitis C RNA positivity / viremia at PrEP initiation or study baseline (among all participants)
3. Hepatitis C incidence – incidence rate per person-years of PrEP use of hepatitis C (primary and re-infection), or cumulative incidence of hepatitis C during PrEP use

Search strategy

We searched the following databases on 20th April 2022; Medline and EMBASE (using OVID), and PubMed. Search strings included medical subject headings and free text relating to (see appendix A3.1 [p237] for full search strings):

1. MSM (men who have sex with men, GBM, gay men);

2. Pre-exposure prophylaxis (PrEP, Truvada, tenofovir, TDF, emtricitabine);
3. Hepatitis C (HCV, hepatitis C virus)

We also conducted manual searches of relevant international HIV and viral hepatitis conferences, including the International AIDS Conference (AIDS), the International AIDS Society Conference on HIV Science (IAS), Conference on Retroviruses and Opportunistic Infections (CROI), the HIV Research for Prevention Conference (HIVR4P), the International Liver Congress (EASL), the Liver Meeting (AASLD) and the International Symposium on Viral Hepatitis and Liver Diseases (ISVHLD).

Results were exported into COVIDENCE software, and abstracts and titles were screened independently by two reviewers (MT and BH). For studies which reported at least one outcome, full texts were obtained and assessed to confirm eligibility. Where multiple publications or conference abstracts reported data from the same cohort or study, the most recent citation or citation with most complete data for the relevant outcomes was included. Where two citations reported data from the same study but reported different outcomes (e.g. HCV antibody prevalence and HCV RNA prevalence), both were included.

Data extraction

Data were extracted and assessed independently by two reviewers using a standardised form to collate the following study characteristics and outcomes where reported:

1. study design;
2. location of study;
3. date of start and end of study follow-up;
4. sample size (number included in hepatitis C outcomes);
5. participant demographics (including the proportion classified as MSM or transgender women, age, ethnicity);
6. hepatitis C behavioural risk characteristics of the cohort and/or hepatitis C cases (if reported):
    a. Sexual behaviour (*e.g.* number of partners, condom use, group sex, fisting); and/or
    b. Drug use (*e.g.* chemsex drug use, injecting drug use);
7. primary outcome measures:
    a. For prevalence and incidence outcomes, numerator and denominator data were extracted separately where available. Where unavailable, reported prevalence rates or incidence rates were extracted.

b. For antibody prevalence calculations (where numerator and denominator were reported), the numerator was taken as the number of participants who tested positive to HCV antibodies at baseline and the denominator was taken as the number of participants tested for HCV antibodies at baseline.
c. For RNA prevalence calculations (where numerator and denominator were reported), the numerator was taken as the number of participants who tested positive to HCV RNA at baseline and the denominator was the number of participants tested for either HCV antibody or RNA at baseline.
d. For hepatitis C incidence calculations (where number of infections and person-time at risk were reported), incidence rate was taken as the number of new hepatitis C infections (including primary and re-infections) divided by the number of person-years accrued.
e. For person-time reported in studies, the point used to begin person-time (e.g. after first HCV negative test) was extracted from each study where reported.

Any disagreements were resolved by consensus, and study authors were contacted via email a maximum of two times to obtain missing data or further information where needed.

Study setting and DAA availability

The rate of hepatitis C transmission among PrEP users is likely linked to community-level hepatitis C viremia among the wider GBM population at the time of PrEP implementation. To explore the potential effect of the timing of DAA availability (and impact on of this on hepatitis C prevalence) on hepatitis C incidence among PrEP users, we searched PubMed, national policy documents and other grey literature as applicable to record when DAAs became broadly available in each respective jurisdiction of the included studies (data sources and results in appendix A3.1, p 237). Each study was categorised according to the broad availability of DAA treatments to GBM during the study follow-up in the respective country; studies were categorised as

(1) **Study initiated prior to broad DAA availability** (limited or no access to subsidised DAAs, or restrictions on DAA prescribing based on liver disease stage or substance use, at the time of PrEP study follow-up initiation); or
(2) **Study initiated after broad DAA availability** (DAAs available with no restrictions based on liver disease stage or substance use at the time of PrEP study follow-up initiation).

Statistical analysis

Random-effects meta-analysis was used to calculate pooled estimates for hepatitis C prevalence (antibody-positivity and RNA-positivity separately) at PrEP initiation/study baseline and incidence during follow-up. To estimate pooled hepatitis C prevalence, a double arcsine transformation was performed in order to constrain confidence intervals between 0.0 and 1.0.[306] For hepatitis C incidence, incidence rates per 100 person-years were calculated for each study based on reported number of incident infections and person-time-at-risk. As some studies reported zero rates (no incident infections) and some did not report confidence intervals, we calculated (or recalculated) standard errors and confidence intervals for each study using the reported number of incident infections and person-time-at-risk using the exact chi squared method, to allow for upper confidence intervals for zero rates to be calculated. The inverse-variance method was used to weight studies in pooled estimates. Statistical heterogeneity between studies was assessed by calculating an I^2 and χ^2 statistic, with a χ^2 significance level of 0.10 and I^2 > 50% considered moderate or high levels of heterogeneity.[307]

Subgroup analyses were performed to identify sources of heterogeneity between studies by stratifying studies by sample size (number of participants contributing to estimate of the respective outcome; dichotomised into < or > than 500 participants), country, and availability of DAAs relative to PrEP rollout. Due to heterogeneity in reported sexual and drug use behaviour measures across studies, meta-analysis by behavioural outcomes was not feasible. As such, we report a narrative review of behavioural outcomes. All statistical analyses were performed using Stata software (Version 15.1 for Windows; StataCorp, College Station Texas).

Risk of bias assessment

A modified Newcastle-Ottawa Scale[308] (appendix A3.4, p 248) was used to assess the risk of bias in the included studies. Risk of bias in individual studies was assessed based on sample representativeness of the population of GBM who use PrEP, evidence for confirmation of outcome (new hepatitis C infection) and adequate follow-up time. Bias was classified using a numerical scale from zero to two for each criterion, with a maximum total score of eight. A score of seven or greater was classified as low risk of bias.

5.4 Results

Search results and included studies

The electronic database search resulted in a total of 408 citations, of which 91 were duplicates, leaving 317 unique citations **(Figure 5.1)**. A total of 23 studies met inclusion criteria and were included in the review. The characteristics of included studies and the outcomes they report are shown in **Table 5.1**. Two publications reported different outcomes from the same cohort; Reyniers et al reports hepatitis C prevalence and Vuylesteke et al reports incidence from the Belgian PrEP study. One study (Harney et al) included data from two other studies (Amin et al and Cornelisse et al) as part of a national-level presentation of data from Australia, and was excluded from meta-analyses due to the determination of person-time in this study (hepatitis C incidence rates calculations for PrEP users in this study potentially included person-time during periods of non-PrEP use).

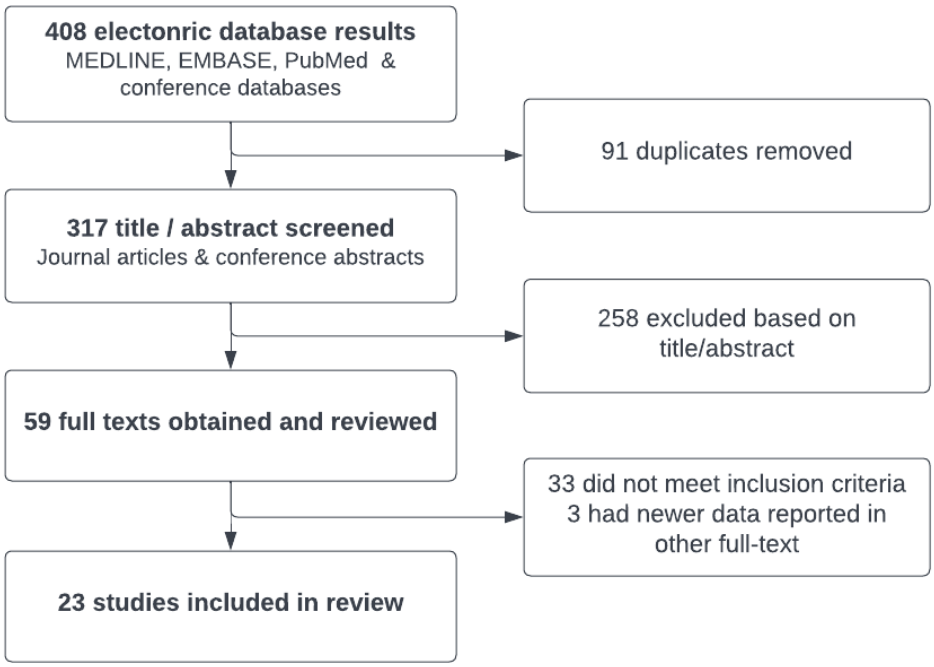

Figure 5.1. Systematic review search results and screening process

Hepatitis C prevalence at PrEP initiation

Eleven studies reported HCV antibody prevalence at study baseline. Antibody prevalence ranged from 0.26% to 4.86% across studies. The pooled estimate of hepatitis C antibody prevalence was 0.96% (95% CI 0.62 – 1.30) and heterogeneity was high across studies (I^2 77.9%, p<0.001) **(Table 5.2).**

Table 5.1 Characteristics of studies included in the systematic review

Study	Project / Study / Clinic	Study type	Start Date	End date	Country (state/province)	Cohort size*	Cohort population	Included in pooled estimates		
								HCV Ab prevalence	HCV RNA prevalence	HCV incidence
Aloysius et al 2017 [309]	InterPrEP	Prospective cohort	Feb-16	Mar-17	UK	573	100% MSM 75% daily PrEP			Yes
Amin et al 2021 [a] [185]	EPIC-NSW Study [a]	Prospective cohort Demonstration study	Mar-16	Apr-19	Australia (New South Wales)	8,658 [a]	98.5% Male 91.8% identify gay 6.7% identify bisexual	Yes	Yes	Yes
Ayerdi Aguirrebengoa et al 2021 [310]	Centre Sanitario Sandoval	Retrospective descriptive	Jan-17	Jan-19	Spain	110	98.2% MSM 1.8% TGW	Yes		Yes
Cornelisse et al 2020 [a] [311]	PrEPX Study [a]	Prospective cohort Demonstration study	Jun-16	Mar-18	Australia (Victoria)	3,202 [a]	99.1% Male 98.7% gay or bisexual	Yes	Yes	Yes
Cotte et al 2018 [179]	French Dat'AIDS cohort	Prospective cohort	Jan-16	May-17	France	903	100% MSM	Yes	Yes	Yes
Desai et al 2020 [312]	PROUD	Open-label deferred RCT	Nov-12	Oct-16	UK	544	100% MSM	Yes	Yes	Yes
Gras et al 2020 [313]	ANRS IPERGAY PrEP	RCT & open-label trial	Feb-12	Jun-16	France	429	100% MSM			Yes
Hamed et al 2018 [314]	Clinic Network in Newark	Clinic-based prospective cohort	May-16	Mar-18	US (New Jersey)	74	74% male 40% MSM 45% reported HIV-positive partners (Eligibility inc. MSM, PWID, HIV-positive partner)		Yes	
Harney et al 2021 [a] [186]	ACCESS surveillance network [a]	Retrospective multi-clinic analysis	Jan-16	Dec-19	Australia	23,373 [a]	100% MSM (algorithm based on self-report and			

							rectal swab history)			
Hassan et al 2019 [315]	CCTG 595 PATH-PrEP	Two prospective cohorts	Feb-13	Jul-16	US (California)	599	99.7% MSM 0.3% TGF	Yes		Yes
Hoornenborg et al 2020 [180]	Amsterdam PrEP project	Prospective cohort	Aug-15	Sep-18	Netherlands	350	99.4% MSM 0.6% TGF	Yes	Yes	Yes
Lalley-Chareczko et al 2018 [316]	Philadelphia FIGHT clinic	Prospective cohort	NR	NR	US (Pennsylvania)	50	90% MSM 10% TGF			Yes
Mikati et al 2018 [317]	NYC Sexual Health Clinics	Retrospective clinic audit	Sep-16	Dec-19	US (New York)	381	100% MSM	Yes	Yes	
Molina et al 2019 [181]	ANRS PREVENIR	Open-label RCT	May-17	Oct-18	France	3067	98.5% MSM			Yes
Nguyen et al 2018 [318]	Clinique l'Actuel		Jan-10	Jan-15	Canada (Quebec)	109	100% MSM			Yes
Noret et al 2018 [319]	Saint-Louis Hospital	Prospective cohort	Nov-15	Apr-17	France	1049	99.4% MSM 0.3% TGW		Yes	Yes
Pečavar et al 2021[320]	Demonstration study	Prospective cohort Demonstration study	Aug-18	Oct-20	Slovenia	74	100% MSM	Yes		Yes
Ramiere et al 2019[b] [182]	Lyon University Hospital	Retrospective clinic audit	Jan-14	Dec-17	France	NR	100% MSM			Yes
Reyniers et al 2018[c] [321]	Belgian PrEP study[c]	Cross-sectional analysis from prospective cohort	Oct-15	NR	Belgium	200[c]	98.5% MSM 1.5% TGW		Yes	
Tabatabavakili et al 2022 [322]	University HIV Prevention Clinic	Retrospective clinic audit	Oct-12	Sep-19	Canada (Ontario)	109	100% MSM	Yes	Yes	Yes
Thompson et al 2022 [323]	BC PrEP Program	Prospective cohort	Jan-18	Aug-19	Canada (British Columbia)	3967	98.5% MSM	Yes	Yes	Yes
Volk et al 2015 [324]	Kaiser Permanente SF MC	Retrospective clinic audit	Feb-11	Dec-14	US (California)	485	100% MSM			Yes
Vuylesteke et al 2019[c] [325]	Belgian PrEP study[c]	Prospective cohort	Oct-15	Jan-18	Belgium	200[c]	98.5% MSM 1.5% TGW			Yes

Six PrEP studies which reported hepatitis C antibody positivity at baseline began follow-up before broad availability of DAA treatments in the respective country or jurisdiction. Among these six PrEP studies the pooled estimate of antibody positivity was 1.74% (95% CI 0.93 – 2.54). Among the five studies where follow-up began after broad availability of DAA treatments, the pooled estimate of antibody positivity was 0.62% (95% CI 0.32 – 0.92). Pooled antibody prevalence was greater in studies with less than 500 participants (2.07% [0.46-3.69]) compared to studies with 500 or more participants (0.81% [0.50-1.13]). Antibody prevalence was greatest (pooled prevalence greater than 1%) in studies from the Netherlands, the UK, France and Slovenia **(Table 5.2)**.

Eleven studies reported HCV RNA prevalence at study baseline. HCV RNA prevalence ranged from 0.09% to 4.29% across studies. The pooled estimate of hepatitis C RNA prevalence was 0.38% (95% CI: 0.19-0.56) and heterogeneity was high (I^2 72.6%, p<0.001) **(Table 5.2)**. Six PrEP studies that reported HCV RNA positivity at baseline began follow-up prior to broad availability of DAA treatments in the respective country or jurisdiction. Among these six studies, the pooled estimate of RNA positivity was 0.97% (95% CI 0.37 – 1.56). Among the five studies which started follow-up after broad availability of DAA treatments, the pooled estimate of RNA positivity was 0.23% (95% CI 0.09 – 0.38). Pooled RNA prevalence was greater in studies with less than 500 participants (2.30% [0.75-3.86]) compared to in studies with 500 or more participants (0.28% [0.15-0.41]). RNA prevalence was greatest (pooled prevalence greater than 1%) in studies from the Netherlands and Belgium **(Table 5.2)**.

Hepatitis C incidence during PrEP use

Nineteen studies reported hepatitis C incidence. In these studies, there were a total of 180 incident hepatitis C infections over a cumulative total of 28,429 person-years of PrEP use. hepatitis C incidence ranged from 0.0 to 2.93 per 100 person-years across studies. The weighted pooled estimate of hepatitis C incidence from random-effects meta-analysis was 0.83 (95% CI: 0.56 – 1.09) per 100 person-years. Heterogeneity was high across studies (I^2, 81.7%, p<0.001)**(Table 5.3).**

Hepatitis C incidence by DAA availability

Twelve PrEP studies began follow-up prior to broad availability of DAA treatments (i.e. DAA treatments became widely available during or after cessation of follow-up). In these twelve studies, the pooled estimate of hepatitis C incidence was 1.29/100 person years (95% CI 0.71 – 1.88); heterogeneity remained high (I^2, 81.8%, p<0.001). Seven PrEP studies reporting hepatitis C incidence began follow-up after broad availability of DAA treatments in the respective country or jurisdiction.

Among these seven studies, less heterogeneity was detected (I^2 = 65%, p=0.009), and the pooled estimate of hepatitis C incidence was 0.32/100 person years (95% CI 0.12 – 0.53).

Hepatitis C incidence by sample size

Among eleven studies which included less than 500 participants, heterogeneity was low (I^2 = 33.9%; p=0.120;) and the pooled estimate of hepatitis C incidence was 1.37/100 person years (95% CI 0.85 – 1.88). Among the eight PrEP studies with more than 500 participants, the pooled estimate of hepatitis C incidence was lower at 0.54/100 person years (95% CI 0.26 – 0.81); heterogeneity was high (I^2 87.2%, p<0.001).

Hepatitis C incidence by country

In subgroup analyses by country, heterogeneity was low across studies within each country except for the two studies from the UK (I^2=77.8%) and the five studies from France (I^2=64.1%). Incidence among studies in Australia, the US, and Canada was lower compared to studies from European countries **(Table 5.3).**

Change in hepatitis C incidence among PrEP users over time

Two studies reported changes in annual rates of hepatitis C incidence among large cohorts of PrEP users over time. Harney et al[186] used data from a national sentinel surveillance system to calculate hepatitis C incidence among 11,661 GBM recently prescribed PrEP across Australia, included participants from two other studies including in the meta-analysis.[185, 311] There were 56 incident infections over 20,886 person-years, for an overall incidence rate of 0.29/100 person-years. In this study, hepatitis C incidence declined from 0.41/100 person-years in 2016 (when DAAs and PrEP became broadly available in Australia) to 0.08/100 person-years in 2019 (IRR = 0.20, 95% CI 0.06 – 0.64).

Ramiére et al[326] reported an increase in hepatitis C incidence among PrEP users attending a hospital in Lyon, France, from 0.3/100py in 2016 to 3.4/100py in 2017 (P<0.001), which was in line with increases in hepatitis C incidence among GBM living with HIV over a similar period reported in the same study (1.1/100py in 2014 to 2.4/100py in 2017).

Table 5.2: Pooled estimates of HCV antibody & RNA prevalence among gay and bisexual men using PrEP

HCV antibody prevalence (%)			
Variable	Number of Studies	Pooled estimate (95% CI)	Heterogeneity χ2 test (I^2)
Overall	11	0.96% (0.62 – 1.30)	P<0.001 (77.9%)
By DAA availability			
Study follow-up started before broad DAA availability	6	1.74% (0.93 – 2.54)	P=0.018 (63.2%)
Study follow-up started after broad DAA availability	5	0.62% (0.32 – 0.92)	P=0.001 (78.7%)
Sample size			
<500	4	2.07% (0.46 – 3.69)	P=0.039 (64.2%)
≥500	7	0.81% (0.50 – 1.13)	P<0.001 (80.4%)
Country			
United States	2	0.35% (0.07 – 0.62)	P=0.216 (34.5%)
UK	1	2.08% (1.04 – 3.68)	-
France	1	1.83% (1.07 – 2.91)	-
Canada	2	0.82% (0.53 – 1.10)	P=0.380 (0.0%)
Netherlands	1	4.86% (2.85 – 7.67)	-
Australia	2	0.72% (0.56 – 0.87)	P=0.003 (89.0%)
Spain	1	0.91% (0.02 – 4.96)	-
Benin	1	1.45% (0.04 – 7.81)	-
HCV RNA prevalence (%)			
Variable	Number of Studies	Pooled estimate (95% CI)	Heterogeneity χ2 test (I^2)
Overall	11	0.38% (0.19 – 0.56)	P<0.001 (72.6%)
By DAA availability			
Study follow-up started before broad DAA availability	6	0.97% (0.37 – 1.56)	P=0.005 (70.0%)
Study follow-up started after broad DAA availability	5	0.23% (0.09 – 0.38)	P=0.014 (67.9%)
Sample size			
<500	4	2.30% (0.75 – 3.86)	P=0.056 (60.3%)
≥500	7	0.28% (0.15 – 0.41)	P=0.017 (61.0%)
Country			
United States	2	0.09% (0.00 – 0.27)	
UK	1	0.57% (0.12 – 1.65)	-
France	2	0.48% (0.17 – 0.79)	
Canada	2	0.19% (0.06 – 0.32)	
Belgium	1	1.50% (0.31 – 4.32)	-
Netherlands	1	4.29% (2.42 – 6.97)	-
Australia	2	0.33% (0.23 – 0.43)	

Table 5.3: Pooled estimates of HCV incidence among gay and bisexual men using PrEP

HCV incidence (rate / 100 person-years)			
	Number of Studies	**Pooled estimate (95% CI)**	**Heterogeneity χ2 test (I^2)**
Overall	19	0.83 (0.56 – 1.09)	P<0.001 (81.7%)
By DAA availability			
Study follow-up started before broad DAA availability	12	1.29 (0.71 – 1.88)	P<0.001 (81.8%)
Study follow-up started after broad DAA availability	6	0.32 (0.12 – 0.53)	P=0.009 (65.1%)
Sample size			
<500	11	1.37 (0.85 – 1.88)	P=0.120 (34.9%)
≥500	8	0.54 (0.26 – 0.81)	P<0.001 (87.2%)
Country			
United States	3	0.04 (0.00 – 0.34)	P=0.520 (0.0%)
UK	2	1.39 (0.00 – 2.87)	P=0.034 (77.8%)
France	5	1.17 (0.74 – 1.60)	P=0.025 (64.1%)
Canada	3	0.29 (0.13 – 0.46)	P=0.787 (0.0%)
Belgium	1	2.93 (1.53 – 5.64)	-
Netherlands	1	2.30 (1.39 – 3.79)	-
Australia	2	0.23 (0.06 – 0.40)	P=0.185 (43.0%)
Spain	1	1.93 (0.52 – 4.93)	-

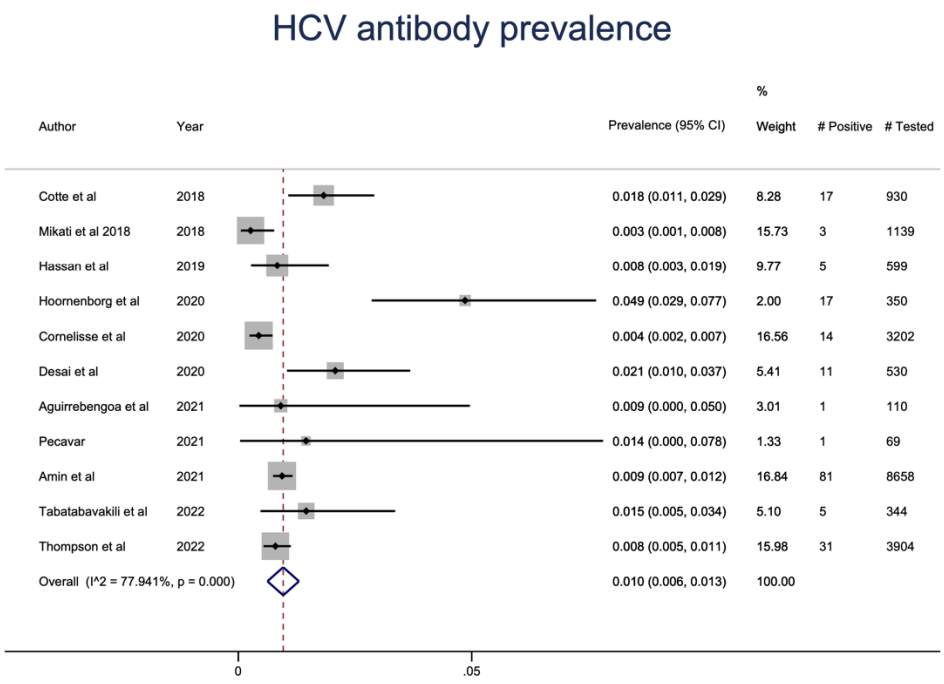

Figure 5.2. Forest plot of random-effects meta-analysis of HCV antibody prevalence at baseline among gay and bisexual men using PrEP

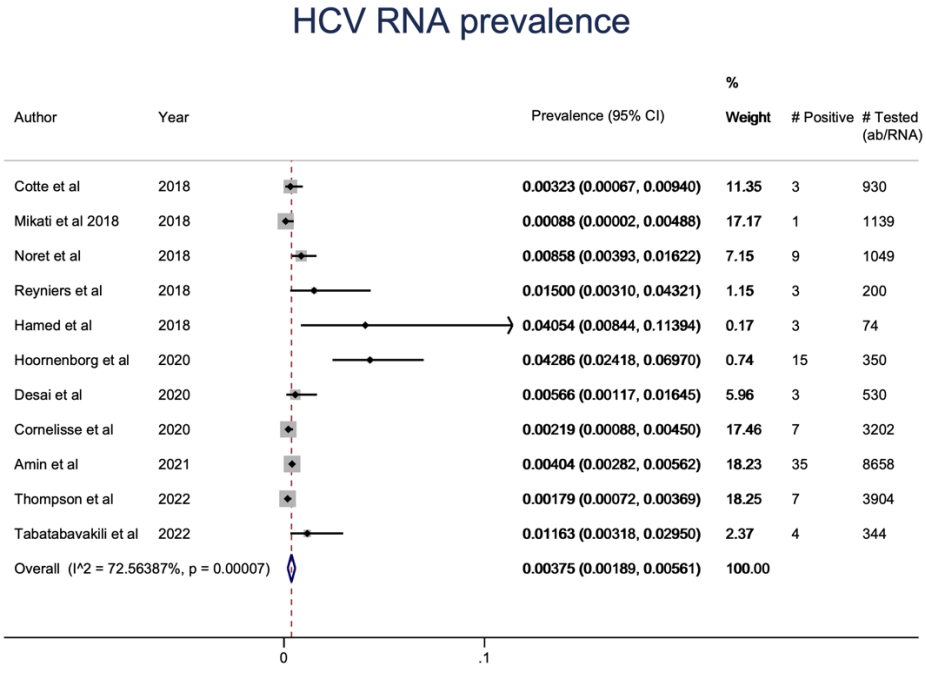

Figure 5.3. Forest plot of random-effects meta-analysis of HCV RNA prevalence at baseline among gay and bisexual men using PrEP

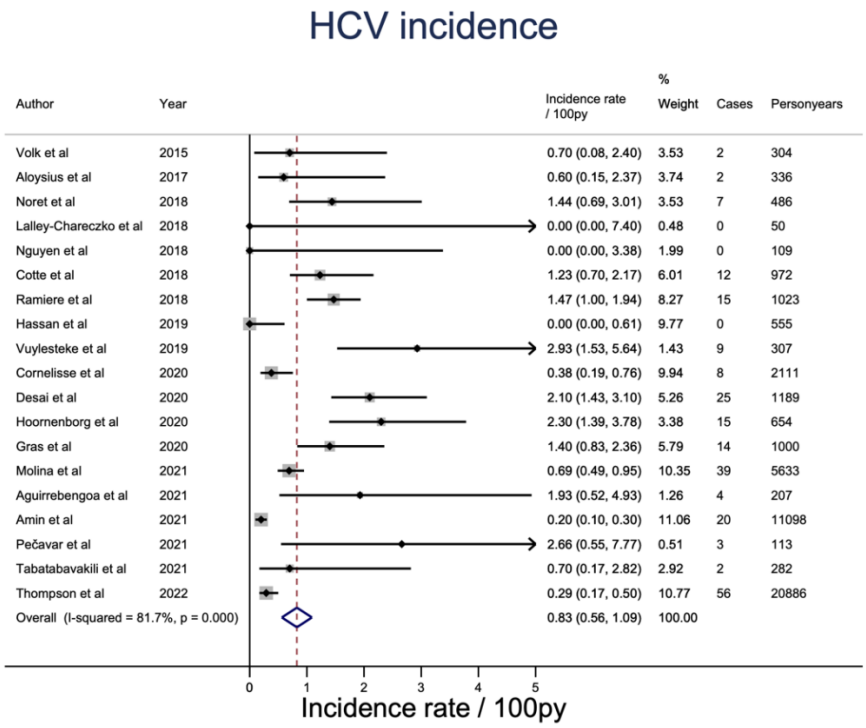

Figure 5.4. Forest plot of random-effects meta-analysis of HCV incidence during study follow-up among gay and bisexual men using PrEP

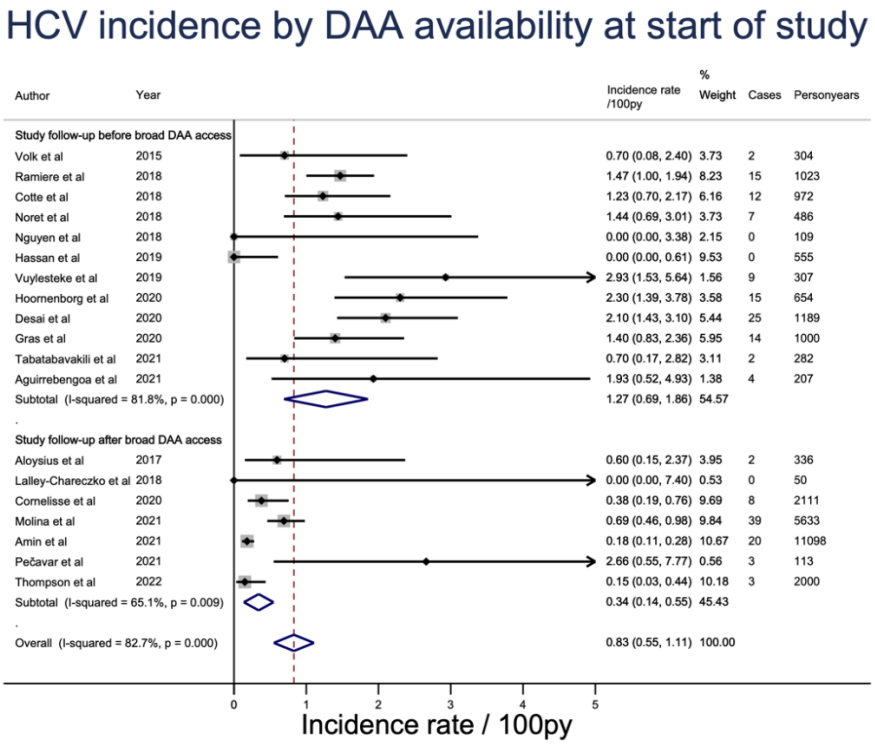

Figure 5.5: Forest plot of random-effects meta-analysis of HCV incidence among gay and bisexual men using PrEP by DAA availability in respective countries/jurisdiction at time of study initiation

Behavioural data

Heterogeneity in reporting of sexual and drug-related behaviours across studies precluded meta-analysis by hepatitis C risk behaviour. Appendix A3.3 (p245) summarises sexual and drug-use-related behaviours reported among study participants and, where reported in studies, behaviours associated with hepatitis C diagnosis. Studies reported different sexual behaviour indicators, including recent condomless intercourse, receptive/insertive condomless intercourse, number of casual partners, reporting HIV positive partners, group sex, sex at sex-on-premises venues and fisting. Many studies also reported recent and lifetime injecting drug use (IDU), as well as engagement in chemsex, for which definitions varied.

Baseline behaviours

Thirteen studies reported sexual and/or drug-use behaviours among all participants at baseline (appendix A3.3, p245). Recent condomless receptive anal intercourse at baseline was common among participants across studies. The proportion of participants reporting drug-use related behaviours at baseline varied across studies; history of lifetime IDU at baseline varied from less than 1% to 10% of participants, and in studies which reported it, recent chemsex prevalence varied from 2.7% to 54%, although recall periods also varied across studies. Among studies with baseline RNA prevalence above 4%, baseline behaviours were reported in only one. In the AMPrEP study (Hoornenborg et al)[180] 2.9% of participants reported IDU in the past three months at baseline, and 43% of participants reported chemsex in the 3 months prior to baseline, which was comparable to a number of other studies where chemsex in the past 3 months was between 40-60%.[310, 312, 313, 319] This study had the highest proportion of participants reporting sex with an HIV-positive partner at baseline (64%).

Behaviours associated with incident hepatitis C

In the IPERGAY Study in France (Gras et al)[313], authors compared baseline characteristics between participants diagnosed with a subsequent incident hepatitis C case during follow up. In this study, reporting chemsex at baseline was far more common in participants with incidence hepatitis C infection (57%) than in participants with no incidence hepatitis C infection (11%) ($P<0.001$). In this study, factors found to be associated with incident hepatitis C diagnosis were receptive fisting (25% among hepatitis C incident cases and 3% among non-cases $P<0.001$), median number of casual partners and sex acts at baseline; however there was no different in the proportion of participants reporting condomless receptive anal sex at baseline (92% in hepatitis C cases vs 85 in non-cases $p=0.70$).

The AMPrEP study (Hoornenborg et al),[180] which reported an incidence rate of 2.30/100py, compared sexual and drug-use related behaviours at follow-up between participants diagnosed with incident hepatitis C and participants not diagnosed incident hepatitis C (i.e. time-updated behavioural data collection, with behaviours reported at time of hepatitis C diagnosis reported for those with an incident hepatitis C diagnosis). In this study, IDU and sharing straws while snorting drugs were significantly associated with hepatitis C diagnosis, whereas sexual behaviours such as having an HIV-positive partner, sharing sex toys and fisting without gloves were not.

Two studies investigated the prevalence of injecting drug use only among participants with an incident hepatitis C diagnosis. These studies were large population-level demonstration studies in Australia, the EPIC-NSW study and the PrEPX study, recent methamphetamine use at baseline was reported by 13-20% of participants respectively, and in the PrEPX study 10% reported a lifetime history of IDU. However, of those with available data at time of hepatitis C diagnosis, only 27% (3/11 with a response) and 50% (4/8) reported IDU during follow-up in each study, respectively. In the PrEPX study, 88% (7/8) of participants with incidence hepatitis C reported group sex and 83% (5/6) reported attending a sex-on-premises venue.

Risk of bias

Fourteen of the 23 studies were considered at low risk of bias (score ≥ 7) when graded using a modified Newcastle Ottawa Scale for cohort studies (appendix A3.5, p 250). The main biases identified were representativeness of the cohort (i.e. smaller studies which recruited participants with specific risk criteria), confirmation of the outcome (i.e. where details of antibody / RNA testing protocols were not reported) and adequacy of follow up (i.e. where reported mean/median follow-up for incidence calculations was less than 6 months).

5.5 Discussion

In this review of hepatitis C among GBM using PrEP, we found high rates of heterogeneity across studies, both in relation to incidence and prevalence estimates, but also sexual and drug-use related behaviours of participants. Our pooled estimates for hepatitis C incidence among PrEP users were lower than previously reported in other meta-analyses,[305, 327] due largely to the inclusion of more recent and larger studies reporting lower rates of hepatitis C. Ours is the first review to explore the difference in hepatitis C incidence by respective country and state-level availability of hepatitis C DAA treatments at the time of PrEP initiation. Pooled hepatitis C baseline prevalence and incidence among PrEP studies which initiated follow-up after broad access to DAAs became available was lower than in studies which initiated follow-up during periods of limited or no DAA access. Hepatitis C incidence was also lower in non-European studies, and studies which enrolled large numbers of GBM and implemented PrEP at scale.

Heterogeneity in baseline hepatitis C prevalence across studies is likely reflective of both HCV prevalence within GBM populations at the time of study enrolment and risk-based enrolment criteria of specific studies. Further, individuals who elected to participate in early PrEP trials, or 'early adopters' of PrEP, likely represent individuals with a higher hepatitis C risk profile, including behavioural characteristics not necessarily included in study eligibility criteria. As with hepatitis C incidence, HCV RNA positivity was also lower in studies where DAAs were available at time of enrolment, and in larger studies and those undertaken outside of Europe. However, while RNA positivity and hepatitis C incidence were approximately 4-fold lower in post-DAA studies, HCV antibody positivity was only approximately 2.7-fold lower in post-DAA studies. This suggests that the enrolment of individuals with a lower risk profile (i.e. fewer individuals with previous HCV-exposure) may not fully explain the lower incidence observed in post-DAA studies. Lower incidence in post-DAA studies may reflect lower community-level hepatitis C viremia due to DAA implementation. Surveillance data from Australia suggest that uptake of DAA treatment among GBM co-infected with hepatitis C and HIV led to rapid declines in both community-level hepatitis C viremia and new diagnoses of hepatitis C.[173]

A number of previous reviews have explored hepatitis C among GBM. A systematic review and meta-analysis of PrEP studies reporting prevalence and incidence of sexually transmissible infections, including hepatitis C, included 4 studies which reported HCV prevalence and 8 studies which reported hepatitis C incidence up to November 2018.[305] In this meta-analysis, prevalence of HCV was 2.0%, and incidence was 0.43/100PY. Heterogeneity in incidence across studies was very high (P<0.001, i^2=87%), however sources of heterogeneity were not explored beyond country income

level. A more recent review (to October 2019) included studies that reported hepatitis C prevalence and incidence among all GBM (HIV-positive and HIV-negative). In this review, four studies reporting hepatitis C incidence among GBM using PrEP were included; the pooled estimate of 1.48/100PY among GBM using PrEP was similar to the hepatitis C incidence among studies of GBM living with HIV, suggesting hepatitis C risk among GBM enrolled in earlier PrEP studies that was comparable to GBM living with HIV.[304] Our review highlights that previous pooled estimates of hepatitis C incidence among GBM using PrEP may not be reflective of current hepatitis C among GBM using PrEP in all settings, in the context of later widespread access to PrEP, or in the post-DAA era.

We did not find any eligible studies of hepatitis C among GBM using PrEP in South-East Asia or Africa, two regions identified as having the highest pooled HCV prevalence in a previous review of studies of GBM (5.0% and 5.8% pooled prevalence in South-East Asia and Africa, respectively).[304] Another recent review restricted to studies in Asia reported a pooled HCV prevalence of 5.2% among HIV-negative GBM, with the highest prevalence detected in studies from Indonesia and Vietnam.[328] While PrEP programmes, clinical trials or demonstration projects have been implemented in 10 countries in Asia and more than 18 countries in Africa,[329] the lack of available data on hepatitis C incidence among PrEP users may hinder appropriate responses and informed testing guidelines for hepatitis C among PrEP users in these regions.

While PrEP users may represent a subgroup of HIV-negative individuals who report higher rates of behaviour associated with hepatitis C risk, PrEP users remain highly engaged in clinical care and testing. Given declining trends in hepatitis C among GBM in countries where DAAs are widely accessible, the impact of PrEP roll-out and associated changes in behaviour and sexual networks on hepatitis C elimination efforts may be offset by coinciding DAA availability in these countries. Consistent with findings previously reported for other sexually transmitted infections,[165] modelling outcomes suggest that a decline in hepatitis C could be seen among GBM in the context of PrEP scale-up via increased rates of HCV screening and treatment, even with moderate to high levels of risk compensation associated with PrEP (i.e. declines in condom use).[302] However, as PrEP continues to be implemented, and people transition in and out of PrEP care, there remains a need to monitor for hepatitis C infection. Further, in settings where DAAs have not been widely rolled out yet or are not subsidised, high prevalence of hepatitis C among HIV-positive individuals may contribute to growing transmission among PrEP users through increased rates of sero-different sex.

While current international WHO guidelines recommend hepatitis C testing among key populations, including GBM, and periodic retesting for hepatitis C among HIV-positive GBM, guidelines on how often HIV-negative GBM, including PrEP users, should be tested for hepatitis C vary

internationally.[330, 331] Australian guidelines recommend testing annually for hepatitis C for all GBM using PrEP or living with HIV, regardless of the presence of drug or sexual-related risk behaviour.[332] Previous findings from Australian PrEP studies show that PrEP users are not homogenous in terms of STI risk,[333] and this review suggests that PrEP use alone may not be strong indicator of hepatitis C risk. Where testing constraints exist, testing guidelines should be centred on the presence of specific risk factors which remain strong indicators of hepatitis C risk, and be informed by local epidemiological contexts. In an Australian PrEP study, only 3 of 8 reported cases were attributable to injecting drug use, with the remaining cases classified as probable sexual transmission. Each of these 5 cases of probable sexual transmission reported condomless receptive anal sex during group sex or at sex-on-premises venues.[311] However, it should be acknowledged that the efficiency of risk-based screening is dependent on clinicians being able to accurately identify risk, which may not be feasible during limited clinical interactions with competing priorities. Hepatitis C antibody testing is relatively cheap, and in countries with developed models of care can be easily added to routine PrEP monitoring tests. In such settings, universal screening of PrEP users is likely to be cost-effective. Hepatitis C self-testing may offer an additional method for increasing screening during periods of risk for PrEP users.[334]

Limitations

There are several limitations of our review which should be acknowledged. First, heterogeneity in reported sexual and drug use behaviours precluded a subgroup analysis disaggregated by prevalence of HCV-related risk factors. While some studies reported behaviours associated with hepatitis C diagnosis, many reported behaviours at baseline, which may not reflect behaviours associated with hepatitis C acquisition during periods of PrEP use. Second, not all studies reported adherence to PrEP and we cannot be sure that all individuals included in pooled estimates were current PrEP users. Third, while we used date of DAA availability extracted from the published literature and national policy documents, it is likely that in some settings DAAs were accessible through clinical trials or special access programs. Further, some of the included PrEP studies spanned long periods of time, and we were not able to disaggregate hepatitis C incidence rates by year for studies with longer follow up periods. This may impact on the validity of our subgroup analysis by DAA availability. Finally, testing protocols in studies differed, and many studies did not report testing frequency. Studies with more frequent testing may be more likely to capture infections which may have spontaneously cleared in the context of less frequent screening. We were unable to account for this in our meta-analysis.

5.6 Conclusions

Early reports of high hepatitis C incidence among cohorts of PrEP users likely reflect specific risk-based eligibility criteria of smaller PrEP studies, which enrolled participants at a time when hepatitis C DAA treatment had not been fully scaled-up. More recent studies in settings where both DAAs and PrEP have been implemented at-scale report lower hepatitis C incidence among PrEP users. PrEP-specific HCV testing guidelines should be guided by local epidemiological contexts and consider the cost-effectiveness of universal HCV screening among PrEP users at a time when HCV prevalence among PrEP users is declining.

Chapter 6

Latent class analysis of sexual behaviours and attitudes towards STI prevention among gay and bisexual men using PrEP

My earlier work on STIs among participants in the PrEPX Study (see appendix C1, p 320), and the findings generated in Chapters 3 & 4, showed that while PrEP users are at increased risk of bacterial STIs in Australia, diagnoses are highly skewed, and rates of reinfection are high. As discussed in Chapter 1, the willingness to use different interventions to prevent STIs among GBM will likely vary depending on acceptability, perceived risk and how the intervention impacts behaviour and pleasure. In this study, I linked survey data from participants of the PrEPX Study to their clinical and pathology data collected through the ACCESS surveillance system. This survey data captured a range of behavioural, sociodemographic and attitudinal data from PrEP users in Victoria, South Australia and Tasmania. Using latent class analysis, I identify four key groups of GBM using PrEP classified according to their different attitudes towards STIs and STI prevention, and explore associations between behaviours and attitudes with STI risk across each class. This analysis improves understanding of important differences among GBM using PrEP and has salient implications for applying the epidemiological findings from Chapters 3 & 4 to public health interventions targeted towards specific groups of GBM PrEP users.

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This chapter is included in the original ***AIDS & Behavior*** format in Appendix B2 (p 282)

Chapter 6

Latent Class Analysis of Sexual Behaviours and Attitudes to Sexually Transmitted Infections among Gay and Bisexual Men using PrEP

Authors

Michael W Traeger[1,2], Dean Murphy[3,4], Kathleen E. Ryan[1,4], Jason Asselin[1], Vincent J. Cornelisse[3,4,5], Anna L Wilkinson[1,2], Margaret E. Hellard[1,4,6], Edwina J. Wright[1,4,6], Mark A. Stoové[1,2,7]

Author affiliations

1. Burnet Institute, Melbourne, Victoria, Australia
2. School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
3. The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia
4. Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia
5. Kirketon Road Centre, NSW Health, Sydney, New South Wales, Australia
6. Peter Doherty Institute, University of Melbourne, Melbourne, Victoria, Australia
7. School of Psychology and Public Health, La Trobe University, Melbourne, Victoria, Australia

6.1 Abstract

Gay and bisexual men (GBM) who use PrEP are at increased risk of sexually transmitted infections (STIs) compared to those who don't use PrEP. Since the implementation of PrEP in Australia, it is possible that attitudes towards STIs have shifted in line with changes in risk and transmission dynamics in the context of increased screening. As the extent to which GBM utilise STI prevention strategies likely depends on their attitudes towards STIs and STI prevention, the aims of this study were to use latent class analysis to classify GBM using PrEP on the basis of their attitudes towards STIs and reported risk behaviours, and examine how these categorisations relate to risk of STI acquisition. 1,225 GBM who were previously enrolled in a PrEP implementation study (The PrEPX Study) completed a survey focused on sexual behaviours and attitudes towards STIs one year post-study follow-up. Data on chlamydia, gonorrhoea and syphilis testing and positivity were available through a sentinel network of participating study clinics. Using latent class analysis, participants were allocated into four classes; Class 1, "Some concern and lowest risk"; Class 2, "Low concern and lower risk"; Class 3, " High concern and higher risk"; and Class 4, "Low concern and highest risk". The majority (78%) of participants were classified into Class 3 or Class 4, two groups which were distinguished by highly disparate attitudes towards STIs but with a similar proportion of participants diagnosed with a bacterial STI in the last 12 months (48% and 57%, respectively). Findings suggest that attitudes towards STIs among GBM using PrEP in Australia vary considerably, and this will likely influence their receptivity to different STI prevention strategies.

6.2 Introduction

In Australia, gay and bisexual men (GBM) are overrepresented in diagnoses of sexually transmitted infections (STIs), including gonorrhoea, chlamydia and syphilis.[121] Decades-long trends of increasing STI incidence among Australian GBM[120, 121] have coincided with steady declines in consistent condom use,[335] and in recent years this decline has accelerated in association with the rapid uptake of HIV pre-exposure prophylaxis (PrEP)[151]. Between June 2016 and April 2018, more than 20,000 Australian GBM accessed PrEP through implementation studies.[66, 97] Since the closure of these PrEP studies following PrEP becoming available through government subsidy on Australia's pharmaceutical benefits scheme (PBS) in April 2018,[336] more than 37,000 individuals have accessed PrEP via the PBS.[337] A previous analysis of a large cohort of GBM accessing PrEP via the PrEPX Study in Victoria, Australia found that STI incidence increased by 21% following PrEP initiation among those starting PrEP for the first time, and was high during PrEP use. Findings also highlighted that a relatively small

proportion of PrEP users, among whom repeat infections were common, carried most of the burden of STI diagnoses.[67]

The extent to which GBM utilise STI prevention strategies, and their preferences for different strategies, likely depends on their behaviour and perceived level of STI risk, as well as their attitudes towards STIs and STI prevention in general. Previous qualitative research has highlighted a degree of anxiety towards STIs among some GBM, with reports of experiencing stigma associated with STI infection common.[338] Research exploring attitudes towards STIs and STI prevention among Australian GBM found that, while most GBM were not overly concerned with being diagnosed with STIs, some reported feelings of shame, embarrassment and annoyance towards STIs.[339] A more recent study found that while the majority of participants described STIs as easy to manage and a natural part of sexual health, some still considered STIs a serious health issue, including having concerns around antimicrobial resistance.[340] These findings suggest that GBM are not homogenous in their attitudes towards and perceptions of STIs. Gay and bisexual men who use PrEP are at increased risk of STIs compared to those who don't use PrEP,[160, 162, 305] and since the implementation of PrEP it is possible that attitudes towards STIs have shifted in line with changes in risk and transmission networks and the frequency with which STIs are acquired, diagnosed, and treated in the context of more frequent testing when attending clinics for PrEP prescribing.

Characterising and identifying people at various levels of risk for acquiring STIs can help inform targeted prevention or the development of screening and testing guidelines. Latent class analysis (LCA) is a statistical method commonly used to identify subgroups of individuals based on specific response patterns across multiple variables. Latent class analysis has been widely applied to data collected from GBM to identify GBM suitable for PrEP[341] and understand perceived barriers to PrEP uptake;[342] identify GBM at increased risk for STIs;[343] describe and categorise attitudes and perceptions towards biomedical HIV prevention[145] and the utilisation of different combination HIV prevention strategies;[344] identify behaviours associated with HIV risk;[345] and to explore associations between sexualised drug use behaviour and STI risk.[346]

To our knowledge, no published research has utilised LCA to classify GBM according to their attitudes towards STIs and sexual behaviours, and explore associations with corresponding STI risk. Understanding how attitudes towards STIs vary among GBM using PrEP, and their potential influence on prevention strategies and behaviours, will help in the development and implementation of appropriately targeted interventions to reduce STI transmission. The aims of this study were to classify GBM who use PrEP on the basis of their attitudes towards STIs and their reported risk behaviours, and examine how these categorisations relate to risk of acquiring an STI.

6.3 Methods

Data were drawn from the Pre-exposure Prophylaxis Expanded (PrEPX) Study, a multisite, open-label PrEP implementation study. The PrEPX Study has been described in detail elsewhere.[66, 67] The PrEPX study enrolled participants from three Australian states, with enrolments commencing in July 2016 in Victoria, May 2017 in South Australia and in September 2017 in Tasmania. Participants were dispensed PrEP every three months until study closure (1st April 2018 in Victoria and 30th June 2018 in South Australia and Tasmania). PrEPX participants completed a clinician-guided survey at enrolment and were scheduled to return to study clinics every three months to receive a prescription for PrEP and undergo comprehensive STI screening.

A total of 5,113 participants were enrolled in the PrEPX study across Victoria (n=4,275), South Australia (n=656) and Tasmania (n=182). All PrEPX participants were invited to complete an online survey in March 2019, approximately one year after PrEPX study visits ceased. In total, 1,469 participants (28.9% of all participants) completed the follow-up survey, of which 1,458 (99.3%) identified as non-heterosexual men (gay, bisexual or 'other' sexuality). For this analysis, we included the 1,225 (84.0%) participants who reported they were still using PrEP at the time of one-year follow-up survey completion. Included participants completed the survey between 19th March and 20th June 2019.

Enrolment and follow-up survey data were collected and managed using REDCap electronic data capture tools hosted at the Burnet Institute.[347] The online follow-up survey asked a range of behavioural, demographic, and attitudinal questions derived from a previous sexual health survey of young people.[348] Participants were asked about condom use, partner numbers, sexual positioning, frequency of drug use before or during sex including alcohol, methamphetamine, GHB, ecstasy, amyl/poppers, marijuana, speed and cocaine, whether participants had ever injected drugs and frequency of injecting drug use. Participants were also asked about how often they had discussed STI testing with partners before having sex (never, some of the time, about half of the time, most of the time, always).

Participants also answered eight items on attitudes towards STIs on a 5-point Likert scale. The questions and available responses are below:

1. I worry about getting an STI
2. Getting an STI is something I think about often
3. Getting an STI could seriously affect my health
4. Getting an STI is no big deal
5. I feel I am unlikely to get an STI

6. I can't picture myself getting an STI

1-Strongly disagree, 2-Disagree, 3-Neither Agree nor Disagree, 4-Agree, 5-Strongly Agree.

7. How important is it to you that you avoid STIs?
8. How important is it to you that you avoid passing on STIs to your sexual partners?

1-Very unimportant, 2-Somewhat unimportant, 3-Neither important or unimportant, 4-Somewhat important, 5-Very important

Statistical analyses

To explore potential for responder bias in the post-study follow-up survey, we compared baseline characteristics from enrolment surveys between those who completed the follow-up survey and were included in this analysis and those who did not using two-sided test of proportions for dichotomous variables and t-test for continuous variables.

Variables considered for LCA

Variables included in the LCA included participant age in years (continuous), condom use with casual partners, number of casual partners (categorised into 0, 1-5, 6-10, 11-20, 21-50, >50; to achieve an approximate even distribution of responses), reporting a regular sex partner (yes/no), sexual position during sex (insertive only, receptive only, both insertive and receptive), chemsex drug use defined as the use of methamphetamine or GHB (with or without other drugs)[349-351] during or before sex (yes/no), discussing STI testing with casual partners and the eight STI attitudinal items dichotomised into agree ('strongly agree' or 'somewhat agree') or not ('neither agree nor disagree', 'somewhat disagree' or 'strongly disagree'). Attitudinal items were included as dichotomous variables to both improve model fit and aid in interpretability; proportion in agreement with each attitude was deemed meaningful in assessing differences in attitudes across classes. Recall period for behavioural variables was last six months.

Latent Class Model

We assessed model fit based on models with between two and eight classes, and used Akaike information criterion (AIC), Bayesian information criterion (BIC), and model entropy,[352] as well as interpretability, to assess the ideal number of classes. The minimum allowed class size was restricted to 5% of the sample. In order to ensure that maximum likelihood estimation converged on a global and not a local maximum, for each model under consideration, we reran the model 100 times with random starting points. For each draw of random starting points, each individual was randomly allocated to a class and an expectation maximization (EM) algorithm was used to select the starting

class values which resulted in the highest log likelihood value after 100 EM iterations. We assumed convergence on a global maximum likelihood if at least 40% of solutions yielded the maximum value of the likelihood function.[353] Individuals were allocated to the class in which they had the highest posterior probability of class membership and average class probability was calculated for each class.

Once the ideal number of classes based on model fit and entropy was determined, we assessed whether the assumption of conditional independence was met in the final model by exploring correlation between included variables within classes. We conducted a conditional analysis by calculating Pearson's correlation coefficient for all variables within each class, with a correlation of 0.5 or greater within one or more classes indicating violation of the assumption of independence. During this process, we observed a high correlation between attitudinal items 7 (How important is it to you that you avoid STIs?) and 8 (How important is it to you that you avoid passing on STIs to your sexual partners?) within three classes. As such, item 8 was removed and the process of running the series of models with 2-8 classes was repeated. We also assessed each class qualitatively to see if any classes were similar across multiple variables. In most model permutations, the mean age of participants was very similar across each class (each within 2 years of the cohort mean), so age was removed from the model.

We report LCA results as class prevalence rates for each classification variable, i.e. distribution of responses across individuals in their respective allocated class. All statistical analyses were conducted in Stata version 15 (StataCorp) and latent class models were run using the gsem command[354].

STI positivity

Participants who enrolled in the PrEPX study were monitored for STIs using linked data extracted from study clinics which were also participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood Borne Viruses and Sexually Transmissible Infections (ACCESS).[243] ACCESS uses specialised data extraction software installed behind patient management software at participating sexual health and general practice clinics to extract de-identified patient data[250]. For the purposes of the PrEPX study, participants consented to having their STI testing data extracted via ACCESS and linked to their study data.

To explore how LCA classes related to risk of acquiring an STI, we calculated the proportion of participants with an available STI test result who tested positive for chlamydia, gonorrhoea and newly identified infectious (primary, secondary or early latent [<2 years]) syphilis within each class.

Test positivity was determined for any clinic visit in the 12-month period prior to date of survey completion and at their last clinic visit prior to completing the survey. To explore potential for selection bias associated with presenting for STI testing at ACCESS clinics, we compared characteristics between those with and without STI testing data available. Log-binomial regression was used to calculate prevalence ratios between each class of having a positive STI result within the past 12 for each STI outcome.

6.4 Results

Participant characteristics and survey responses

Among the 1,225 participants included in analyses, the mean age was 42.1 years and 94% identified as gay **(Table 6.1)**. The distributions of participant responses to the eight STI attitudinal questions are shown in **Table 6.2**.

Based on enrolment survey responses, compared to PrEPX participants not included in the analysis, those included were older at enrolment (mean age, 39.7 years compared to 35.0 years; p<0.001), less likely to have reported methamphetamine use in the three months prior to PrEPX study enrolment (9.1% compared to 12.4%; P=0.001), more likely to have used PrEP prior to enrolment (30.7% compared to 22.1%; P<0.001), and less likely to be report injecting drug use at enrolment (3.1% comparted to 4.9%; P=0.009). There was no difference between those included and not included in analyses on other enrolment survey responses, including reporting condomless receptive anal sex with a casual partner, reporting an STI diagnosis prior to enrolment, or reporting more than one episode of insertive condomless anal sex with a casual partner, in the three months prior to enrolment.

Latent class model

In addition to removing participant age from consideration in the LCA (see Methods section), item 8 (How important is it to you that you avoid passing on STIs to your sexual partners?) was removed due to high correlation with item 7 (How important is it to you that you avoid STIs?) within three classes (Pearson's correlation coefficient = 0.59, 0.64, and 0.69). Item 7 was retained over item 8 as it was deemed more relevant to the participant's attitudes towards avoiding STIs. In the final model specification, entropy was greatest in a model with three classes (0.74), AIC was lowest in a model with eight classes (22284.7) and BIC was lowest a model with four classes (22944.8) **(Table 6.3)**.

Table 6.1. Characteristics of PrEPX participants included in the latent class analysis at follow-up survey

	n (N=1,225)	%
Age, years (mean, sd)	42.1 (11.1)	
Sexual Identity		
Gay	1153	94.1
Bisexual	64	5.2
Other	8	0.7
Ever injected drugs		
No	1,111	90.7
Yes	108	8.8
Prefer not to answer	6	0.5
Has regular partner	595	48.6
Number of casual partners in the last 6 months		
0	115	9.39
1-5	301	24.6
6-10	233	19.0
11-20	258	21.1
21-50	233	19.0
More than 50	85	6.9
Condom use with casual partners in the last 6 months[#]		
Never	437	39.4
Some of the time	451	40.6
About half the time	97	8.7
Most of the time	77	6.9
All of the time	33	3.0
No response	15	1.4
Drug use before or during sex in the last 6 months		
Methamphetamine	196	16.0
GHB	162	13.2
Alcohol	930	75.9
Ecstasy	209	17.1
Popper/amyl	878	71.7
Marijuana	274	22.4
Cocaine	185	15.1
Ketamine	101	8.2
Speed	56	4.6
Sexual positioning with casual partners in the last 6 months[#]		
Insertive / 'top' only	220	19.8%
Receptive / 'bottom' only	169	15.2%
Both insertive and receptive	708	63.8%
No response	13	1.2%
In the last 6 months, how often did you discuss STI testing with a casual partner?		
Never	296	24.2
Some of the time	439	35.8
About half of the time	151	12.3
Most of the time	215	17.6
Always	124	10.1

#Among those who reported a casual partner in the last 6 months (n=1110)

Table 6.2. Participant responses to attitudinal questions in PrEPX follow-up survey

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
	n (%)	n (%)	n (%)	n (%)	n (%)
Getting an STI could seriously affect my health	47 (3.8)	117 (9.6)	157 (12.8)	518 (42.3)	386 (31.5)
Getting an STI is no big deal	244 (19.9)	338 (27.6)	225 (18.4)	338 (27.6)	80 (6.5)
I feel I am unlikely to get an STI	236 (19.3)	478 (39)	319 (26)	145 (11.8)	47 (3.8)
I can't picture myself getting an STI	481 (39.3)	420 (34.3)	206 (16.8)	82 (6.7)	36 (2.9)
I worry about getting an STI	91 (7.4)	186 (15.2)	260 (21.2)	490 (40)	198 (16.2)
Getting an STI is something I think about often	135 (11)	272 (22.2)	340 (27.8)	344 (28.1)	134 (10.9)
	Very unimportant	**Somewhat unimportant**	**Neither important or unimportant**	**Somewhat important**	**Very important**
How important is it to you that you avoid STIs?	38 (3.1)	57 (4.7)	99 (8.1)	537 (43.8)	494 (40.3)
How important is it to you that you avoid passing on STIs to your partners?	49 (4)	18 (1.5)	30 (2.5)	294 (24)	834 (68.1)

Table 6.3: Model goodness of fit measures for latent class models with 2 to 8 classes.

Classes	AIC	BIC	Entropy
2	23272.3	23512.6	0.68
3	22643.8	23001.6	0.74
4	**22510.4**	**22944.8**	**0.62**
5	22420.6	22967.5	0.46
6	22345.7	23005.0	0.28
7	22317.5	23073.9	0.26
8	22284.7	23158.6	0.39

As entropy was 0.62 in the 4-class model and decreased substantially with increasing classes thereafter, a model with four classes was selected and inspected for interpretability and conditional independence. Response patterns across classes were deemed reasonable and classes made interpretative sense in relation to distinguishing common attitudes across classes. The model satisfied the assumption of conditional independence (no correlation between variables within a class of greater than 0.5) and so a model with four classes was chosen for the final model. In the final model, the average posterior probabilities for class membership were 99% for Class 1, 81% for Class 2, 89% for Class 3 and 89% for Class 4.

Table 6.4 shows the distribution of variables included in the LCA across participants according to their allocated class. The latent class model revealed two smaller classes, Class 1 (9% of participants) and Class 2 (13%), and two larger classes, Class 3 (44%), Class 4 (35%). The four classes exhibited varying combinations of behaviours and perceived risk and concerns regarding STIs.

Class 1 – 'Some concern and lowest risk'

GBM classified as belonging in Class 1 were most likely to report having a regular partner and the majority reported no casual partners in the past 6 months. Despite fewer reporting casual partners, GBM in Class 1 reported some concerns about STIs, indicating moderate levels of agreement for the item 'I worry about STIs' and the vast majority agreeing that 'STIs could seriously affect my health'.

Class 2 –'Low concern and lower risk'

GBM in Class 2 reported fewer casual partners than Classes 3 and 4, reported the highest proportion of insertive sex only with casual partners and the lowest level of chemsex drug use, but the proportion reporting never using condoms with casual partners was similar to Class 4. While some GBM in Class 2 still agreed they 'worry about STIs' and a large majority agreed that 'getting an STI could seriously affect their health' and wanted to avoid STIs, they had the lowest agreement with the item 'getting an STI is something I think about often'.

Class 3 – 'High concern and higher risk'

Almost all of the GBM in Class 3 reported they 'worry about getting an STI', and GBM in Class 3 had the highest agreement with 'getting an STI is something I think about often' and 'avoiding STIs is somewhat or very important'. A high proportion also agreed with the statement 'STIs could seriously affect my health'. GBM in Class 3 had more partners than those in Class 2, but fewer than in Class 4, and a moderate level of condom use. GBM in Class 3 were most likely to report discussing STIs with their casual partners most or all of the time in the past 6 months (35.4%).

Class 4 – 'Low concern and highest risk'

GBM classified as belonging to Class 4 were least likely to agree they 'worry about STIs' or that they were concerned about avoiding STIs. GBM in Class 4 also reported the lowest agreement rate for the items; 'getting an STI could seriously affect my health', ' I feel I am unlikely to get an STI', and 'I can't picture myself getting an STI'. GBM in Class 4 reported higher numbers of casual partners than those in Classes 1-3, the lowest level of condom use, and more commonly reported both insertive and receptive sex with casual partners and chemsex drug use. GBM in Class 4 were least likely to report discussing STIs with their casual partners most or all of the time in the past 6 months (15.1%).

STI positivity

A total of 957 participants (78% of those in the latent class model) were linked to a test result for chlamydia, gonorrhoea or syphilis at an ACCESS clinic in the 12 months prior to completing the survey **(Table 6.5)**. Of these, 45.8% had at least one positive syphilis, chlamydia or gonorrhoea result in this period. The proportion of those with a test result who had any positive STI diagnosis in the 12 months prior to survey completion was 18.8% in Class 1, 24.1% in Class 2, 48.2% in Class 3 and 56.7% in Class 4 **(Figure 6.1)**. At their most recent STI test (occurring a median of 53 days prior to survey completion), positivity for any STI was 2.4% in Class 1, 3.6% in Class 2, 14.8% in Class 3 and 23.0% in Class 4 **(Figure 6.2)**.

There was a significant difference in the prevalence of any STI in the past 12 months between each of the classes, except for between Class 2 and Class 1 (PR=1.28 [95% CI=0.74 – 2.22]). The greatest difference in prevalence of any STI in the past 12 months was between Class 4 and Class 1 (PR=3.01 [95% CI=1.92– 4.73]). Between the two higher-risk classes (Classes 3 and 4), prevalence of any STI in the past 12 months was greater in Class 4 (PR=1.18 [95% CI=1.02 – 1.36]), with the largest relative increase between Class 4 and Class 3 observed for rectal infections (PR=1.29 [95% CI=1.07– 1.56]). **(Table 6.6)**.

Table 6.4: Distribution of characteristics, behaviours and responses to attitudinal survey items according to class membership among PrEPX participants included in the latent class analysis

	Class 1	Class 2	Class 3	Class 4
	N (%)	N (%)	N (%)	N (%)
Total	114 (9.3)	158 (12.9)	537 (43.8)	416 (34.0)
Mean age, years *	41.4	43.0	42.4	41.5
Number of casual partners in last 6 months				
0	107 (93.9)	0 (0)	3 (0.6)	5 (1.2)
1-5	5 (4.4)	108 (68.4)	159 (29.6)	29 (7)
6-10	2 (1.8)	41 (26)	122 (22.7)	68 (16.4)
11-20	0 (0)	5 (3.2)	131 (24.4)	122 (29.3)
21-50	0 (0)	2 (1.3)	100 (18.6)	131 (31.5)
>50	0 (0)	2 (1.3)	22 (4.1)	61 (14.7)
Mean casual partner number in last 6 months*	0.1	8.9	17.9	32.8
Median casual partner number in last 6 months*	0.0	4.0	10.0	20.0
Condom use with casual partners in last 6 months				
No casual partners / no response	107 (93.9)	12 (7.6)	6 (1.1)	5 (1.2)
Always	5 (4.4)	7 (4.4)	21 (3.9)	0 (0)
Most of the time	0 (0)	10 (6.3)	59 (11)	8 (1.9)
About half the time	0 (0)	24 (15.2)	60 (11.2)	13 (3.1)
Some of the time	0 (0)	32 (20.3)	234 (43.6)	185 (44.5)
Never	2 (1.8)	73 (46.2)	157 (29.2)	205 (49.3)
Ever injected drugs	5 (4.5)	1 (0.6)	39 (7.3)	63 (15.2)
Chemsex drugs^ before or during sex in the last 6 months	15 (13.2)	3 (1.9)	101 (18.8)	124 (29.8)
Has regular partner	79 (69.3)	69 (43.7)	267 (49.7)	180 (43.3)
Sexual position				
No casual partners / no response	108 (94.7)	10 (6.3)	5 (0.9)	5 (1.2)
Insertive only	0 (0)	67 (42.4)	105 (19.6)	48 (11.5)
Receptive only	2 (1.8)	31 (19.6)	99 (18.4)	37 (8.9)
Both insertive and receptive	4 (3.5)	50 (31.6)	328 (61.1)	326 (78.4)
I worry about getting an STI				
n (agree or strongly agree)	57 (50.0)	58 (36.7)	522 (97.2)	51 (12.3)
Getting an STI is something I think about often				
n (agree or strongly agree)	36 (31.6)	10 (6.3)	393 (73.2)	39 (9.4)
Getting an STI could seriously affect my health				
n (agree or strongly agree)	99 (86.8)	131 (82.9)	461 (85.9)	213 (51.2)
Getting an STI is no big deal				
n (agree or strongly agree)	26 (22.8)	40 (25.3)	112 (20.9)	240 (57.7)
I feel I am unlikely to get an STI				
n (agree or strongly agree)	38 (33.3)	60 (38.0)	58 (10.8)	36 (8.7)
I can't picture myself getting an STI				
n (agree or strongly agree)	23 (20.2)	32 (20.3)	49 (9.1)	14 (3.4)
How important is it to you that you avoid STIs?				
n (important or very important)	107 (93.9)	140 (88.6)	518 (96.5)	266 (63.9)
In the last 6 months, how often did you discuss STI testing with a partner?				
n (most of the time or all the time)	33 (29.0)	53 (33.5)	190 (35.4)	63 (15.1)

*Indicates variables that were not included in the latent class model, but which are reported here for each class.
^Defined as use of either methamphetamine or GHB

Table 6.5: Proportion of participants with a linked test result in ACCESS within 12 months prior to survey completion and proportion positive by class membership

	Class 1	Class 2	Class 3	Class 4	Total
n in class (% of total sample)	114 (9.3)	158 (12.9)	537 (43.8)	416 (34.0)	1,225 (100)
Number with test present in ACCESS in last 12m (% of class)					
Any STI test (gonorrhoea, syphilis or chlamydia)	85 (74.6)	112 (70.9)	425 (79.1)	335 (80.5)	957 (78.1)
Gonorrhoea or chlamydia test	85 (74.6)	111 (70.3)	424 (79.0)	334 (80.3)	954 (77.9)
Gonorrhoea test	85 (74.6)	111 (70.3)	424 (79.0)	334 (80.3)	954 (77.9)
Chlamydia test	85 (74.6)	111 (70.3)	424 (7.09)	334 (80.3)	954 (77.9)
Rectal NG or CT test	83 (72.8)	108 (68.4)	421 (78.4)	332 (79.8)	944 (77.1)
Urethral NG or CT test	85 (74.6)	111 (70.3)	422 (78.6)	333 (80.0)	951 (77.6)
Pharyngeal NG or CT test	85 (74.6)	111 (70.3)	422 (78.6)	334 (80.3)	952 (77.7)
Syphilis	81 (71.1)	100 (63.3)	401 (74.7)	321 (77.2)	903 (73.7)
Any positive result in the last 12 months (% of tested)					
Any STI (gonorrhoea, syphilis or chlamydia)	16 (18.8)	27 (24.1)	205 (48.2)	190 (56.7)	438 (45.8)
Gonorrhoea or chlamydia	16 (18.8)	26 (23.4)	197 (46.5)	180 (53.9)	416 (43.6)
Gonorrhoea	6 (7.1)	11 (9.9)	113 (26.7)	98 (29.3)	227 (23.8)
Chlamydia	12 (14.1)	16 (14.4)	142 (33.5)	133 (39.8)	303 (31.8)
Rectal (NG or CT)	14 (16.9)	17 (15.7)	136 (32.3)	138 (41.6)	305 (32.3)
Urethral (NG or CT)	8 (9.4)	13 (11.7)	80 (19.0)	68 (20.4)	169 (17.8)
Pharyngeal (NG or CT)	5 (5.9)	9 (8.1)	81 (19.2)	76 (22.8)	171 (18.0)
Syphilis	2 (2.5)	3 (3.0)	33 (8.2)	38 (11.8)	76 (8.4)
Positive result at the most recent test within 12m (% of tested)					
Any STI (gonorrhoea, syphilis or chlamydia)	2 (2.4)	4 (3.6)	63 (14.8)	77 (23.0)	146 (15.3)
Gonorrhoea or chlamydia	1 (1.2)	3 (2.7)	58 (13.7)	67 (20.1)	128 (13.4)
Gonorrhoea	0 (0)	2 (1.8)	25 (5.9)	27 (8.1)	54 (5.7)
Chlamydia	1 (1.2)	2 (1.8)	37 (8.7)	44 (13.2)	84 (8.8)
Rectal (NG or CT)	1 (1.2)	3 (2.8)	43 (10.2)	46 (13.9)	93 (9.9)
Urethral (NG or CT)	2 (2.4)	1 (0.9)	22 (5.2)	24 (7.2)	49 (5.2)
Pharyngeal (NG or CT)	1 (1.2)	1 (0.9)	18 (4.3)	19 (5.7)	39 (4.1)
Syphilis	1 (1.2)	1 (1.0)	6 (1.5)	16 (5.0)	24 (2.7)

Table 6.6: Prevalence ratios for STI diagnosis in the past 12 months between classes

	Class 2 compared to Class 1		Class 3 compared to Class 1		Class 4 compared to Class 1		Class 3 compared to Class 2		Class 4 compared to Class 2		Class 4 compared to Class 3	
	PR (95% CI)	p-value	PR (95% CI)	p-value	PR (95% CI)	p-value	PR (95% CI)	p-value	PR (95% CI)	p-value	PR (95% CI)	p-value
Any STI	1.28 (0.74-2.22)	0.378	2.56 (1.63-4.03)	<0.001	3.01 (1.92-4.73)	<0.001	2.00 (1.42-2.82)	<0.001	2.35 (1.67-3.31)	<0.001	1.18 (1.03-1.35)	0.019
GC or CT	1.24 (0.71-2.17)	0.440	2.43 (1.54-3.83)	<0.001	2.86 (1.82-4.50)	<0.001	1.95 (1.37-2.78)	<0.001	2.30 (1.62-3.27)	<0.001	1.18 (1.02-1.36)	0.025
GC	1.15 (0.54-2.43)	0.717	2.29 (1.25-4.18)	0.007	2.37 (1.29-4.34)	0.005	1.99 (1.21-3.27)	0.007	2.06 (1.25-3.40)	0.005	1.04 (0.82-1.31)	0.769
CT	1.12 (0.59-2.14)	0.733	2.33 (1.39-3.90)	0.001	2.76 (1.65-4.62)	<0.001	2.08 (1.35-3.19)	0.001	2.47 (1.61-3.78)	<0.001	1.19 (0.99-1.42)	0.063
Rectal (NG or CT)	0.93 (0.49-1.78)	0.826	1.95 (1.18-3.21)	0.009	2.51 (1.53-4.12)	<0.001	2.09 (1.32-3.31)	0.002	2.70 (1.71-4.26)	<0.001	1.29 (1.07-1.56)	0.008
Urethral (NG or CT)	1.24 (0.54-2.87)	0.607	2.00 (1.01-3.99)	0.048	2.16 (1.08-4.32)	0.029	1.61 (0.93-2.79)	0.088	1.74 (1.00-3.02)	0.050	1.08 (0.81-1.44)	0.607
Pharyngeal (NG or CT)	1.38 (0.48-3.96)	0.551	3.25 (1.36-7.77)	0.008	3.87 (1.62-9.26)	0.002	2.36 (1.22-4.54)	0.010	2.81 (1.46-5.41)	0.002	1.19 (0.90-1.57)	0.218
Syphilis	1.22 (0.21-7.10)	0.829	3.33 (0.82-13.61)	0.094	4.79 (1.18-19.46)	0.028	2.74 (0.86-8.76)	0.089	3.95 (1.24-12.51)	0.020	1.44 (0.92-2.24)	0.107

PR = prevalence ratio

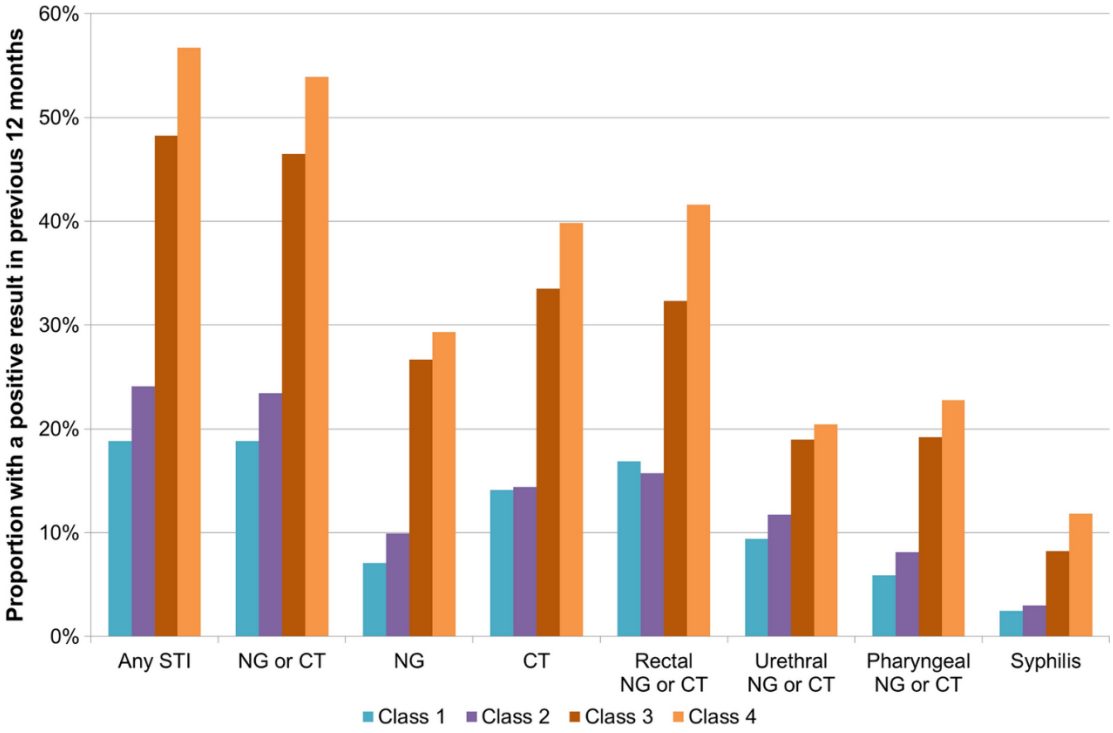

Figure 6.1. Proportion of PrEPX participants in each class with a positive test result within 12 months prior to survey completion

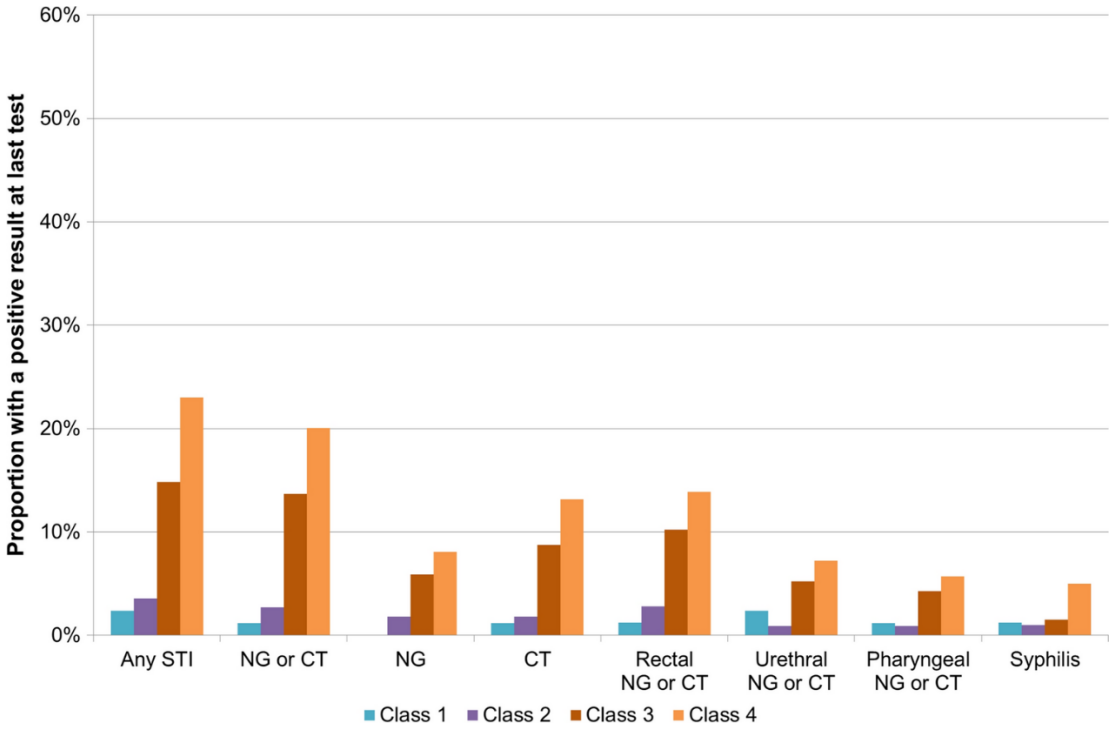

Figure 6.2. Proportion of PrEPX participants in each class with a positive test result at the most recent visit prior to survey completion

6.5 Discussion

In this cohort of Australian GBM previously enrolled in a PrEP implementation study and who were still using PrEP one year post-study closure, we observed highly heterogeneous attitudes towards STIs and levels of sexual risk behaviours. Using latent class analysis, we described four distinct groups of PrEP users exhibiting characteristic differences in behaviours, attitudes and risk related to STIs. Class 1 and Class 2 were comprised mostly of GBM with no or very few casual partners, respectively. The majority (78%) of the cohort were classified into Classes 3 and 4, two groups that were distinguished by disparate attitudes towards STIs but had similarly high patterns of risk and STI diagnosis rates when compared to the others in the cohort. While GBM in Class 4 reported low concern about being diagnosed with an STI, GBM in Class 3 worried about STIs and considered STIs to be a serious health issue.

Approximately half of GBM allocated to Class 3 (high concern, higher risk) and Class 4 (low concern, highest risk) were diagnosed with an STI in the 12 months prior to completion of the follow-up survey. Given this relatively high incidence of STIs, GBM from both classes would benefit from additional STI prevention strategies. However, the receptiveness and motivation of each class to take up different interventions will likely vary considerably. When considering Class 4, there is an apparent degree of conflicting attitudes towards STIs; many (51%) acknowledge that getting an STI could seriously affect their health and that it is important to avoid STIs (64%), however few worried about getting an STI (12%), despite high rates of STI diagnoses detected in the previous 12 months. This may translate to a recognition that, while their current behaviour does put them at risk of the potential harms of STIs, the cost of reducing that harm (e.g. having fewer sexual partners) is greater than the perceived derived benefit (i.e. having fewer STIs). GBM in class 4 may therefore be most receptive to strategies with minimal imposition on their sexual practices, such as rapid point-of-care testing or home testing, STI prophylaxis,[224, 225] or, in the future, STI vaccines.[239] In contrast, GBM in Class 3, who worry about STIs yet still have high rates of STI diagnosis, may be more willing to adopt prevention strategies involving behavioural change if they can see that the direct benefit would be less STIs.

Classes 3 and 4 also reported different levels of drug use. Compared to those in Class 3, those in Class 4 were more likely to have ever injected drugs (15% vs 7%), and more likely to have engaged in chemsex in the last six months (30% vs 19%). As the sexual behaviours that participants were asked about revolved mostly around condom use, partner number and sexual positioning, we were unable to explore the frequency of more specific sexual practices associated with increased STI risk across classes, including participation in group sex or sex at sex-on-premises venues. While GBM in Class 4

had the highest positivity across each STI outcome, the greatest relative increase in past-12-month positivity compared to Class 3 was observed for rectal infections (29% higher) and syphilis (43% higher), indicating that Class 4 may be more likely to engage in high-risk receptive anal sex (e.g. condomless receptive sex in group sex setting). Taken together, these data suggest that respondents in Class 4 may benefit from comprehensive harm reduction strategies that address both STI risk and risks arising from substance use.

Our analysis also revealed a level of anxiety towards STIs among some PrEP users. In particular, Class 3 was characterised by high levels of concern around STIs, with 73% saying they think about STIs often, in contrast with only 9% in Class 4 participants. Novel prevention strategies that reduce risk of STI acquisition risk, such as doxycycline pre- or post-exposure prophylaxis[224, 225], may be beneficial in reducing and improving both mental and physical wellbeing among some PrEP users at heightened risk of STIs. Research has shown that PrEP has been associated with large reductions in HIV-related anxiety among Australian GBM.[80] However, in the case of doxycycline prophylaxis, the potential benefit of reduced anxiety would need to be balanced against the theoretical potential harms caused by long term antibiotic use. A further distinction between classes 3 and 4 was the frequency at which they reported discussing STI testing with their partners; 35% of Class 3 said they discussed STI testing most or all of the time, compared to only 15% of Class 4. However, overall more than three-quarters of PrEP users in our analysis reported discussing STI testing with partners at least some of the time. PrEP users who express comfort in discussing STI testing with casual partners may be good candidates for partner-centred prevention strategies, such as partner notification technologies, as well as for approaches relying on community diffusion of health promotion messages.

Biobehavioural data collected annually among GBM in Melbourne show that consistent condom use with casual partners has declined from 41% in 2016 to 22% in 2020.[355] In our cohort of PrEP users, less than 3% of participants reported consistent condom use with casual partners in the past six months. Compared to GBM in Class 4 and 2, GBM in Class 3 had a higher level of overall condom use with casual partners, with only 29% reporting never using condoms, compared to 49% in Class 4 and 46% in Class 2. Although condom use was higher among GBM in Class 3 than in Class 2, STI positivity was higher in Class 3 compared to Class 2. In contrast, GBM in Class 2 reported fewer casual partners in the past 6 months (median, 4) than those in Class 3 (median, 10). These findings reflect a previous survival analysis among the PrEPX cohort in which greater number of casual partners was independently associated with greater STI risk, whereas decreased condom use was not.[67] It is evident that selective use of condoms with casual partners is common among some GBM, with approximately half of those in Class 3 reporting using condoms some or about half of the time.

Whilst acknowledging the potential complexity of health promotion messaging associated with this finding, it is an issue worth addressing. Without diminishing the message of the importance of condom use overall, it is important to understand how to communicate that there are circumstances when condom use likely provides the greatest benefit and protection against STI risk – such as with a new partner or in a group sex setting.

Our findings that certain subgroups of GBM are at increased risk of STIs are consistent with previous research utilising LCA.[341, 343] However, while previous work has shown associations between certain characteristics and behaviours among groups of GBM and increased STI risk, this is the first LCA to our knowledge which incorporates both behaviours and attitudes towards STIs as class indicators. We believe that in the context of PrEP users, individuals' behaviours are so closely intertwined with their attitudes towards STIs, that neither can truly be said to be causing the other. Rather, behaviours and attitudes are likely driven by a single construct which we aimed to model as latent class membership. This is also the first LCA to be undertaken specifically among GBM who have been using PrEP for a considerable length of time. Attitudes among GBM may change in the context of increasing PrEP use, including through the normalisation of frequent testing and increasing STI incidence. The way in which PrEP users utilise particular STI prevention strategies will likely depend on their attitudes towards STIs. Successful targeting of strategies may need to rely not only on behavioural indicators and previous STI risk, but also on individuals' attitudes and motivation to utilise different strategies. Our findings suggest that tools used to screen patients for STI risk could be guided not only behavioural risk factors, but also by items on patients' attitudes towards STIs. Future research should aim to identify and refine which attitudinal questions are most indicative of STI risk in this population. Engaging in conversation to better understand patients' attitudes around STIs may help clinicians recommend interventions most likely to be adopted by the patient.

Limitations

There are several limitations to our analysis. First, only one quarter of participants in the PrEPX Study responded to the survey one year after study completion. Sensitivity analysis of characteristics of those who responded and those who did not revealed that respondents were older and less likely to report injecting drug use and methamphetamine use at enrolment. However, there was no difference in the HIV-related sexual risk criteria between groups. Second, some key behavioural variables which have been shown to be strong indicators of STI risk among GBM using PrEP, such as participation in group sex,[67] were not included in the survey. Further analysis of specific sexual practices associated with STI risk among this cohort may be warranted. Third, only 78% of those

included in the LCA had available STI testing data from the ACCESS surveillance system. However, missing testing data is likely due to some participants accessing their PrEP, and therefore being tested, outside of the ACCESS clinical network, rather than not being tested for STIs; all participants were still using PrEP at the time of the survey completion and 98% of participants reported being tested for STIs at their most recent PrEP clinic visit prior to survey completion. It is unlikely that attending a different clinic for STI testing is greatly influenced by STI risk. Fourth, we were only able to look at associations between class membership and risk of bacterial STIs, and not viral STIs. As the attitudinal questions included in the survey did not explicitly mention bacterial STIs, we were not able to discern any differences in attitudes towards curable bacterial STIs compared to non-curable STIs, such as human papillomavirus or herpes simplex virus. Concern towards contracting life-long viral STIs may have influenced some participants' responses. Finally, this analysis was restricted to GBM currently using PrEP and may not be generalisable to GBM not using PrEP or GBM in general. However, the issues explored in this work are particularly relevant to STI control in the era of PrEP, given rapid uptake of PrEP among Australian GBM has coincided with declines in condom use and increases in STI incidence.

6.6 Conclusions

Gay and bisexual men using PrEP in Australia are a priority population for bacterial STIs, however, our study shows that their beliefs and attitudes towards STIs vary considerably, and this will likely influence their receptivity to different STI prevention strategies. We found that PrEP users with the highest risk of STIs reported the highest rates of injecting drug use and chemsex, suggesting that this group of PrEP users would benefit from harm reduction strategies that address both STI risk and risks resulting from drug use. A multifaceted and targeted public health response which considers and monitors how different interventions are received and adopted by PrEP users will be required to curtail the high incidence of STIs among this population.

6.7 Article information

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Conflicts of interest

MWT received speaker's fees from Gilead Sciences. DM received grants from Alfred Health. VJC has received speaker's fees and conference assistance from Gilead Sciences and advisory board fees from ViiV Healthcare. EJW reports receipt of grants from the Victorian, Tasmanian and the South Australian governments for PrEPX; other from Gilead Sciences compensation to her institution for chairing a nursing education session and for attending an advisory board meeting, and uncompensated attendance for attending 2 Gilead meetings regarding listing of Truvada on the Australian pharmaceutical benefits scheme); grants from, Gilead Science and Merck Sharp & Dohme outside the submitted work; and financial support from, Gilead Sciences, Abbott Laboratories, Janssen-Cilag, Boehringer Ingelheim, ViiV Healthcare, and Merck Sharp & Dohme. MH received grants from the Australian Department of Health, Gilead Sciences, Abbvie and BristolMyers-Squibb. JA received grants from the Australian Government's Department of Health. MS received a research fellowship from the National Health and Medical Research Council, and investigator-initiated grants from Gilead Sciences and Bristol-Myers-Squibb. All other authors declare no potential conflicts of interest.

Ethics approval

The PrEPX study was approved by the Alfred Health Human Research and Ethics Committee (HREC100/16) and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12616001215415). Ethics approval for the ACCESS project in Victoria was provided by the Alfred Hospital Human Research Ethics Committee (Project 248/17), as well as several specialised committees for key populations, including ACON, Thorne Harbour Health, and the Aboriginal Health and Medical Research Council.

Informed consent

Informed consent was obtained from all individuals in the PrEPX study

Authors contributions

MWT lead the data analysis and manuscript preparation. MWT, EJW and MAS conceived the analysis. EJW, KR, JA and DM designed the follow-up survey. JA curated the data. EJW was the principal investigator of the PrEPX study. All authors contributed to data interpretation and have contributed to the intellectual content and preparation of the manuscript.

The PrEPX Study Team

Edwina Wright, Brian Price, Mark Stoové, Simon Ruth, Colin Batrouney, Michael West, Dean Murphy, John de Wit, Luxi Lal, Jennifer Audsley, Christina Chang, Carol El-Hayek, Anne Mak, Alison Duncan, Joe Sasadeusz, Brent Allan, Michael Whelan, Daniel McPhail, David Wilson, Olga Vujovic, Martin Holt, Chris Williams, Steve Wesselingh, James Ward, Danny Gallant, Alison Ward, Alistair Chong, Alonso Navarro Mendoza, Katharine McKinnon, Kathleen Ryan, Michael Traeger, Christopher Fairley, Lucy Donovan, Ivette Aguirre, Ban Kiem Tee, Norman Roth, Vincent Cornelisse, Timothy Read, Richard Moore, Jeff Willcox, George Forgan-Smith, Matthew Penn, Helan Lau, Danielle Collins, Sian Edwards, Susan Boyd, Clair Pickett, Emma Paige, Amanda Wade, Charlotte Bell, William Donohue, Sam Elliot, Helen Calabretto, Louise Owen.

The ACCESS Study

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Chapter 7

The potential impact of a gel-based point-of-sex intervention in reducing population-level gonorrhoea incidence among gay and bisexual men: a modelling study

So far, the data presented in this thesis have explored the changing epidemiology of bacterial STIs among GBM in the era of PrEP in Australia and have highlighted key insights into characteristics and groups at increased risk. In Chapter 6, I show that attitudes towards STIs among PrEP users are highly variable, and that different groups of GBM are likely to embrace different prevention strategies. In Chapter 1, I discussed a range of current and potential biomedical prevention strategies for bacterial STIs. One strategy which has been proposed and found to be highly acceptable to GBM is antimicrobial gel or lubricant for use during anal sex. However, the development of such interventions has largely stalled due to challenges producing a product with high efficacy. In the context of PrEP and population-level declines in condom use, interventions which have even a modest efficacy at reducing STI acquisition may have population-level benefits. In Chapter 7, I use mathematical modelling to explore the population-level impact of a hypothetical gel-based intervention in reducing gonorrhoea incidence in GBM.

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This chapter is included in the original ***Sexually Transmitted Diseases*** format in Appendix B3 (p 296)

Chapter 7

The potential impact of a gel-based point-of-sex intervention in reducing gonorrhoea incidence among gay and bisexual men: a modelling study

Authors

Michael W. Traeger[1,2],Tom Tidhar[1], Martin Holt[3], Chris Williams[4,5], Edwina J. Wright[6,7], Mark A. Stoové[1,2,8], Nick Scott*[1,2], Margaret E. Hellard*[1,2,6]

*co-senior authors

Author affiliations

[1] Burnet Institute, Melbourne, Victoria, Australia

[2] School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[3] Centre for Social Research in Health, University of New South Wales, Sydney, Australia

[4] PrEP'D For Change, Melbourne, Victoria, Australia

[5] Thorne Harbour Health, Melbourne, Victoria, Australia

[6] Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia

[7] Peter Doherty Institute, University of Melbourne, Melbourne, Victoria, Australia

[8] School of Psychology and Public Health, La Trobe University

7.1 Abstract

Background

Increases in sexually transmitted infections (STIs) among gay and bisexual men (GBM) over the past decade have coincided with declines in condom use and rapid uptake of HIV pre-exposure prophylaxis (PrEP). We explored the impact of an antimicrobial gel-based point-of-sex intervention (gel-PSI) with a lower efficacy for reducing gonorrhoea transmission risk than condoms on population-level gonorrhoea incidence among GBM in Victoria, Australia.

Methods

A deterministic compartmental model of HIV and gonorrhoea transmission was used to project annual gonorrhoea incidence from 2020 to 2025. Individuals were classified as HIV-negative (PrEP or non-PrEP-users) or HIV-positive, and further stratified gonorrhoea risk (high/low). All possible scenarios where between 0-100% of GBM using condoms transitioned to gel-PSI (considered a downgrade in protection) and 0-100% of GBM not using condoms transitioned to gel-PSI (considered an upgrade in protection), with gel-PSI efficacy ranging from 20-50% were run.

Results

The baseline scenario of no gel-PSI uptake (status quo) projected 94,367 gonorrhoea infections between 2020-2025, with an exponentially increasing trend in annual infections. For a gel-PSI efficacy of 30%, a net reduction in cumulative gonorrhoea incidence was projected, relative to the status quo, for any ratio of proportion of condom-users 'downgrading' to proportion of non-condom-users 'upgrading' to gel-PSI use of less than 2.6. Under the supposition of equal proportions of condom-users and non-condom-users switching to gel-PSI, a relative reduction was projected for any gel-PSI efficacy greater than 16%.

Conclusions

Our model suggests that the introduction of a gel-PSI could have benefits for controlling gonorrhoea transmission among GBM, even in scenarios where the gel-PSI is considerably less efficacious than condoms and when gel-PSI uptake leads to consequent reductions in consistent condom use.

7.2 Introduction

Globally, gay and bisexual men (GBM) are disproportionately affected by sexually transmissible infections (STIs), with recent data showing sharp increases in gonorrhoea, chlamydia and syphilis infections in recent years among GBM in Australia, the United States and across Europe.[121, 274, 356] While the introduction of highly-sensitive nucleic acid amplification tests (NAAT) and increases in testing among GBM[121, 357] have likely contributed to rising STI notifications, declining condom use among GBM[358, 359], coinciding with wide-scale implementation of multiple HIV biomedical interventions, including treatment as prevention (TasP) for HIV[37] and HIV pre-exposure prophylaxis (PrEP),[151, 162] is also considered a key factor driving increased STI transmission risk.

Mathematical modelling has suggested that the high frequency of STI testing associated with PrEP uptake among GBM may help reduce STI incidence in the years following PrEP implementation.[165] However, there is little real-world evidence showing reduced STI incidence as a result of increased STI testing frequency among PrEP users, and findings from a recent modelling study of various testing scenarios on syphilis epidemiology suggest that despite having overall benefits, increased testing due to PrEP implementation alone is unlikely to reverse the background trend of increasing syphilis transmission.[166]

In contrast to efforts to increase testing, interventions used at the time of sex may offer a more affordable and acceptable method of STI prevention for GBM, and be more effective in preventing transmission. Various point-of-sex interventions aimed at reducing STI transmission risk have been suggested, such as antimicrobial lubricants, rectal gels and creams.[360-362] Microbicidal products to prevent HIV transmission have also been explored, however there has been limited success in developing a highly efficacious product,[363] and there is limited data on efficacy of microbicidal interventions on STI transmission. Additionally, acceptability and willingness to use antimicrobial products vary among GBM, depending on availability, effectiveness, cost and perceived risk.[360, 364, 365]

Antimicrobial gel-based products may not reduce the risk of STI transmission as much as condoms, but even a product used during sex with modest efficacy would provide individual-level benefits for GBM who are currently not using condoms or using them infrequently. However, the population-level impact of a partially-effective, point-of-sex intervention on STI transmission will be influenced by a number of factors, including product efficacy and acceptability. Another important consideration is how risk reduction practices used by GBM may alter with the availability of a new product that is less effective at preventing STIs, but has less of an impact on sexual pleasure, than condoms. Importantly, reductions in STI transmission resulting from uptake of such an intervention

by some GBM may be counteracted by increases in STI risk among GBM who transition from using condoms to using the less effective product. In other words, GBM who transition from no condom use to using the new intervention will experience an 'upgrade' in protection from STI acquisition, while GBM who transition from condom use to using the new intervention will experience a 'downgrade' in protection. Alongside product effectiveness, the population-level benefits of such a product are dependent on the level of uptake among GBM who do and do not engage in more efficacious STI prevention strategies.

Given concerns around increasing gonorrhoea incidence among Australian GBM [120], including in the context of the rapid uptake of PrEP,[67] we used a mathematical model of HIV and gonorrhoea transmission among GBM in the state of Victoria to evaluate the population-level effectiveness of differential uptake of a new antimicrobial gel-based point-of-sex intervention (gel-PSI) in reducing gonorrhoea incidence among GBM. We estimated the threshold of uptake among non-condom users and condom users required for an overall reduction in gonorrhoea incidence based on varying hypothetical levels of product efficacy.

7.3 Methods

We used a population-level, deterministic, compartmental model of HIV and gonorrhoea transmission among GBM in Victoria, Australia **(Figure 7.1).** The model utilised a series of ordinary differential equations representing compartment transition rates; individual sex acts were not explicitly modelled. Estimates and sources for model parameters described below are provided in **Table 7.1**. Analysis was conducted using R (version 3.5).

HIV model dynamics

The model population was classified into three subpopulations; HIV-negative GBM using PrEP, HIV-negative GBM not using PrEP, and HIV-positive GBM. HIV-positive individuals were stratified by current stage in the HIV care cascade (undiagnosed, diagnosed but not on treatment, on HIV treatment and not virally supressed, or on HIV treatment and virally supressed), and were able to progress through the cascade. During each time step, HIV-negative individuals seroconverted to HIV-positive, moving to the HIV-positive undiagnosed compartment, at a rate dependant on (1) average condom use in the population; (2) PrEP coverage among HIV-negative individuals; (3) the dynamic prevalence of HIV in the model (weighted to account for a removal of infectiousness among HIV-positive people who were virally supressed); and (4) a force of infection constant that was used to fit

the model to observed HIV notification data over time in Victoria. Calibration parameters, such as the force of infection constant above, are used in population-level models to fit to data without explicitly modelling individual behaviours which influence transmission risk, such as rate of partner change and sexual positioning, for which data are limited.

Gonorrhoea model dynamics

A gonorrhoea model was included for each HIV subpopulation **(Figure 7.1)**. The gonorrhoea models classified individuals as being susceptible (S), exposed (E), infected and asymptomatic (Ia), or undergoing treatment (T). GBM with symptomatic gonorrhoea were assumed to commence treatment immediately. In the model, susceptible individuals could become infected with gonorrhoea at a rate which was dependent on; (1) average condom use in the subpopulation; (2) the dynamic gonorrhoea prevalence among each of the subpopulations and their level of sexual mixing between subpopulations; and (3) a force of infection constant that was used to fit the model to observed gonorrhoea notification data among HIV-negative (PrEP and non-PrEP users combined) and HIV-positive GBM over time in Victoria. Individuals who became infected with gonorrhoea moved from susceptible (S) to exposed (E), and after an incubatory period of five days a proportion became symptomatic and were assumed to commence gonorrhoea treatment (T), while the remaining proportion became infected and asymptomatic (Ia). Individuals in the exposed or asymptomatic gonorrhoea infection stages were only treated following a test (testing rates described below). Following gonorrhoea treatment, individuals returned to the susceptible compartment after seven days, the recommended period of abstinence after receiving treatment. To capture heterogeneous levels of risk among the GBM population, each gonorrhoea model (i.e. among the subpopulations HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive) included a stratification for gonorrhoea infection risk (high risk versus low risk for gonorrhoea infection).

Model parameters

Annual Victorian GBM population size, PrEP coverage and HIV prevalence were estimated using Australian notification and surveillance data (appendix A4.1, p 256). For each subpopulation (HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive), the gonorrhoea testing rate was modelled as a constant parameter, estimated using surveillance data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-borne Viruses and Sexually Transmitted Infections (ACCESS) surveillance project (appendix A4.3, p 257). Condom use was

included as a time-varying parameter for each subpopulation, reflecting average condom use in that population and was estimated using Victorian biobehavioural surveillance data (appendix A4.4, p 257). Condom effectiveness, gonorrhoea symptomatic rate and sexual mixing were estimated from the literature (appendix A4.5, p258) and the proportion of individuals across each subpopulation classified as 'high-risk' for gonorrhoea, and the relative increase in gonorrhoea acquisition risk, were calculated from previously reported STI data from GBM enrolled in a Victorian PrEP study (appendix A4.6, p258).

Model calibration

The force of infection constant for HIV and the diagnosis rate for HIV in the model were calibrated to best fit time series data for the estimated number of HIV-positive GBM in Victoria and Victorian HIV notifications attributed to male-to-male sex. Among people diagnosed with HIV, the proportion who were on treatment and the proportion who were virally supressed in the model were fitted to time series data from Victoria (appendix A4.8, p 262). For all forward projections, the HIV care cascade was modelled to continue to follow Australian trends towards achieving and maintaining 95% of people living with HIV diagnosed, 95% of people diagnosed started on treatment and 95% of people on treatment virally supressed by 2030 (appendix A4.7, p 259).

Once the HIV-model was calibrated, the force of infection constants for gonorrhoea among HIV-negative and HIV-positive GBM were calibrated to best fit time-series data for gonorrhoea notifications (appendix A4.13, p 263). Both the HIV and gonorrhoea model were calibrated by minimising the sum of squares between the model and data, using the Nelder-Mead method. A sensitivity analysis was conducted in which the gonorrhoea force of infection was held constant from 2018 onwards, rather than dynamic and dependent on gonorrhoea prevalence, to test the impact of gel-PSI if background exponential growth trends in gonorrhoea incidence became more linear in the projected years.

Introduction of a gel-based point-of-sex intervention and model outcomes

Uptake threshold ratios for net benefit

The main model outcome was cumulative gonorrhoea incidence between 2020 and 2025 (inclusive). Each subpopulation (HIV-positive, HIV-negative PrEP and HIV-negative non-PrEP) consisted of GBM whose primary method of gonorrhoea prevention was either no STI prevention, using condoms, or using the gel-PSI. As the coverage of different prevention methods changed among each

subpopulation, this was modelled to scale the force of infection according to an effectiveness-weighted prevention factor (i.e. the sum of prevention methods of coverage multiplied by their effectiveness).

First, differential levels of gel-PSI uptake by current condom use were explored, with no differential uptake by HIV or PrEP status. Scenarios were run where between 0-100% of GBM currently using no prevention (across HIV-positive, HIV-negative PrEP and HIV-negative non-PrEP) upgraded to gel-PSI; and 0-100% of GBM using condoms downgraded to gel-PSI. These changes were implemented to be phased in over a two-year period (2020-2022) and held constant out to 2025. The threshold ratio of percentage 'downgrading' (from condoms to gel-PSI) to 'upgrading' (from no prevention to gel-PSI) for a net reduction in cumulative gonorrhoea incidence from 2020 to 2025 was calculated. This was repeated for theoretical levels of gel-PSI effectiveness for preventing gonorrhoea of 20%, 30%, 40% or 50%. In all of these scenarios the effectiveness of the gel-PSI was assumed to be lower than the effectiveness of condoms in reducing gonorrhoea transmission-risk.

Differential uptake among subpopulations

Several specific scenarios of gel-PSI uptake were then explored with differential uptake across the three subpopulations (HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive) and across those already using or not using condoms prior to gel-PSI introduction. In these scenarios, we used a gel-PSI efficacy of 30% for reducing gonorrhoea transmission-risk.

Scenario a: Use of the gel-PSI increased to a threshold of 50% of each subpopulation (HIV-positive, HIV-negative not on PrEP, HIV-negative on PrEP), with only those not using condoms 'upgrading' to gel-PSI and condom users remaining as condom users.

Scenario b: 50% of condom users 'downgrade' to gel-PSI and 50% of non-condom users 'upgrade' to gel-PSI.

Scenario c: All condoms users across each subpopulation 'downgrade' to gel-PSI.

Scenario d: All PrEP users (condom and non-condom users) switch to gel-PSI.

Given that the uptake of the gel-PSI among individuals at risk of HIV (HIV-negative not on PrEP) would likely depend on the gel-PSI's effectiveness at also reducing HIV, we then explored scenarios with differential levels of uptake between those at risk of HIV (HIV-negative not on PrEP) and those not at risk of HIV (HIV-negative on PrEP and HIV-positive):

Scenario e: 50% of PrEP users and HIV-positive GBM (both condom users and non-condom users) switch to gel-PSI, while non-PrEP users have no gel-PSI uptake.

Scenario f: 50% of GBM not on PrEP (condom users and non-condom users) switch to gel-PSI, while PrEP users and HIV-positive GBM have no gel-PSI uptake.

We report the net absolute difference and relative difference in cumulative gonorrhoea infections from 2020 to 2025 (inclusive) between each scenario and the baseline scenario of no gel-PSI uptake (status quo).

Sensitivity analyses

Sensitivity analyses were run to examine the influence of key assumptions in model parameters. Using Scenario b (50% 'upgrade' and 50% 'downgrade' in STI prevention among non-condom users and condom users respectively, and a gel-PSI efficacy of 30%), we explored the effect of varying the following parameters on cumulative gonorrhoea incidence from 2020 to 2025 and the relative reduction between scenario b and no gel- PSI uptake: the effectiveness of condoms at reducing gonorrhoea transmission risk from 75% to 50% and 100%; sexual mixing by changing the proportion of serodiscordant sex acts to 0% (complete serosorting), 50% of sex acts serodiscordant and mixing at random (no serosorting); increasing PrEP uptake post-2020 to reach 50% and 75% of HIV-negative GBM by 2025; proportion of gonorrhoea cases (any anatomical site) which were symptomatic from 45% to 25% and 75%; increased risk factor for the high-risk for gonorrhoea group from 7.5 to 2, 10 and 20; condom use among HIV-negative GBM from remaining stable at 29% to 2025 to reducing to 15% and 5% by 2025 (with condom use among PrEP users and HIV-positive GBM 0.3 times that of non-PrEP users); and increased gonorrhoea testing rates among non-PrEP users by reducing mean number of days between tests by 25% and 50% by 2025.

7.4 Results

Projected gonorrhoea notifications to 2025

Calibration of the gonorrhoea model to notification data was fairly accurate among both HIV-negative and HIV-positive populations **(Figure 7.2)**. (See appendix A4.7 [p 259] for calibration of the HIV model to HIV notification data). In the baseline scenario of no gel-PSI uptake (status quo), projected annual gonorrhoea incidence increased exponentially, reaching approximately 23,848 infections among Victorian GBM in the year 2025 **(Figure 7.3)** equating to a cumulative incidence of 94,367 gonorrhoea infections from 2020 to 2025. Appendix A4.10 (p 261) shows projected annual incidence attributable to each subpopulation (HIV-positive, HIV-negative on PrEP and HIV-negative not on PrEP).

Prevention upgrade and downgrade thresholds

Following the introduction of a gel-PSI with an efficacy of 30%, compared to the baseline scenario of no gel uptake among the population, a relative reduction in cumulative gonorrhoea incidence from 2020 to 2025 was observed for any ratio of the proportion of condom-users 'downgrading' to proportion of non-condom-users 'upgrading' to gel-PSI use of less than 2.6 **(Figure 7.4)**. For example, if 50% of condom users downgraded to gel-PSI, provided that at least 20% of non-condom users upgraded, a relative reduction in gonorrhoea incidence was observed for a gel efficacy of 30%. If 50% of condom users downgraded to gel-PSI under a gel efficacy of 50%, a net benefit was observed provided at least 7% on non-condom users upgraded, with the threshold ratio of proportion of condom-users 'downgrading' to proportion of non-condom-users 'upgrading' to gel-PSI use equal to 7.4 **(Figure 7.4)**. If the proportion of condom users downgrading to gel-PSI was equal to the proportion of non-condom users upgrading to gel-PSI, a net reduction in gonorrhoea notifications was projected for a gel-PSI with efficacy of 16% or higher.

Intervention uptake scenarios

Changes in cumulative gonorrhoea incidence across each scenario relative to the baseline scenario of no gel-PSI uptake are shown in **Table 7.2**. All but one scenario (Scenario c, only condom users 'downgrading' to gel-PSI) projected a relative reduction in cumulative gonorrhoea incidence from 2020-2025 **(Figure 7.4)**. All scenarios project an increasing trend in annual gonorrhoea incidence among GBM to 2025 and beyond.

Sensitivity analyses

Having a constant force of infection from 2018 onwards led to a moderate reduction in both the cumulative gonorrhoea incidence and relative reductions following gel-PSI uptake scenarios (appendix A4.15, p 263), however benefits were still observed across the majority of scenarios (appendix A4.15, p 264). Altering the specified model parameters moderately affected the cumulative gonorrhoea incidence projected to 2025 (appendix A4.16, p 265), however altering these parameters only had small effects on the relative impact of the gel-PSI intervention (under scenario B; 50% uptake among condom users and 50% uptake among non-condom users, assuming a gel-PSI efficacy of 40%) (appendix A4.17, p 266). All sensitivity scenarios returned a relative reduction in cumulative gonorrhoea incidence from 2020 to 2025 of between 19% to 28% compared to no gel-PSI uptake (appendix A4.18, p 267).

7.5 Discussion

Our model demonstrated that the introduction of a hypothetical gel-based point-of-sex intervention, which is less efficacious than latex condoms in reducing gonorrhoea acquisition-risk per sex act, led to a population-level decrease in gonorrhoea incidence among GBM relative to the status quo in most uptake scenarios. Intuitively, greater reductions in gonorrhoea incidence were projected with greater uptake of the intervention among those not already using condoms.

The rate of uptake of such a point-of-sex intervention among GBM already using and not using condoms will depend on a range of factors including efficacy, product availability, acceptability, cost, safety and effect on sexual pleasure. The proportion of HIV-negative GBM not using PrEP who would transition from using condoms to using the gel-PSI would also likely depend on the product's efficacy in reducing not just gonorrhea risk, but reducing acquisition riskrisk of HIV and other bacterial STIs. However, among HIV-negative GBM on PrEP and HIV-positive GBM, reduction in HIV transmission risk would not have a substantial impact on the likelihood of uptake, given the negligible risk of HIV acquisition or transmission in these groups.

A key factor in determining the impact of the gel-based intervention is estimating the negative effects of reduced condom use among GBM who switch to the lower-efficacy gel-based intervention. In our model, we explored this trade-off in protection and found that, in the majority of scenarios, it was outweighed by the benefits of non-condom users 'upgrading' to gel-based prevention. In scenarios where all condom users downgraded to using the less-efficacious gel-based intervention, even with an intervention which reduces gonorrhoea transmission risk per sex act by only 50%, net benefits were observed provided 12% or more of non-condom users started using the gel-PSI.

The likelihood of overall benefits is further enhanced by the different risk profiles of condom users who may 'downgrade' to gel-based prevention compared to non-condom users who may 'upgrade' to gel-based prevention. Given the risk-based eligibility criteria for PrEP in Australia[75] and the estimated high level of PrEP coverage among those eligible for PrEP,[366, 367] it is reasonable to suggest that HIV-negative GBM not using PrEP are a population at reduced risk of gonorrhoea infection. Therefore, reductions in condom use among this population will likely have a modest effect on gonorrhoea transmission when compared to the beneficial effects of uptake of the gel intervention among PrEP users. It is also reasonable to suggest that an intervention with minimal effect on sexual pleasure would have a high uptake among those who do not use condoms, as reduced sexual pleasure is a well established barrier to condom use among GBM.[368] In considering these factors, our

model suggests that in the Australian context, a new intervention with minimal impact on sexual pleasure would likely lead to a net reduction in gonorrhoea incidence among GBM.

While we did not explicitly model sexual network dynamics in our study, it is likely that the population-level impact of a new point-of-sex intervention would be maximised through high uptake among sexual networks of high STI transmission. Recent data from Victoria show that STIs among PrEP users are highly concentrated among GBM experiencing repeat infections, and that increased partner numbers and participation in group sex are associated with increased STI risk in the context of PrEP, suggesting networks of high STI transmission exist within populations of PrEP users.[67] Interventions targeted towards a relatively small proportion of GBM at increased risk of STIs could have substantial impact on interrupting STI transmission.

Despite previous research showing the high acceptability of hypothetical antimicrobial products among GBM,[365, 369] early research showing the potential for such products in reducing STI acquisition risk,[370] and our findings that antimicrobial products with low efficacies could still be beneficial at the population level, there remain no such products with regulatory approval or commercial availability in any country. A barrier to the promotion and uptake of such products is the potential for antimicrobial resistance, a growing concern for gonorrhoea. More recent qualitative research reports that while some GBM show interest in antimicrobial interventions, including the use of antibiotics for STI prophylaxis, many have concerns around the potential for antimicrobial resistance and adverse health effects, and show hesitance towards the widespread use of antibiotics for such purposes [340]. Although such attitudes may hinder community-level uptake of a gel-based antimicrobial intervention, our projections suggest that even relatively low levels of uptake may have population-level benefits. To offset the potential threat posed by increased antibiotic resistance following uptake, it would be important to couple the antimicrobial-based intervention with regular screening and comprehensive resistance testing. Additionally, further research would be required to assess any adverse effects of the regular use of microbicides on the rectal microbiome.

Despite the introduction of the gel-based point-of-sex intervention leading to a net reduction in gonorrhoea incidence in the majority of scenarios, almost all scenarios projected an increasing trend in gonorrhoea incidence to the year 2025 and beyond. These findings highlight that even with a fairly efficacious product and reasonable uptake among the GBM population, a point-of-sex intervention which reduces gonorrhoea acquisition risk will likely not be enough to curtail the rise in incidence of gonorrhoea. A combination of preventive measures, including high rates of asymptomatic screening and a gonorrhoea vaccine, will likely be required to reverse the trend of increasing gonorrhoea

transmission. While we have explored a hypothetical gel-based product, many interventions could be used to partially reduce the risk of gonorrhoea transmission. The implications of our findings could be applicable to other novel prevention strategies, such as using mouthwash before or after oral sex to reduce risk of pharyngeal gonorrhoea,[371] microbicidal rectal enemas used before or after receptive sex, or antibiotic pre-exposure or post-exposure prophylaxis for the prevention of STIs.[224, 225] Furthermore, an antimicrobial intervention would likely have concurrent benefits for other infections not explored in this model, such as chlamydia and syphilis.

Limitations

There are several limitations to our analysis. First, we did not model anatomical site-specific gonorrhoea transmission. Recent evidence suggests that oral transmission of gonorrhoea may account for a large proportion of new infections,[372] and this would not have been captured in our model. Second, while we were able to add parameters for sexual mixing between populations, these were based on behavioural surveys conducted among a select sample of GBM, and data were aggregated rather than event-level. The lack of setting-specific, individual level sexual partnership data precluded accurate estimates of sexual mixing patterns between subpopulations of GBM, including mixing based on HIV status, PrEP status and STI risk. Further, it is possible that following the introduction of such a product, sexual networks may change as individuals' use of the product may influence partner selection. However, altering our sexual mixing parameters in sensitivity analysis had little effect on model projections. Third, we were not able to incorporate more complex network dynamics, such as heterogeneity in partner turnover across groups of GBM, differentiation of casual and regular partnerships, or overlap of concurrent partnerships, all of which would have important implications for gonorrhoea transmission. Fourth, while our model projects an exponentially increasing annual incidence of gonorrhoea among the population, it is important to note that this is in the scenario of no other interventions being introduced or additional behaviour changes in response to increasing transmissions. In reality, it is likely that some other limiting factor or factors would curtail the exponential growth in gonorrhoea incidence. Finally, there is also uncertainty associated with recency and representativeness of data and parameter estimates, however sensitivity analyses indicated that these were unlikely to alter our main conclusions.

7.6 Conclusions

Our study shows that interventions used at the point-of-sex which may only have a modest effect in reducing individual STI acquisition risk, such as gel-based antimicrobial lubricant, are likely to provide population-level benefits among GBM. Commercial development and regulatory approval of these products should be expedited. Despite potential benefits, such interventions are alone unlikely to reverse the increasing trend of increasing STIs, and additional interventions will be required.

7.7 Article information

Authors contributions

MWT lead the drafting of the initial manuscript. MWT, TT and NS accessed data sources and developed the mathematical model. MEH conceived the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval for the ACCESS project in Victoria was provided by the Alfred Hospital Human Research Ethics Committee (Project 248/17).

Conflict of interest

All authors declare no conflicts of interest.

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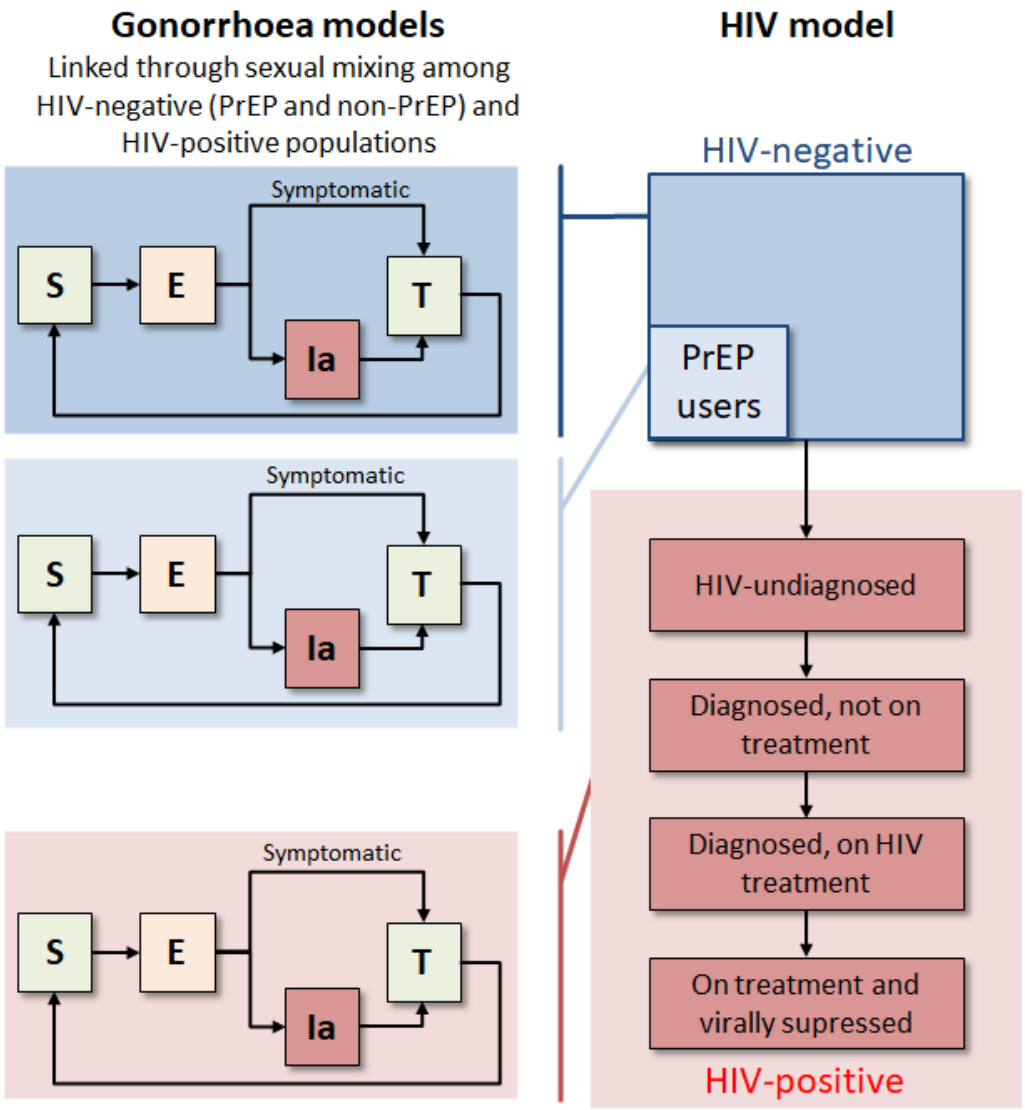

Figure 7.1: Schematic of mathematical model of HIV and gonorrhoea transmission among GBM in Victoria

Footnote: An HIV transmission and care cascade progression model was coupled with a gonorrhoea model for three subpopulations of gay and bisexual men (GBM): HIV-positive, HIV-negative not using PrEP and HIV-negative using PrEP. The gonorrhoea models are linked through sexual mixing among the three subpopulations. Gonorrhoea model compartments represent susceptible (S), exposed (E), infected and asymptomatic (Ia), and treatment (T) (GBM with symptomatic gonorrhoea were model to commence treatment immediately). Each subpopulation was further stratified so that a fraction were at higher risk of gonorrhoea (not shown).

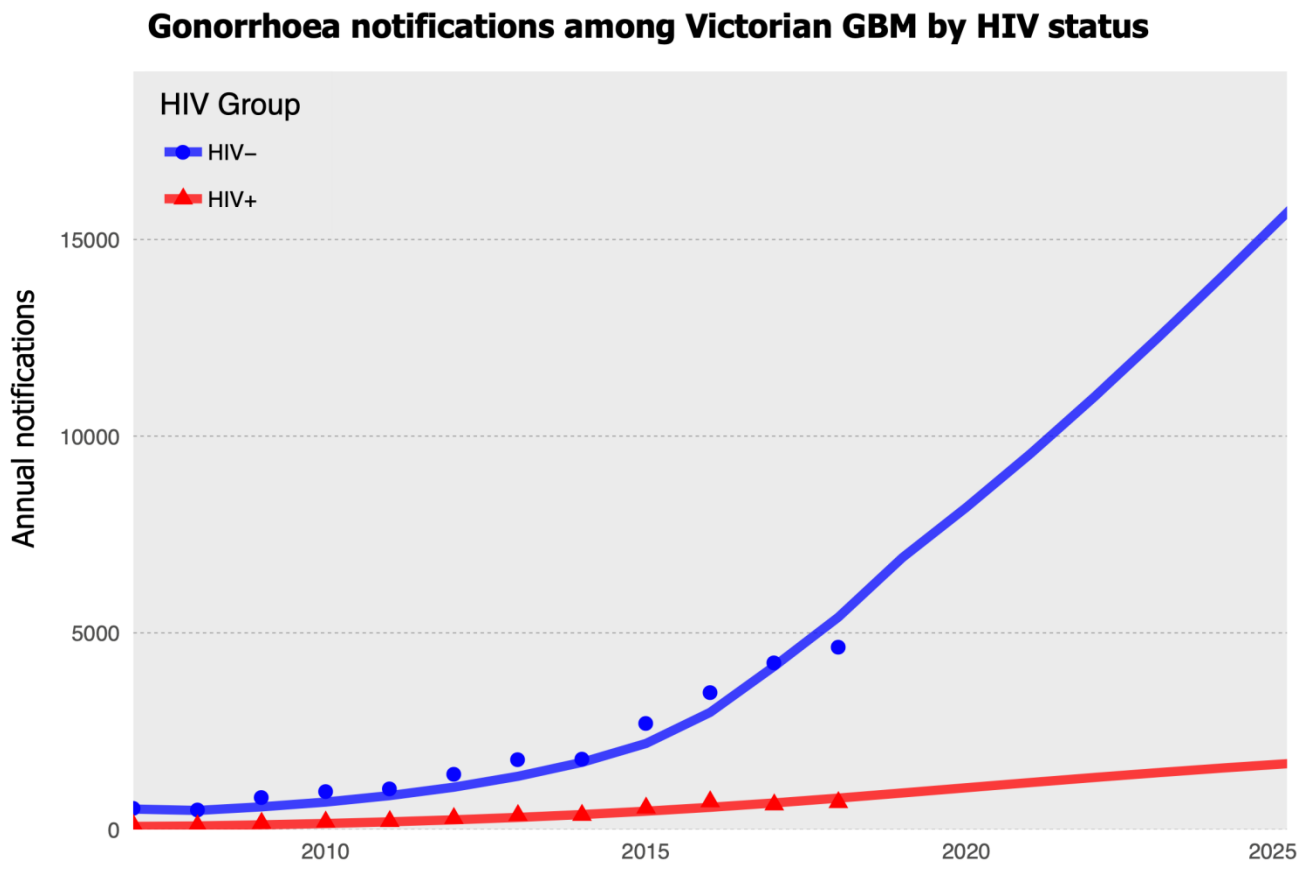

Figure 7.2: Annual gonorrhoea notifications among gay and bisexual men in Victoria versus calibrated model projections for gay and bisexual men.

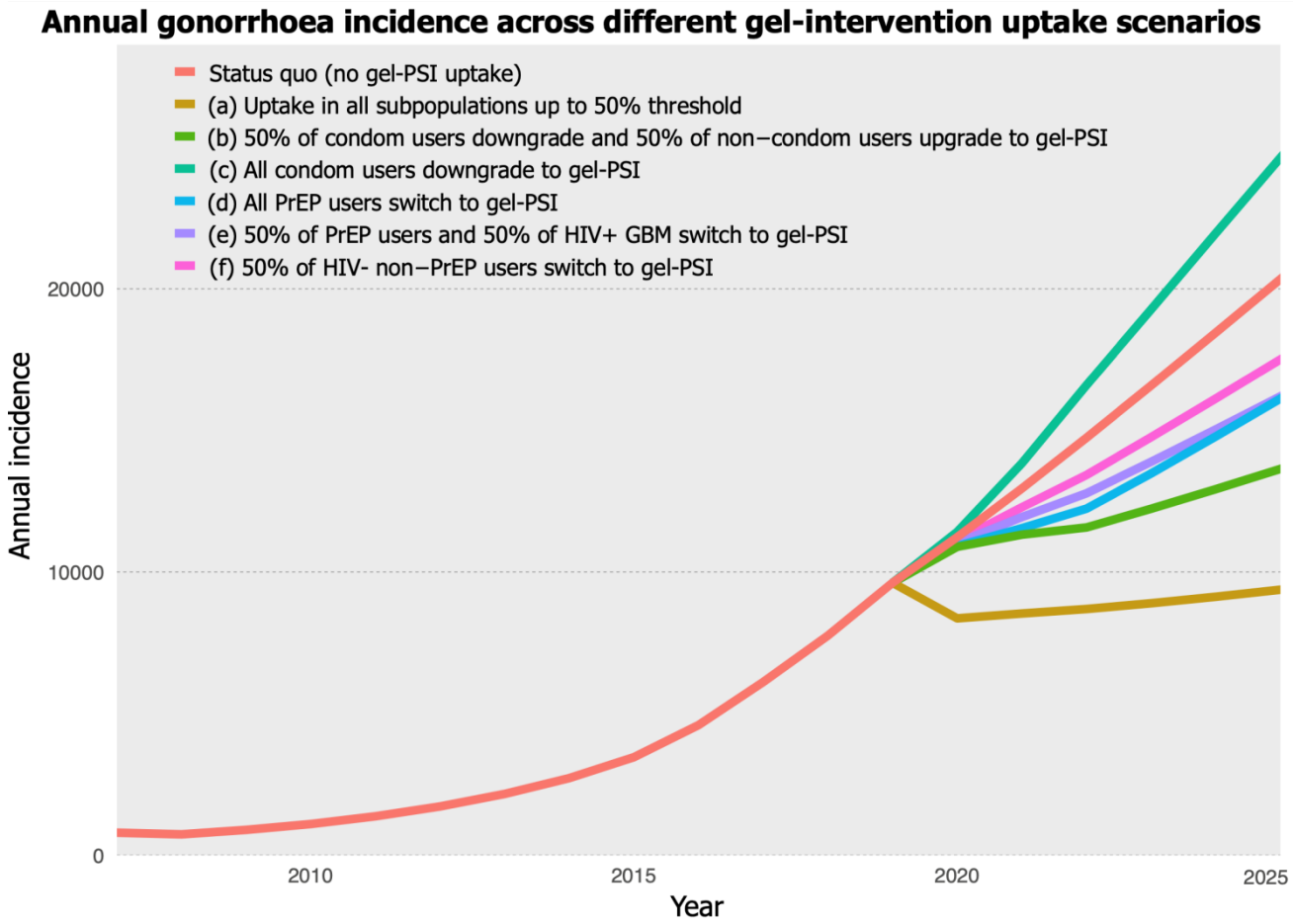

Figure 7.3. Projected annual gonorrhoea incidence among Victorian GBM from 2007 to 2025 for different model scenarios of uptake of a gel-based point-of-sex intervention according to HIV-status, PrEP use and condom use.

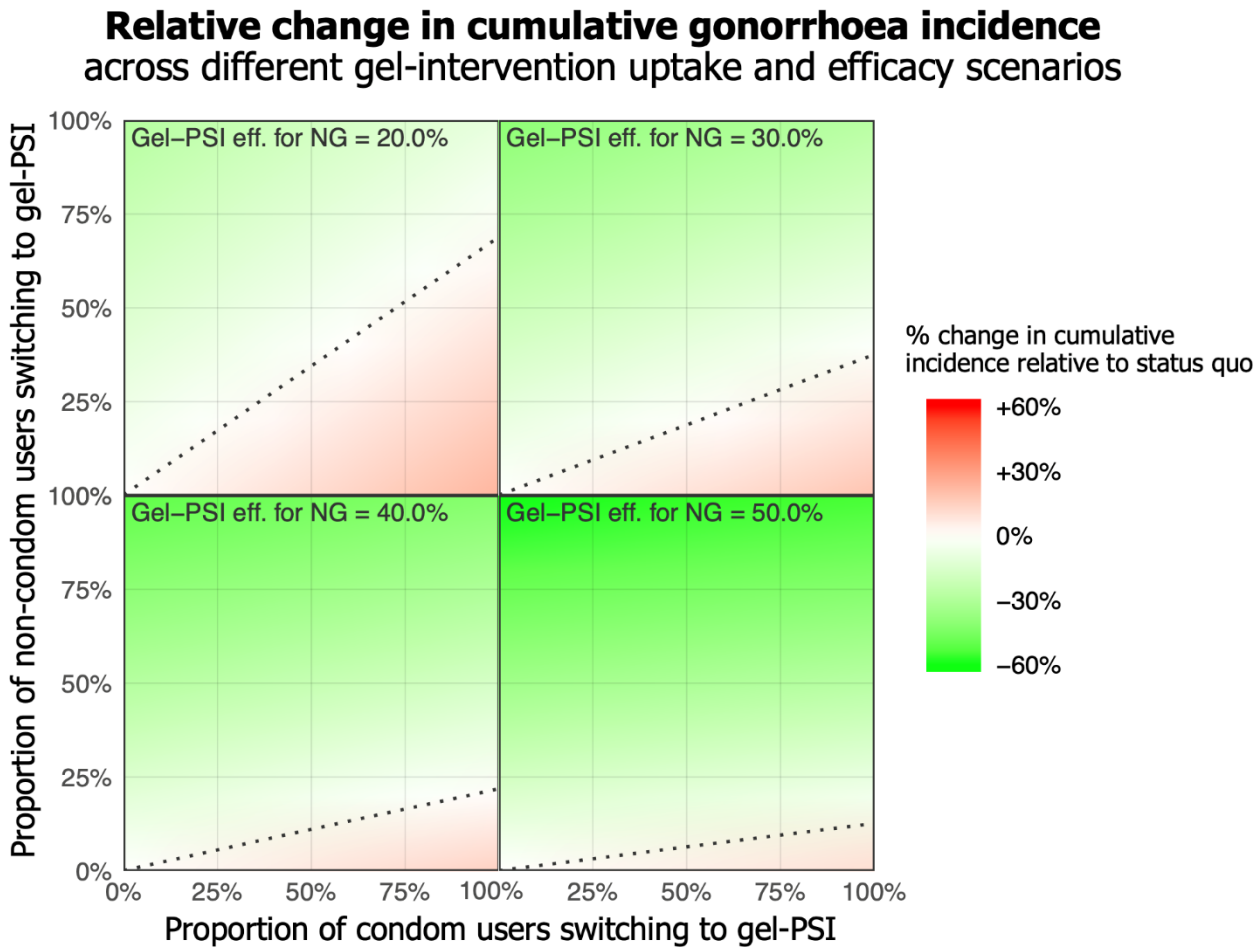

Figure 7.4: Population-level impact of gel-based intervention according to gel efficacy, intervention uptake among non-condom users and intervention uptake among condom users.

Footnote: Compared to the status-quo scenario of no gel-based point-of-sex intervention (gel-PSI), heat maps show the difference in cumulative gonorrhoea incidence from 2020 to 2025 among GBM in Victoria according to: the proportion of condom users who "downgrade" to gel-prevention (x-axes); the proportion of non-condom users who "upgrade" to gel-prevention (y-axes); and the effectiveness of the intervention for reducing gonorrhoea transmission (panels for 20%, 30%, 40% or 50% efficacy). Green and red shadings represent positive and negative population-level benefits respectively, with the dotted line representing zero net effect on cumulative gonorrhoea incidence.

Table 7.1. Model Parameters

HIV parameters		
Effectiveness of latex condoms at preventing HIV	91%	Estimated condom effectiveness during anal sex between men in two prospective cohort studies
Effectiveness of latex condoms at preventing gonorrhoea	75%	Conservative estimate (see appendix A4.5, p258)
Effectiveness of PrEP at preventing HIV transmission	99%	US CDC PrEP effectiveness estimate
Reduction in HIV infectiousness when on treatment	100%	Reduction in HIV transmission from Opposites Attract study [S3]
Gonorrhoea parameters		
Duration of exposed stage for symptomatic individuals	5 days	[S4]
Duration of treatment	7 days	Australian STI guidelines recommend abstaining from sex for 7 days post treatment [S5]
Proportion of GBM with gonorrhoea who are symptomatic	29%	Calculated from ACCESS study data. Proportion diagnosed with either rectal infection only or including urethral infection, and corresponding probabilities of being symptomatic (see appendix A4.3)
Increased gonorrhoea risk for high-risk GBM	7.5	Estimated from the PrEPX study (see appendix (A4.6, p258)
Proportion of GBM at high-risk of gonorrhoea	13%	
Gonorrhoea testing frequency		
HIV-negative GBM on PrEP	1/90 days	Australian PrEP guidelines recommend quarterly testing
HIV-negative GBM not on PrEP	1/224 days	Previous analysis of Victorian GBM in ACCESS data
HIV-positive GBM	1/133 days	Previous analysis of Victorian GBM in ACCESS data
Sexual risk parameters		
Proportion of sex acts which are HIV serodiscordant (HIV-negative non-PrEP)	10%	Estimated from large cross-sectional survey of GBM
Proportion of sex acts which are HIV serodiscordant (HIV-negative PrEP users)	17%	
Proportion of sex acts which are HIV serodiscordant (HIV-positive GBM)	34%	
Relative condom use of GBM on PrEP and HIV-positive GBM compared to HIV-negative GBM not on PrEP	0.3	Estimated from Melbourne Gay Community Period Survey 2019
See appendix A4.1 for full list of parameters are references, p256		

Table 7.2. Cumulative gonorrhoea incidence among Victorian GBM from 2020 to 2025 across different model scenarios of uptake of a gel-based point-of-sex intervention according to HIV-status, PrEP use and condom use.

	Scenario	Cumulative incidence 2020 - 2025	Difference in cumulative incidence to status quo	Relative reduction in cumulative incidence
	Status quo (no gel-PSI uptake)	94367		
a	Uptake in all subpopulations up to 50% threshold*	52988	-41379	-44%
b	50% of condom users downgrade and 50% of non-condom users upgrade	72559	-21808	-23%
c	All condom users downgrade to gel-PSI	107720	13353	14%
d	All PrEP users switch to gel-PSI	79081	-15286	-16%
e	50% of PrEP users and HIV-positive GBM switch to gel-PSI	80860	-13507	-14%
f	50% of non-PrEP users switch to gel-PSI	85203	-9164	-10%

Gel-PSI, gel-based point-of-sex intervention

*50% of each population upgrade to using the gel-based point-of-sex intervention, assuming no change to those already using condoms

Chapter 8

Why risk matters for STI control: who are those at greatest risk and how are they identified?

Chapter 8 is a research synthesis and commentary article commissioned for a special issue for the journal *Sexual Health*. Focused on STI Prevention in the 2020's, this chapter describes the importance of risk identification for STI control and explores new and emerging risk populations. Citing data generated from studies reported in earlier chapters, I describe increasingly diversifying STI risk, including in the context of PrEP use. In this chapter I also discuss important considerations for the future STI control among GBM, including the benefits and harms of risk-based screening, and novel methods for targeting new STI interventions towards those most at risk. These considerations for future STI control are informed by the data generated in earlier thesis chapters and offer a consolidation of key issues associated with broad STI risk identification prior to the consolidated thesis discussion presented in Chapter 9.

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This chapter is included in the original ***Sexual Health*** format in Appendix B4 (p 306)

Chapter 8

Why risk matters for STI control: who are those at greatest risk and how are they identified?

Authors

Michael W. Traeger[1,2], Mark A. Stoové[1,2]

Author Affiliations

1. Disease Elimination, Burnet Institute, Melbourne, Australia
2. School of Public Health and Preventive Medicine, Monash University, Melbourne Australia

8.1 Abstract

Identifying groups most at risk of sexually transmissible infections (STIs) is important for prioritising screening, targeting prevention strategies and alleviating the burden of STIs. However, identifying those at risk of STIs is complicated by stigma associated with STIs, undisclosed risk behaviour, and the fact that STI epidemics are diversifying beyond traditional risk groups typically characterised by demographics and sexual behaviours alone. In this review, we describe the epidemiology of STIs among traditional and emerging risk groups, particularly in the context of uptake of HIV pre-exposure prophylaxis (PrEP), increasing STI transmission among heterosexual people, and the concentration of STI burden among specific subgroups not readily identifiable by health services. Risk diversification poses significant challenges, not only for risk-based testing, but also for the costs and resources required to reach a broader range of constituents with preventive and health promotion interventions. As drivers of STI risk are not purely behavioural, but relate to relative STI prevalence within sexual networks and access to sexual healthcare and testing, localised surveillance and research is important in ensuring risk is appropriately understood and addressed within local contexts. Here, we review the evidence on the benefits and harms of risk-guided versus population-based screening for STIs among key populations, discuss the importance of risk-guided interventions in the control of STIs, and explore contemporary approaches to risk determination.

8.2 Introduction

There are an estimated 374 million new infections of curable sexually transmissible infections (STIs), such as chlamydia, gonorrhoea, syphilis and trichomoniasis, annually.[212] If left untreated, these infections can lead to serious sequelae, including pelvic inflammatory disease (PID), infertility, increased risk of HIV acquisition and, in pregnancy, neonatal death. With the majority of acute bacterial STIs being asymptomatic, identifying groups most at risk of infection is important for prioritising screening, targeting prevention strategies and alleviating the burden of STIs. Not adequately identifying people at high risk of STIs can limit the effectiveness of preventive interventions and lead to unnecessary testing and health-systems costs. Identifying those at risk of STIs risk is also complicated by the stigma associated with STIs and associated behaviours that limit individuals' disclosure of risk practices. Risk-based STI testing guidelines have traditionally centred on grouping people according to demographics and behaviours that have been identified in research and clinical practice as being associated with greater likelihood STI diagnoses. However, the periodic

emergence of STI epidemics among non-traditional risk populations, and the clustering of STIs in behaviourally specific subgroups within traditional risk populations, complicates the delivery of preventive interventions and care.

In this review, we describe the epidemiology of STIs among traditional and emerging risk groups, and explore contemporary approaches to risk determination. We review the evidence on the benefits and harms of risk-guided versus population-based screening for STIs among key populations, describe novel methods to identify risk, and discuss the importance of risk-guided interventions in the control of STIs.

8.3 Traditional and emerging risk populations

The burden of STIs has historically been concentrated among what are typically referred to as "key populations". The World Health Organization's (WHO) global health sector strategy on STIs suggests that each country needs to "define the specific populations that are most affected by STI epidemics" and that their response should be "based on epidemiological and social context".[212] These key populations are broadly categorised based on demographics such as gender and age, and specific sexual behaviours, such as number and gender of sexual partners. Specific populations that are highlighted in WHO guidance include adolescents and young people, men who have sex with men (MSM), transgender people, sex workers, and people who use drugs.

Adolescents

While young people and adolescents have been long recognised as a priority population for STIs,[373] targeted approaches are challenged by the fact they represent a substantial percentage of the general population and a behaviourally heterogeneous group. An analysis of data from the Global Burden of Diseases study found that adolescents have a higher STI burden than other age groups, and while overall the age-standardised incidence rate of STIs is trending down globally, the actual number of incident infections is increasing, likely due to the growth in the sexually active population and an increasing number of infections in adolescents.[112] Although there are biological factors which increase risk (e.g. young females can be more susceptible to chlamydia and HPV due to lower production of cervical mucous and increased cervical ectopy[374]), key drivers of risk among young people and adolescents include simultaneously being more likely to engage in sexual risk behaviour (e.g. concurrent partners and condomless sex)[373] and less likely to access sexual health services.[375] Low rates of seeking sexual healthcare among adolescents are likely, in part, to be associated with

concerns about confidentiality and discomfort in discussing sexual health concerns, as well as lack of knowledge about available services.[376] Typically lower rates of general health-seeking behaviours among males drive lower rates STI screening in general practice,[377] with testing among heterosexual males more likely to be driven by symptomatic presentation or partner notification.[378]

Trends in STI diagnoses among young people are dynamic and fluctuate across many settings. A recent analysis of data from the US found that among the youngest group, 12-17 years old, chlamydia and gonorrhoea positivity decreased, whereas it increased for the other age groups.[379] Insights garnered from behavioural epidemiology data can be used to understand such changes and also guide priorities for risk-based screening and other interventions. In this study, the authors suggest decreasing positivity among 12-17 years-olds may be associated with a declining proportion of high school students who report ever having sex, having fallen from 47.4% in 2011 to 39.5% in 2017.[380] In contrast, repeated behavioural surveillance of high school students in Australia found the proportion of students reporting ever having penetrative sex increased from 34.7% in 2002 to 46.6% in 2018.[381] As routine presentation to primary care remains the main access point to the healthcare system for many young people, opportunistic STI screening relies on clinicians being comfortable asking young people about sex and sexual risk, and creating "safe" clinical environments where young people feel comfortable discussing and disclosing sexual practices.

Heterosexuals

While MSM in high-income countries carry a significant burden of STIs, there is evidence that prevalence of STIs is increasing among heterosexual populations. For example, while gonorrhoea has been historically concentrated among MSM in Australia,[382] there has been a 475% increase in gonorrhoea notifications among females in the state of Victoria, Australia from 2010 to 2019.[200, 383] Similarly, whereas syphilis diagnoses in Australia remains concentrated among MSM residing in inner urban locations, syphilis is increasing in heterosexual men and women in Australia, especially those residing outside of inner-city suburbs.[201] Although the reasons for STI increases among heterosexuals in outer-suburbs are not fully understood, they may be reflective of less access of sexual health services.[200] Australian HIV surveillance data shows that, for HIV, women are often diagnosed late and report no prior history of HIV testing.[384] Genomic analyses also suggest that transmission of gonorrhoea into heterosexual populations may be facilitated through the bridging of sexual networks via populations of men who have sex with men and women.[202]

Further, while the burden of STIs among young heterosexuals has been well described, more evidence is coming to light of emergent STI epidemics among older heterosexual populations. In the US, the CDC reports a doubling of STIs among those aged over 65 over the last 10 years.[385] Reasons for increasing STI rates among older populations may relate to lower levels of sexual health knowledge[386] and inaccurate risk perception[387] among older generations.

Men who have sex with men

While STI epidemics may be diversifying beyond traditional risk groups, STI burden remains clustered within networks of people who may share specific risk practices with high rates of assortative partner mixing. MSM are at increased risk of STIs due to a combination of biological and behavioural factors (e.g., more partners, more concurrent partners, type of partners) and the relative prevalence of STIs within sexual networks that contributes transmission risk. While MSM are recognised as a priority group for STIs globally, the population of MSM comprises a diverse group, with different behaviours, identities and healthcare needs, and consequently risk varies across specific subgroups. For example, MSM living with HIV have historically had higher rates of STIs such as syphilis[124] and sexually acquired hepatitis C,[388] likely associated with smaller sexual networks with high rates of partner mixing which sustain high prevalence and onward transmission. Given the often differing prevalence of STIs between the two groups, and specific sexual network dynamics, behavioural and demographic predictors of STI risk often vary between HIV-negative MSM and MSM living with HIV.[389] Further, rates of specific STIs within risk populations often vary based on age. For example, among MSM in Australia, gonorrhoea is more common among those aged 20-29 years compared to syphilis, which is most common among those aged 30-39 years.[121]

The concentration of STI risk among subgroups of MSM is also diversifying. Advances in biomedical interventions for HIV over the past decade, including Treatment as Prevention (TasP) and pre-exposure prophylaxis (PrEP), have led to changes in behaviour and STI epidemiology among MSM. While declines in condom use at the population[151, 390] and individual level[162, 391, 392] associated with the roll-out of PrEP in high-income countries have occurred in parallel to increases in STI incidence,[67, 393] disentangling and quantifying the direct effect of PrEP rollout on STI incidence is difficult.[159] Some countries that have seen significant uptake of PrEP were observing increases in STIs and declines in condom use among MSM prior to this scale-up.[120] Even prior to epidemiological evidence emerging, assumptions regarding declines in condom use in the context of PrEP has led to specific STI testing guidelines for PrEP delivery.[75] STI testing guidelines for PrEP also acknowledge the risk-based criteria for PrEP prescribing [78, 394, 395] and high rates of STI diagnosis prior to PrEP initiation.[67, 305] Surveillance

data from Australia, where PrEP has been available since early 2016 through large demonstration projects[66, 68] and more widely available since April 2018 when PrEP was approved as a government subsidised medicine, has shown that, while rates chlamydia and gonorrhoea have stabilised among MSM using PrEP, syphilis continues to increase.[267] Continuing increases in syphilis among PrEP users is likely reflective of greater comfort in[144] and increased rates of[154] serodiscordant sex in the era of HIV TasP and PrEP, and the greater differential in syphilis prevalence between MSM living with HIV and HIV-negative MSM compared to chlamydia and gonorrhoea. Further still, within risk groups such as PrEP users, the burden of STIs is highly skewed towards those experiencing repeat or concurrent infections. Analysis of PrEP users enrolled in an early demonstration project in Australia found that 50% of PrEP users were not diagnosed with an STI during follow-up, and that one-quarter of PrEP users accounted for three-quarters of STIs.[67] These trends have continued to be observed into the years following widespread PrEP implementation in Australia[267] and in other settings such as the UK.[396]

Travelers and migration

With early detection and treatment of STIs to prevent onwards transmission a key STI prevention strategy, there is an increasing focus on the impact of higher risk behaviours and settings associated international travel and migration on local STI transmission. International travellers returning from high-prevalence settings are at increased risk of STIs,[397] and if not identified upon arrival, risk introducing new strains of STIs and seeding new clusters of transmission. Pre-emptive sexual risk screening during clinical visits prior to travel, for example for vaccines, could provide an opportunity to offer STI interventions, such as STI immunization, PrEP or self-initiated antibiotic treatment of bacterial STIs, while also prompting travellers to be screened for STIs when they return.[398]

Migrants arriving in high-income countries often face additional barriers to accessing sexual health care driven by cultural aspects of stigma, knowledge gaps in health literacy, and ineligibility for subsidised care.[399] For example, in Australia, newly arrived Asian-born MSM have been identified as an emerging priority group for HIV,[400] with qualitative work highlighting that lack of access to subsidised PrEP introduces a cost-barrier for many newly-arrived MSM.[401] Similar structural barriers exist for access to routine HIV and other STI testing for this group, which potentially contribute to higher observed incidence of HIV among Asian-born MSM and high rates of testing positive for HIV at first presentation for testing.[402] Newly-arrived Asian-born MSM may also be more likely to have sexual partners with similar demographics, with assortive mixing within this higher prevalence population contributing to higher incidence. The impact of inequitable access to healthcare on STI

risk may be compounded by changes in sexual risk-taking behaviour following migration, especially among MSM emigrating from countries with typically repressive social norms to countries with more progressive views and greater access to gay venues and community.[403] Similarly, migrant sex workers are often at greater risk of STIs than non-migrant sex workers, although the interaction between migrant status and country income-level has been shown to vary depending on local epidemiology and legal contexts.[404] STI risk has been shown to be higher among migrant sex workers who do not have contact with outreach workers,[405] further highlighting the impact of unequal access to health care and harm reduction services on STI risk among migrant populations. Lastly, movement across communities within countries may also be contributing to STI transmission. Recent modelling work suggests that high population mobility likely contributes to high levels of STI prevalence among remote indigenous communities in Australia.[406]

Technology and risk environments

Across a diverse range of traditional and non-traditional risk groups, specific behaviours may be associated with particular risk environments or the use of digital technologies to meet partners that pose challenges for risk-based screening in clinics and for targeted interventions and health promotion. For example, among MSM, meeting partners at sex-on-premises venues may be associated with increased risk, as STI prevalence is high among MSM attending these venues.[407] Meeting partners online or through hook-up apps has also been shown to be associated with greater STI risk among MSM.[408] For heterosexual people, while a recent review found no evidence of an association between online-partner seeking and lower condom use or STI status,[409] among young heterosexual people, use of geo-social dating apps has been linked to increased rates of casual sex, having multiple partners and having sex without discussion about STI status.[410] Other subcultural behaviours associated with increased STI risk, such as 'swinging',[411] may not be readily identified at STI clinics. Practices such as those mentioned above typically cluster within specific geographic and social or sexual networks, and therefore relative risk can be temporally and significantly elevated in the context of undiagnosed infections entering specific networks, resulting in outbreaks of STI infections.

With more evidence of diversifying STI risk, there is a need to go beyond broad, risk-group categorisations based on age, sex and sexuality. Risk diversification poses significant challenges, not only in terms of risk-based diagnostic testing, but also in relation to the costs and resources associated with reaching a broader range of constituents with preventive and health promotion interventions. Here, continued STI surveillance and research, including qualitative and ethnographic

research to understand contextual factors that drive risk, is important and emerging data need to be monitored closely to guide and inform policy and practice. Early detection of risk diversification is crucial, given STI control becomes increasingly challenging as prevalence increases in emergent risk populations. Strategies must continue to promote high intervention coverage among known risk groups, but also consider targeted interventions that focus on individuals at greatest risk within these groups.

8.4 Rethinking risk – more than just behaviours

As described above, defining traditional risk groups on the basis of broad demographic and sexual behaviour may be inadequate for efficient and effective STI prevention and clinical interventions. To guide targeted interventions towards those at greatest risk, strategies which include non-behavioural considerations may be beneficial. For example, while condom use may be strongly associated with HIV risk, there is mixed evidence of the association between condom use and STI risk, relative to other factors; evidence suggests that among MSM using PrEP, condom use is less predictive of STI risk than sexual networks and the practices that contribute to defining these networks.[67] The estimated per-partner effectiveness of condoms for bacterial STIs[412] is also much lower than for HIV[413, 414], and high levels of extra-genital transmission of STIs among MSM have been reported.[415] Practitioners should therefore consider, dependent upon local epidemiology and context, a broader suite of factors when screening for risk, beyond traditional notions of broad demographic risk or condom-based definitions of “safe sex”.

Neighbourhoods and access to healthcare

Key drivers of STI risk are not purely behavioural, but relate to STI prevalence within respective communities and sexual networks, as well as individuals’ access to sexual healthcare and testing. Less access to testing and healthcare means that STIs remain undiagnosed for a long period of time, and individuals have more chance of passing infections on to their sexual partners. This is evident among populations of black MSM in high-income countries such as the US, the UK and Canada, who are at increased risk of HIV compared to white MSM, despite there being no evidence that black MSM have more partners or engage in more serodiscordant condomless sex than other MSM[416]. A wealth of data highlights that black MSM in the US are often faced with poor access to culturally competent health services, including HIV and STI testing, and experience stigma and discrimination that impede access to services.[417] Similarly, Aboriginal communities living in remote regions of

Australia experience disproportionately high rates of STIs, with chlamydia and gonorrhoea prevalence among young people in these communities among the highest in the world.[418, 419] With others demonstrating similar numbers of sexual partners and a similar average age at sexual debut among young Aboriginal Australians compared to non-Indigenous young people,[420] discrepancies in STI incidence are likely driven by structural barriers (e.g. access to testing affecting rates of undiagnosed infections). Despite clinical guidelines and specialist support for primary health-care clinicians visiting these remote communities, rates of re-testing and clinical follow-up within recommended timeframes in Aboriginal communities are suboptimal.[421] Remote Aboriginal communities are faced with significant clinician-level barriers to STI testing, such as high-levels of clinician turnover, a lack of familiarity with STI protocols, and prioritisation of other urgent health concerns by clinicians.[422] The impact of access to healthcare on HIV outcomes is also reflected in Australian migrant communities, especially those from South-East Asia and Sub-Saharan Africa and those from countries which are ineligible for reciprocal healthcare agreements, where larger gaps in the HIV care-cascade are observed compared with non-migrants.[423] Lower rates of repeat HIV testing are also observed among HIV-negative migrants.[402] Addressing disproportionate rates of STIs among both Aboriginal and migrant communities will require systemic change and removal of structural barriers to accessing healthcare.

Further highlighting the important role of environmental and socio-structural factors in contributing to STI risk, differences in laws and practices which maintain racialized inequities (e.g. inequitable urban housing policies) at the neighbourhood level have been shown to be greater predictors of HIV risk than sexual risk behaviours.[424] In the US, higher rates of gonorrhoea have been linked to neighbourhood-level determinants of health, including higher rates of single mothers and lower socio-economic status.[425] Analysis of syphilis distribution in Canada suggests that spatial clustering of syphilis diagnoses are not fully explained by distribution of MSM populations or different rates of testing across areas, suggesting that additional neighbourhood-levels factors are likely driving transmission.[426] These data highlight the importance of localised surveillance and research to ensure risk is appropriately understood and addressed within local contexts.

Changes in risk

It is also important to consider that risk changes over time, and that if an individual does not meet certain risk criteria for screening or a prevention intervention, they may in the future. For example, early PrEP guidelines in Australia recommended prescribing PrEP even in the absence of recent risk, if individuals anticipated risk-behaviour in the near future.[75] Similar considerations for STI

interventions should be considered. Latent transition analysis among both heterosexuals[427] and gay and bisexual men[428] show that individuals' allocation into specific risk groups remains relatively stable. However, changes in risk are often observed when people move out of monogamous relationships. This is reflected in risk-based STI guidelines for young heterosexuals,[429] and latent transition analysis of MSM regularly attending for STI testing.[428] Further, these data reflect states of risk prior to the introduction of PrEP. Given the evidence of changes in STI risk follow PrEP initiation[162], and that people transition in and out of PrEP use based on personal risk perception over time,[430] regular assessment of current risk among people presenting to health services with any history of PrEP use is warranted. Further, the COVID-19 pandemic and associated public health orders have led to significant changes in sexual behaviour[101] and breaks in PrEP use[254, 431] among MSM, decreases in casual sex among heterosexuals,[432] and significant declines in the frequency of STI testing.[433] Drops in testing in the presence of ongoing sexual risk have the potential to increase pools of undiagnosed infection.

8.5 Screening for STIs

While testing is crucial for the control of STIs, guidelines on who to test, and how often, vary. Many guidelines highlight specific populations that should be considered for STI screening, or recommend clinicians take a sexual history to determine if individuals should be screened. Among populations where STIs are highly asymptomatic, e.g. extra-genital infections among MSM, informed decisions around how to screen in the absence of symptoms rely on understanding epidemiological contexts (historical and emerging). While broad-based guidelines which recommend testing of entire populations, for example regular testing of all sexually-active MSM or STI testing at each PrEP prescribing visit, may lead to greater testing coverage and frequency, they present challenges for managing clinic capacity and may impact the cost and cost-effectiveness of sexual health services. Such strategies consume a lot of resources and are not often feasible in resource-constrained settings or where testing is not fully subsidised. Further, broad-based recommendations obfuscate the need for nuanced risk screening and targeted higher frequency testing for those at particularly high risk or those who are diagnosed with STIs recurrently.

Opportunistic testing during routine visits

Opportunistic testing, when a test if offered in-clinic during a routine patient visit, often occurs after clinicians take a sexual history, following an electronic prompt, or if the patient is identified as

belonging to a specific high-risk group for which STI testing is recommended. For example, in the US, the CDC and US preventive Services Task Force recommend annual chlamydia and gonorrhoea screening for all sexually active females aged <25 years, and annual screening for women aged over 25 with a risk factor (more than 1 sex partner, a sex partner with concurrent partners, a new partner).[434] While such recommendations allow clinicians to assess risk on an individual basis, significant challenges associated with risk screening exist. Clinician barriers include discomfort around engaging in sexual health discussion or asking sensitive questions, feeling inadequately trained, and difficulty incorporating a sexual screen into a regular visit due to time constraints.[435] Barriers may also be magnified among doctors who serve ethnically diverse populations.[436] Patient sexual history may also be hindered due to patient concerns around confidentiality and stigma, lack of perceived risk and lack of sexual health awareness.[437] Some of these barriers can be overcome by implementing computer-assisted self-interviewing in clinic waiting rooms, where patients complete an electronic survey which asks about sexual history and specific risk factors.[438]

Universal screening of key populations

In contrast to its screening recommendations for women (women under 25 years screened annually, those over 25 only screened if risk factor present), the US CDC recommends annual screening for all sexually active MSM, and more frequent screening (3-6 months) for MSM at increased-risk (define has having multiple partners or persistent risk behaviours).[439] In Australia, guidelines were updated in 2019 by removing specific risk based recommendations for screening frequency among MSM and recommending uniform three-monthly testing for bacterial STIs for all sexually active MSM, regardless of number of partners, STI history or presence of specific risk behaviours.[284] While increasing rates of STIs among MSM may warrant high-frequency screening, in the context of highly skewed STI incidence among certain subgroups of MSM[267] and resource and time constrains in general practice, not distinguishing between high and low-risk MSM may lead to ineffective or less cost-effective STI screening practices.

It is not clear whether the implementation of ambitious guidelines which recommend high-frequency screening for all MSM regardless of risk-factors, such as those in Australia, will lead to greater increases in testing frequency among those already being tested, or in testing coverage across the whole population, with little evidence to suggest this strategy would have an impact on STI prevalence. While sexual health clinics may be able to achieve such testing rates, in jurisdictions where STI testing is mainly done in general practice, the burden of trying to screen all MSM four times a year might mean adequate screening is not achieved among those who it would benefit the

most, and universal screening at high frequency is likely not feasible in settings where testing is not covered by universal healthcare arrangements.

Effect of screening on STI prevalence

Evidence for the effectiveness of broad-based population-level screening on test uptake and STI prevalence is mixed, and the benefits and harms of broad-based population testing versus more specific risk-guided testing protocols vary between population. Risk-based opportunistic screening in the US, based on taking a sexual history, has largely not been successful in achieving high rates of chlamydia screening among high-risk young women[440], largely due to low rates of practitioners in general practice undertaking a sexual history. A 2006 survey found that only 55% of primary care physicians asked about sexual histories as part of regular examinations.[441] Data from Australia reports that 46% of general practice clinicians would not take a sexual history of an MSM presenting for a routine check-up.[435]

Even if clinician and patient-level barriers are overcome, there is little evidence to suggest that high coverage of opportunistic screening among heterosexuals has an impact on STI prevalence. A large cluster randomised controlled trial of opportunistic chlamydia testing in rural GP services in Australia, which implemented a protocol involving clinician education, computer alert prompting and reimbursements, found that, even with increased testing of eligible patients, the intervention was not associated with a decline in chlamydia prevalence. [214] However, it was associated with a decline in PID presentations at nearby hospitals. Additional data from the US shows that while screening among heterosexuals may not reduce chlamydia prevalence, it is a potentially effective approach to reduce PID.[442] Another large cluster-randomised controlled trial which assessed a multi-pronged intervention of continuous quality improvement (review of clinical data, education, implementation of systems-level changes aimed at improving STI practice) in general practice clinics serving remote indigenous populations in Australia again found increases in testing but no changes in population-level prevalence of STIs.[443]

Strategies to increase STI testing capacity

Consideration of adapted service models and strategies to enhance STI testing efficiency in established services may be required to maintain capacity for broad risk-based STI screening practices, while also increasing testing coverage and frequency among those at particularly high risk. While technology-based systems to reduce the burden of high frequency testing on patients have been implemented at the clinic and laboratory level (e.g. results delivered by SMS[219]), frequent

testing can be challenging because of restricted clinic operating times. These types of health systems barriers make increasing patient-driven demand for STI testing difficult. For example, evaluation of large Australian health promotion campaign targeting MSM for HIV and STI testing found that despite substantial investment in health promotion and a high proportion of MSM recalling campaign messages, only a modest increase in chlamydia and gonorrhoea testing was achieved, and the campaign had minimal impact on HIV or syphilis testing.[444] Social marketing initiatives aimed at creating demand for testing must also be accompanied by structural changes that make STI testing more convenient.

In order to achieve high rates of testing, adaptive and convenient service models which reduce the burden on patients will be required. A recent scoping review of HIV and STI testing preferences among MSM in high-income countries identified the convenience and privacy of self-testing, and the need to provide a variety of testing options, as key themes of testing preferences.[445] A 2016 review of interventions aimed at increasing STI screening found that the most effective interventions included incorporating collection of STI specimens as standard procedure regardless of reason for visit, and the use of electronic health records as a reminder to offer screening.[446] Models which streamline clinic visits, including patients self-collecting specimens, computer-assisted questionnaires, test-and-go services, and rapid testing with same-day results have been shown to increase screening while also reducing costs and time between testing and treatment.[447] The incorporation of all these elements into a single, free, express testing service, Dean Street Express in London, was shown to reduce mean time between test and notification to 0.27 days, compared to the standard clinic's 8.95 days, which was projected to have prevented 196 chlamydia and/or gonorrhoea infections over one year of implementation.[448] Nurse-led test-and-go services which remove the need for doctor consultation and reduce testing times have also been shown to capture clients with different demographics, yet still detect a similar rate of STI positivity, compared to standard doctor-led testing.[449] Regulation in Australia and implications for introducing these devices

Opt-out testing

Another strategy, opt-out testing, involves testing all patients in a specific risk group, regardless of the presence of sexual risk factors, with the aim of increasing screening rates. Population-based opt-out screening methods remove the burden of clinicians to initiate sexual history taking, and decide if a test is appropriate or needed. However, opt-out testing does place the burden on clinician to ensure appropriate disclosure of the test to patients in pre-test discussions to ensure they are aware of the implications of a positive result and have the opportunity to opt out. Surveillance data from

Australia showed opt-out testing increased rates of syphilis testing among MSM living with HIV.[450] Modelling work suggests that an opt-out testing strategy for all women aged 15-24 in the US would likely reduce chlamydia prevalence, and be more cost-effective compared to a risk-based screening strategy, however was dependent on individuals' insurance coverage.[451] In limited-resource settings or where universal healthcare is not available, overall effectiveness and cost-effectiveness of such strategies would be significantly reduced.

Targeted testing of those at greatest risk

A modelling study of syphilis among Canadian MSM found that increasing screening frequency among those already engaged in testing had a greater reduction on syphilis incidence than increasing screening coverage (i.e. the proportion of the population tested).[217] Another modelling study of MSM in the US found that both increasing the rate of screening from current levels to biannual among all sexually active MSM currently being tested, and increasing the coverage of biannual screening to 30% of all 'high-risk' MSM, each reduced CT and NG incidence by approximately a 75% reduction over 10 years. The authors suggest that more frequent screening for all MSM, and scaling up targeted screening for men with multiple recent partners, were the most effective strategies.[452] US guidelines recommend syphilis screening in MSM, people with HIV and pregnant women, but do not provide routine screening recommendations for HIV-negative heterosexual populations. Modelling work suggests that achieving such a strategy may have an impact on transmission in states with more MSM-focused outbreaks, but would have little or no impact on transmission in states where syphilis is more evenly distributed between MSM and heterosexual populations.[285]

Guiding public health strategies to increase active case-finding using epidemiological trends can quickly and efficiently respond to new STI outbreaks. For example, many countries utilise existing networks of general practice clinicians to issue alerts around increasing rates of STIs in certain geographical areas or subpopulations. In the UK, outbreaks are detected by local surveillance undertaken by clinicians or health protection teams via the detection of higher than expected numbers of diagnoses.[453] These are sometimes supplemented by more systematic approaches that utilise automated spatiotemporal detection tools to routinely analyse notification data.[454] Following an investigation to declare and determine the spread of an outbreak, initial stages of outbreak response usually involve alerting clinicians and appropriate organisations through established communication systems. Similar alerts in Australia are commonly issued through the general practitioner network.[197] Sustained outbreak control can then include strategies such as active case

finding, qualitative data collection to understand drivers of the outbreak, outreach programs targeting specific venues or populations, and widespread promotion through social and traditional media.[453] These strategies can also facilitate targeted communication to non-primary care clinicians who may not be routinely involved in STI care. For example, recent increases in congenital syphilis, likely related to low rates of syphilis screening and issues with continuity of care and treatment during pregnancy among patients tested in antenatal hospital clinics in Australia[196] led to specific guidance targeted at increasing syphilis testing during pregnancy. The success of such strategies relies on surveillance infrastructure to identify and characterise new STI outbreaks in a reliable and timely manner, and appropriate levels of funding and technical support to resource a timely response.

Over-screening

In addition to the burden of frequent STI testing incurred by the patient, there are potential harms associated with over screening for STIs, including anxiety, psychological harm associated with false positives or negatives, or possible change in risk behaviour. However, the US CDC reports there is currently limited data on psychological or other harms associated with screening for chlamydia and gonorrhoea among women and heterosexual men.[455] Among MSM, there is growing evidence that high antibiotic consumption among PrEP users may be driving antibiotic resistance. Given high rates of bacterial STIs among PrEP users, and high frequency screening and treatment, PrEP users have high-levels of macrolide consumption, as well as for cephalosporins, fluoroquinolones and tetracyclines.[456] In some European countries, consumption of macrolides is 52 times higher among PrEP users compared to community-level consumption.[456] Cohorts of PrEP users around the world are commonly characterised by having high rates of partner change,[162] translating to high and stable prevalence of chlamydia and gonorrhoea. Long-term surveillance data in Australia suggests that sustained high-frequency testing of PrEP users (3-monthly) for more than 4 years has not curbed rates of chlamydia or gonorrhoea in this group.[267] In contrast, such high-frequency screening is costly and may be driving antimicrobial resistance.[457] Modelling work suggests that even low-levels of screening for the largely asymptomatic STI *mycoplasma genitalium* among MSM is leading to increased antibiotic resistance through increased, arguably unnecessary treatment.[211] In its resistance threats 2019 report, the US CDC has listed drug-resistant gonorrhoea on its Urgent Threats list, and *mycoplasma genitalium* on its watch-list.[204] Surveillance of antimicrobial resistance is crucial in the context of high frequency screening and transmission. In light of the threat of antimicrobial resistance, there is a growing case for reconsidering the evidence base for high-

frequency screening of STIs, which are mostly asymptomatic, among populations with high and stable prevalence.[458]

8.6 Identifying risk

With the aforementioned barriers to clinician-led discussions on sexual history during routine care, and the need for increased client-driven demand for testing, methods to appropriately and efficiently identify risk, both from the clinician-perspective and including individuals' self-perception of risk, are crucial.

Service-identified risk

For clinical services aiming to identify risk, strategies can go beyond broad testing protocols based on risk group and utilise clinical data and automated screening tools. For example, previous infection can be used as an indicator of risk. History of an STI has consistently been shown to be one of the strongest indicators of future risk among both MSM[459] and adolescent heterosexuals.[460] The strong predictive value of previous diagnosis is reflective of high rates of reinfection, such as that of syphilis reinfection widely observed among MSM[461], especially those living with HIV.[459] It is unsurprising then that modelling work suggests that increasing screening frequency among MSM with a prior syphilis diagnosis is equally effective in reducing syphilis prevalence as testing focused on those reporting high partner numbers, and far more effective than distributing testing equally among all MSM.[286] Targeting individuals with a prior diagnosis of syphilis can be done through clinician-led history taking, patient management system alerts or through demand creation approaches such as community-driven awareness-raising of reinfection risk.

Novel methods for identifying those at risk, including machine learning and prediction modelling using electronic medical records, have also been explored, with varying levels of efficacy. For example, the use of computer-assisted sexual history taking allows data on behavioural risk factors to be analysed using risk prediction models and machine learning. Machine learning has been successfully used to identify those who are eligible for PrEP based on medical records,[462] however, the use of machine algorithms of structured health record data have been shown to poorly differentiate patients with and without repeat STI diagnosis, indicating that they may be less useful for predicting STI risk.[463] Prediction models of routinely collected healthcare data have been used in emergency room settings where laboratory variables are collected and can be used for risk prediction.[464] Despite growing work on machine learning, such techniques require technical capacity,

education and training, and access to "big data" through which to generate predictive algorithms. Also, as prediction methods rely on patient history, they would likely provide less benefit in determining STI risk for patients attending clinics sporadically or for the first time.

Risk self-identification

Along with clinical services being able to adequately identify STI risk, patient-driven demand for STI testing relies heavily on individuals recognising their risk, and seeking STI testing. An analysis of adults in the UK found that both men and women underestimate their self-risk of STIs, and that many who did perceive themselves as at-risk had not recently accessed STI care.[465] Health promotion therefore should not only focus on improving self-identification of risk, but also encourage people to act on their perceived self-risk by accessing care. Perception of the seriousness of STI have been shown to vary considerably among specific subgroups of MSM at high risk of STIs,[333] and may influence an individuals' decision to present for testing following possible exposure to an STI or following windows of risk, if they perceive the health-risk of an STI going undiagnosed to be low. Along with perceptions of risk, STI knowledge has also been linked to recent STI testing,[466] highlighting the importance of health promotion campaigns for increasing STI awareness and access to information on STIs. Peer-led models of care have been shown to provide opportunities for MSM to enhance their risk-reduction knowledge around STIs, with greater benefits among young and less gay community-attached MSM.[467]

Finally, technology is also playing a role in the self-identification of STI risk. As described earlier, MSM who use geo-social networking apps are at increased risk of STIs. This highlights a potential opportunity for community and health organisations to deliver reliable, trusted and easily accessible sexual health information at scale to those at greatest risk via social networking apps. Further, specific mobile-phone applications have been designed to screen for STI risk, as well as to help users identify STI symptoms. While mobile phone apps for the care and prevention of STIs are of high interest to the general public,[468] a 2016 review of available STI-related apps found that many contained incorrect and potentially harmful information.[469] Recent data also suggests that while digital methods of sexual healthcare deliver (i.e. through video consultation) may be acceptable, many still prefer human interaction over automated chat-bots when accessing sexual health information.[470] Further, disparities in utility and uptake of digital health information and interventions exist, with older people[471] and those from racial and ethnic minorities less likely to engage in technology based interventions.[472]

8.7 Conclusion: Adopting an adaptive risk-guided approach to STI control

Alongside historically high-risk groups, new risk groups for STIs continue to emerge and diversify. While the evidence for the effect of population-based screening compared to higher-frequency, targeted screening strategies on STI prevalence varies within and across MSM and heterosexual populations and for specific STIs, strategies which reduce clinician and patient-level barriers, and are adaptive to local epidemiological contexts, have the greatest potential for achieving optimal screening rates and controlling new outbreaks. Such strategies need to remove the burden on clinicians and the assumption of risk, and improve patient convenience in order to increase testing coverage, while still including sufficient nuance to identify those at greatest risk for targeted testing and prevention.

Chapter 9

Discussion

9.1 Contributions to knowledge

9.1.1 Interplay between PrEP uptake, serosorting and STI transmission

The epidemiological analyses of surveillance data from the ACCESS sentinel surveillance network presented in Chapters 3 & 4 represent, respectively, the largest cohorts of PrEP users and GBM from which trends in STI incidence rates have been reported globally. The Australian context of PrEP implementation and scale-up, and the pre-existing surveillance systems in place, offered the opportunity to explore how rapid implementation influenced STI epidemiology. The ACCESS surveillance system, which utilises state-of-the-art technology and captures a high proportion of GBM accessing sexual health care in Australia, allowed for near-population-wide coverage when analysing trends in STIs among PrEP users specifically and GBM more broadly. The unique combination of high coverage of sexual health and high caseload general practice clinics, across-service linkage of patients' clinical data, availability of decades-long historical data, and the ability to produce individual-level data to characterise individuals and monitor patient-level outcomes over time, make ACCESS one of the only systems in the world able to produce such high-quality estimates of the impact of rapid PrEP scale-up on STIs in a real-world setting.

Major findings of Chapters 3 & 4 were that while incidence rates of gonorrhoea, chlamydia and syphilis were high among GBM using PrEP in Australia, the transition from large yet targeted PrEP implementation studies to widespread access to subsidised PrEP, and resultant high coverage among GBM, did not lead to immediate or exponential increases in STI incidence rates, as was a genuine concern prior to the introduction of PrEP.[146, 473, 474] In contrast, incidence of the most common bacterial STIs, gonorrhoea and chlamydia, largely stabilised among GBM using PrEP after four years of PrEP implementation. Stratified analysis highlighted the changing risk-profile of GBM initiating PrEP over time, with prospective STI incidence among those starting PrEP in 2019 being 21% lower than those starting in 2016. While this change in risk-profile in PrEP initiates over time explained most of the declines in incidence for chlamydia and gonorrhoea, after adjusting for this effect, a slight decline in gonorrhoea was still observed. This finding emphasises potential biases associated with studies based on early implementation periods and early PrEP adopters and that high coverage of PrEP among GBM without HIV did not lead to exponentially increasing rates of STIs. While the population-level impact of frequent STI testing associated with PrEP uptake is difficult to untangle, and longer periods of follow-up may be required to measure this effect, the observed declines in chlamydia and gonorrhoea incidence in our analysis may also reflect the interruption of transmission chains through frequent testing.

In contrast to chlamydia and gonorrhoea, syphilis incidence among PrEP users steadily increased during the first four years of PrEP implementation, including the period of widespread PrEP availability. To further understand the drivers of these diverging trends, in Chapter 4 I utilised the strengths of the ACCESS system to explore syphilis trends over a decade among three distinct subgroups of GBM. The inclusion of GBM with HIV, and the further stratification of GBM without HIV into those with and without evidence of any PrEP prescription, allowed for a comparison of testing and incidence trends among subgroups of GBM with different syphilis risk, and provides deeper insights into how syphilis transmission is likely being driven by changes in serosorting and sexual network dynamics. While syphilis incidence among GBM with evidence of PrEP use steadily increased over the past decade, increases were observed prior to PrEP rollout in 2016, suggesting that presence of a PrEP prescription is likely a marker of pre-existing risk characteristics among a subgroup of GBM without HIV. Indeed, prior STI diagnosis is a clinical indication for PrEP suitability.[79] Converging trends between GBM with and without HIV, commencing before PrEP implementation, likely reflect longer-term trends in the decline in the use of serosorting as an HIV prevention strategy. Declines in condom use following the introduction of PrEP in 2016[151] may have accelerated increasing incidence among GBM without HIV, however testing for syphilis almost doubled among those initiating PrEP from 2016 onwards, making it difficult to attribute any one factor as the driving cause of greater syphilis detection. Taken together, analyses of surveillance data presented in this thesis highlight that PrEP, when combined with accompanying STI screening (as demonstrated through my earlier work; see Appendix C1), can be scaled up rapidly and at a national-level without significantly compounding the burden of STIs among GBM. Further, our group's work found that scaling up PrEP among GBM in Australia did not impact HIV or STI testing rates among GBM not using PrEP who were also attending clinical serves where PrEP users were recruited (see Appendix C4, p 341).

The findings from studies across this thesis underscore the influence of dynamic sexual networks of GBM with and without HIV in Australia on STI transmission. The only STI which steadily increased among GBM using PrEP in our analyses was syphilis; the differential between syphilis incidence in GBM with HIV and GBM without HIV at the time of PrEP rollout was the greatest for any STI.[121] Chlamydia and gonorrhoea were relatively stable among PrEP users in Australia, and national surveillance reports show that incidence of chlamydia and gonorrhoea between GBM with and without HIV were more similar compared to syphilis, and were already relatively high among HIV-negative GBM attending sexual health services prior to PrEP roll-out. Finally, hepatitis C incidence among PrEP users in Australia was among the lowest observed in PrEP studies globally, and may

have been influence by reductions in hepatitis C prevalence among GBM with HIV which was rapidly reduced with public subsidy of DAA therapies.[173] The timing of PrEP implementation in Australia, which occurred in parallel to rapid uptake of hepatitis C DAA treatments, likely led to the low incidence of hepatitis C observed in Australian PrEP users. While PrEP and DAAs became available in the same year in Australia (2016), survey data from Australian GBM show that there was a delay in PrEP users reporting increased comfort relying on PrEP for condomless sex with people of different HIV status.[144] As PrEP became more normalised, rapid uptake of DAA treatments among GBM coinfected with HIV and hepatitis C would have already lead to significant declines in HCV viraemia in the population.[173] Taken together, these key differences in STI rates between GBM with and without HIV, and the corresponding conflicting trends among GBM using PrEP, support the hypothesis that observed trends in STI/hepatitis C acquisition among GBM using PrEP are being strongly influenced by trends in serosorting and condomless sex with people with HIV.

9.1.2 Insights into STI epidemiology and attitudes towards STIs in the context of PrEP

Alongside novel insights into the interplay between HIV biomedical prevention and STI transmission among GBM, this thesis generated a number of noteworthy findings in relation to the current epidemiology of STIs among Australian GBM. Consistent with my previous research on PrEP implementation studies in Australia,[67] data presented in Chapters 3 and 4 showed that during the subsequent period of wider access to publicly-subsided PrEP, STI diagnoses remained highly concentrated among a subgroup of GBM. Among 22,730 PrEP users over more than 25,000 person years of follow-up, 56% of individuals were not diagnosed with an STI, and 6% of GBM diagnosed with >5 STIs accounted for 36% of all STI diagnoses over the observation period. For syphilis specifically, rates of repeated syphilis infection were more than 4-fold greater than overall syphilis infection. In particular, while there were stark differences in syphilis incidence between GBM with HIV and GBM using and not using PrEP, among those with a diagnosis, rates of reinfection were similar across each group. Previous syphilis diagnosis was the strongest indicator of prospective STI risk.

The above findings that STI risk is highly variable among GBM in Australia is also congruent with my findings from the latent class analysis presented in Chapter 4. While most PrEP users in this study still reported that avoiding STIs, and avoiding passing on STIs to sexual partners, is of high priority, we also found that PrEP users vary considerably in terms of their STI acquisition risk, behaviours and attitudes to STIs. Two smaller classes of GBM had low rates of recent STI risk, despite being current

PrEP users. The two largest classes, which reported very different attitudes towards STIs and STI prevention, both had high rates of recent STI diagnosis. The way in which PrEP users utilise particular STI prevention strategies is likely to be influenced strongly by their attitudes towards being diagnosed with an STI and receptivity to adopting new interventions. Considering these findings alongside my previous work which showed that traditional behavioural indicators (i.e. condom use) may be less indicative of STI risk in the era of PrEP than behaviours associated with specific sexual networks (e.g. group sex, serosorting) (see appendix C1, p 320], effective targeting of STI strategies may need to consider not only behavioural indicators or current use of PrEP, but also previous STI diagnosis in the context of individuals' attitudes and motivation to utilise different prevention strategies.

9.2 Implications of findings

9.2.1 Implications for STI control in GBM

STI testing

While clinical interactions that occur alongside PrEP prescribing provide an opportunity to offer comprehensive STI testing, testing all PrEP users at a similar rate and disproportionately focusing testing efforts on PrEP users alone may be an inefficient testing strategy. As described in the commentary article presented in Chapter 8, modelling work suggests that different testing strategies which focus on increasing screening coverage (among the population) or screening frequency (among those already being tested) have different impact on population-level STI transmission; strategies which increase screening frequency among people with a prior infection, especially for syphilis, yield a greater impact.[217] Accounting for risk heterogeneity and skewed distribution of STI diagnoses in testing strategies may increase population-level benefits and improve cost-effectiveness.

Chapter 8 discussed the pros and cons of testing using a risk-based versus population-level testing strategy for specific groups (*e.g.,* all GBM or all PrEP users). Australian guidelines currently recommend three-monthly testing for STIs for all GBM.[213] While we observed a median of 84 days between testing in our analysis of STI incidence among PrEP users (Chapter 3), follow-up was censored when individuals ceased PrEP use (four months after their last prescription). In the more wide-ranging analysis on syphilis incidence in all GBM (Chapter 4), which also included observation among PrEP users during periods of non-PrEP use, the average rate of testing was less than 2 per

year for all subgroups of GBM, including those with a past or future PrEP prescription in the ACCESS database. While guidelines which adopt a universal screening recommendation may help promote testing in general practice by removing the impetus of clinicians to initiate discussions on risk, achieving three-monthly testing among all GBM, especially when many access testing in general practice clinics which do not specialise in sexual health care, seems improbable. The data on clustering of STI diagnosies among GBM presented in Chapters 3 and 4 suggest that in the Australian context of high PrEP coverage, an approach which aims to target testing to those most at risk of STIs may have a greaer public health benefit. Further, Australia's Fifth National STI Strategy (currently in development) will recommend that testing guidelines for GBM be underpinned by the goal of reducing STI-related morbidity, rather than STI prevalence among GBM. Such a strategy would further support more nuanced approach to STI screening, including a focus on the testing for and treatment of mostly symptomatic infections among GBM.

Our analysis on syphilis suggests that the current average rate of testing of less than 2 tests per year is not sufficient to reverse the trend in syphilis incidence among GBM, and in light of patient and clinic burden associated with three monthly testing for all GBM, a more nuanced testing strategy may be needed. Such a strategy should take account of differential risk, while balancing the burden on providers and patients to determine who and how often GBM should test for STIs. Further, as new modalities of long-acting PrEP are adopted, including injectable cabotegravir PrEP which requires two-monthly injections, STI screening guidelines for PrEP users will need to be revised to align with frequency of clinic attendance. Innovative models of testing, including online ordering of mail-in self-sampling or event-based sample collection in locations associated with high STI risk should also be considered.

While reducing the recommended frequency of STI screening among GBM may reduce the burden on clinical practice, and may also help slow the rise in antimicrobial resistance,[211] less frequent clinic visits would also likely lead to reduced HIV screening among some subpopulations of GBM, which may have negative consequences for the timely diagnosis of new HIV infections. Further, recent qualitative work in Australia found that GBM would not necessarily be comfortable with screening for STIs less often (specifically if recommendations were changed to test for STIs every six months instead of every three).[475] Many GBM reported that maintaining three-monthly screening was important for them to feel confident they were STI free and not passing STIs on to their partners. Adapted STI testing models should also consider the role of STI self-testing in the future, contingent upon the successful development of high-performing STI rapid tests currently in the pipeline. Further to benefits for population-level STI incidence, self-testing may also be associated with a reduction in anxiety among GBM; in our Latent Class Analysis, a group of GBM with high rates of STIs responded

that they worry about getting an STI often. In 2020, Australia's Therapeutic Goods Administration made a number of changes to regulations for self-testing diagnostic medical devices, which now allow a number of self-tests to be made available in Australia where there are particular benefits to public or individual health. This includes self-tests for HIV, viral hepatitis and some bacterial STIs.

Testing strategies should consider not only individuals' risk of having an infection but the potential for an individual's undiagnosed infection to be transmitted onwards. For example, a recommendation may be for individuals to test for STIs prior to anticipated increases in sexual activity or partners, such as group sex, sex parties, or international travel, so that undiagnosed infections can be treated and prevented from being passed on to partners. The latent class analysis presented in Chapter 6 highlighted that most GBM prioritise preventing the onward transmission of STIs to their sexual partners as much as do preventing themselves from acquiring an infection, suggesting that promoting this strategic testing strategy would likely be acceptable to many GBM. Such event-based testing would likely require education and promotion which could be supported by clinicians or driven by community.

Biomedical interventions

Although modelling work suggests that specific screening strategies may help reduce incidence of some STIs among GBM, there is no empiric evidence that broad-based asymptomatic STI screening among GBM leads to declines in prevalence. Biomedical interventions which prevent the acquisition of STIs may offer greater benefits for reducing population-level prevalence, and may also reduce the proportion of STIs which are symptomatic among GBM. The use of doxycycline as prophylaxis is a new, highly efficacious[231] and highly acceptable[283, 476] method of preventing bacterial STIs among GBM. Despite concerns around growing AMR, GBM are already using doxycycline prophylaxis and in the United States multiple health services are prescribing doxycycline prophylaxis to GBM. The extent to which doxycycline prophylaxis is taken up among GBM in Australia will depend on endorsement from peak sexual health bodies and release of clinical guidelines, as well as provider willingness and education, and community-driven demand generation. Prior to local regulatory approval of PrEP and the large implementation studies in Australia, many high caseload clinics were developing their own internal protocols for prescribing PrEP to patients and assisting them with self-importation from international suppliers. It is likely that many providers may be similarly prescribing doxycycline off-label for PEP, however this is not fully known. If approved for clinical use in Australia, national doxycycline PEP guidelines will likely aim to minimise the number of individuals and amount of doxycycline prescribed to reduce the threat of AMR and individual unintended patient outcomes,

while maximising the benefits on STI incidence. The data presented in this thesis highlight that maximising prevention benefits could involve doxycycline prescribing strategies that focus on targeting individuals with previous infections (rates of reinfection were high) and not just on people using PrEP or with HIV (many people not using PrEP or living with HIV also experienced reinfections).

It is unknown whether doxycycline use in a real-world setting will have the same effectiveness as reported in clinical trials, which recruited participants with pre-existing risk criteria and who reported a high number of condomless partners during follow-up, and were also highly adherent to doxycycline. However, even if adherence or persistence on doxycycline PEP is lower in the real world, or if doxycycline PEP leads to changes in behaviour, my modelling work exploring a partially efficacious intervention suggests that population-level benefits may still be observed if doxycycline is taken up by enough people. There is little evidence from PrEP trials that PrEP use significantly increased the number of casual partners among GBM, rather PrEP influenced condom use, sexual networks and serosorting.[162] This suggests that, in the context of already low condom use and high rates of sera-different sex between GBM, risk compensation is unlikely to be a prominent feature of newer interventions such as doxycycline prophylaxis or STI vaccines. However, different patterns of adherence and persistence for biomedical interventions in the real world may have implications for AMR, and surveillance for resistant strains will be important, especially in the context of wider doxycycline PEP use. Finally, it will be crucial to ensure that access to innovations in STI control, such as doxyPEP and vaccines for STIs, does reflect current inequities in access to HIV prevention. In Australia, PrEP use among certain subgroups of GBM at risk of HIV, especially newly arrived Asian-born GBM, remains far lower than among other groups of GBM.[400] Identifying and understanding systemic and cultural barriers to accessing and adopting new STI interventions among specific subpopulations of GBM will be vital to maximizing population-level benefits of these interverventions.

9.2.2 Recommendations for future research

Surveillance and data linkage

Sentinel surveillance systems such as ACCESS provide rich data sources to explore longitudinal trends in testing and incidence across key clinical characteristics. For GBM, the network of clinics participating in ACCESS provides good coverage of the population, as the majority of GBM live in Victoria and NSW[248] where the majority of ACCESS clinics are located, and notifications of STIs among GBM are largely concentrated in urban areas, where sexual health clinics are located.

However, while the ACCESS network was designed to capture a high proportion of HIV and STI diagnoses among GBM in Australia, diversifying epidemics of HIV and STIs and increasing transmission in other populations, such as adolescents and young people, and heterosexual adults, mean that ACCESS's ability to monitor STIs among all priority populations outlined in Australia's National Strategy to STIs[247] may be reducing. Among heterosexual people, the distribution of both the population and STI diagnoses is more geographically dispersed, with a growing number of notifications in outer-urban areas and from general practice, low caseload clinics.[200] Further, there is a current shift of government focus and investment to improve sexual health care in low-caseload general practice settings, including through "hub and spoke" models that support professional networks and enhance patient care pathways.[477] This makes monitoring the response to STIs in Australia using sentinel surveillance, which relies on the recruitment of specialised high-caseload clinics, more difficult. Enhanced surveillance, the collection of epidemiological and demographic data following a notification of a diagnosis (*e.g.,* gender of sex partners, PrEP use, sex worker status) offers some insights to risk factors for STIs, however lack denominator data for incidence calculations (i.e. testing rates).

To address these issues, incorporating and linking other data sources may provide insights into trends in testing and diagnoses. In Australia, providers are reimbursed for pathological testing for STIs through the rebate system known as Medicare benefits scheme (MBS). Along with the corresponding pharmaceutical benefits scheme (PBS), population-level data on STI testing and treatment is available within these databases. By undertaking data linkage of MBS and PBS data systems with data from sentinel surveillance systems and larger pathology laboratories, data can be triangulated to offer both broad estimates of population-level testing and treatment (a proxy for diagnosis) with more nuanced epidemiological data from people attending sentinel clinics.

My work has also highlighted specific sexual network characteristics among subgroups of GBM associated with a growing burden of STIs. To further understand complex transmission dynamics among these high-burden groups, whole genome sequencing of STI isolates can provide insights into sexual networks and how new outbreaks are seeded, for example through bridging of transmission from GBM with HIV to GBM without HIV following the rollout of HIV PrEP.[202] In Australia, routine sequencing of STI isolates, including gonorrhoea and syphilis, occurs for both surveillance and research purposes.[202, 268] Linkage of whole-genome sequencing data of STI specimens with clinical and biobehavioural data extracted from ACCESS clinics can provide a rich data source for understanding specific drivers of STI transmission among sexual networks of GBM. This linkage could also help monitor how antibiotic resistance genes are transmitted through specific sexual networks of GBM, help monitor the potential emergence of AMR within these networks in the context of

doxycycline PrEP/PEP, and help guide STI interventions which specifically aim to interrupt chains of transmission of resistant strains. Linkage of genomic data to prescription data from sentinel clinics and treatment data from the PBS could also help understand how individual-level and population-level antibiotic consumption is linked to increased AMR. Beyond collection and anlaysis of genomic data, there is an opportunity to intergrate sexual mixing data that could be empirically collected through biobehavioural surveys into disease surveillance systems and mathematical modelling. Ego-centric network analysis could be used in the context of PrEP to explore the size and constituents of sexual networks, and the impact of networks of STI transmission.

STI control in other populations and settings

Given the concern for harmful sequalae of STIs among women, more research should be done on disaggregating testing and incidence trends, specifically for syphilis, among gay men, bisexual men, heterosexual women and heterosexual men. For example, if it were possible to observe a delayed effect of increasing incidence among bisexual men following an increase among gay men more broadly, and a subsequent delayed increase among women, this could help understand how trends among gay men (for which surveillance systems are well established) may be able to alert potential outbreaks among heterosexual populations. Real-time whole genome sequencing could be integrated with such surveillance to help guide a timely response to outbreaks among heterosexual populations.

While my thesis provided novel insights into the interplay between PrEP and STIs in a developed country with a well-resourced healthcare system, established surveillance systems, and universal healthcare, future research should aim to monitor the impact of wider PrEP implementation in other settings. Our data suggest that fear of increasing STIs should not hinder implementation of PrEP in other countries, with significant achievements in HIV reductions outweighing increases in some STIs (i.e. syphilis). However, the extent to which these findings are generalisable to other settings where resources are limited, especially in low-middle income countries which may lack adequate laboratory services to test and monitor for STIs and AMR and may not be able to deliver care quickly to those diagnosed, may be limited.

9.3 Concluding remarks

The research outlined in this thesis provided novel insights into the interplay between HIV prevention, sexual networks and STI transmission. I demonstrated that trends in STIs among GBM are likely being influenced by long-term trends in changes in serosorting, with sexual networks playing an integral role in STI transmission dynamics in the context of PrEP. PrEP was effectively scaled up in Australia, with widespread coverage, high rates of STI testing and reductions in HIV achieved without causing exponentially increasing rates of bacterial STIs. By integrating innovative surveillance methods, primary data collection, and mathematical modelling, this research has key findings which will help guide future implementation research and STI prevention among GBM in Australia and globally. The risk of bacterial STIs is heterogenous across subgroups of GBM, and important differences in health seeking behaviours and attitudes towards STIs and STI prevention exist among GBM in Australia. Strategies and interventions to reduce STIs among GBM need to be equally nuanced and account for differential risk and the potential of sexual networks to drive onwards transmission. Further research into sexual networks and transmission dynamics of STIs among GBM, and the connection to transmission among populations, should be guided by surveillance and incorporate genomic analysis to better understand transmission of, and monitor for, antimicrobial resistance. Reducing the burden of STIs among GBM in Australia will require a multifaceted response which acknowledges the distinct and changing risk characteristics, behaviours and attitudes of GBM, especially in the context of significant achievements in HIV prevention.

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Appendices

Appendix A Supplementary materials for thesis chapters

Appendix A1. Supplementary materials for Chapter 3

Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis in Australia following nation-wide pre-exposure prophylaxis implementation: an analysis of sentinel surveillance data

Michael W. Traeger, Rebecca Guy, Jason Asselin, Prital Patel, Allison Carter, Edwina Wright, Andrew Grulich, Hamish McManus, Christopher K. Fairley, Eric P.F. Chow, Anna McNulty, Robert Finlayson, Charlotte Bell, Louise Owen, Lewis Marshall, Darren Russell, Darryl O'Donnell, Basil Donovan, Margaret Hellard, Mark Stoové

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Primary Analysis Supplementary Materials

A1.1: Supplementary information for statistical analyses.

Determination of GBM status and PrEP use

For sexual health clinics, GBM status was extracted from patient management systems or inferred from survey data where participants reported sex with men, whereas for general practice clinics (where GBM-status records are less complete) GBM status was inferred using a previously validated algorithm based on history of a rectal swab as a marker of male-to-male sex [Ampt et al 2017]. Gender was extracted as recorded in patient management systems. PrEP use was determined by an electronic prescription for Tenofovir + Emtricitabine recorded in patient management systems. Prescriptions for post-exposure prophylaxis (PEP) and for treatment of established HIV infection were excluded.

Ampt FH, El Hayek C, Agius PA, et al. Anorectal swabs as a marker of male-to-male sexual exposure in STI surveillance systems. *Epidemiology and Infection.* 2017;145(12):2530-2535.

Inclusion period of PrEP-time following PrEP prescription

Individuals who were not re-prescribed PrEP within four months of a previous PrEP prescription were considered to have ceased PrEP use and were censored at the date four months following their last PrEP prescription. We chose a period of four months since last PrEP prescription prior to censoring, rather than 90 days (standard PrEP prescribing interval), to allow individuals an extra month to return for their PrEP script, as clinical visits may have been delayed or GBM may have been using PrEP intermittently; inspection of time between PrEP prescriptions showed that 26.0% of non-initial PrEP prescriptions were prescribed between 90 and 120 days since an individual's previous prescription (79.6% were prescribed within 120 days).

Allocation of infection data using the mid-point method

Date of STI acquisition was assigned as the mid-point between date of diagnosis and date of previous test. Where an individual was censored prior to a positive STI diagnosis due to PrEP cessation, that diagnosis was included in incidence calculations if the assigned date of infection (using the midpoint method) was prior to the individual's censor date. The midpoint method was selected, rather than random point of binomial approximation [McManus et al 2021], given the

relatively short intervals between STI testing events. Tests within 14 days of a positive result were considered tests of cure and were excluded. Positive STI test results at time of entry or re-entry were not included in incidence rate calculations.

McManus H, Callander D, Asselin J, et al. A New Method for Estimating the Incidence of Infectious Diseases. *Am J Epidemiol.* 2021;190(7):1386-1395.

Inclusion criteria for each STI outcome incidence determination

To be included in incidence determinations for specific STIs, individuals must have had at least two test events for the respective STI. For the *any STI* outcome, entry date and censor date were determined using any STI test event, and individuals were only included if they had at least two tests for each of chlamydia, gonorrhoea and syphilis. Incidence of any STI was defined as the sum of chlamydia, gonorrhoea and infectious syphilis diagnoses divided by total person-time. Concurrent diagnoses of the same STI at different anatomical sites (e.g. rectal chlamydia and urogenital chlamydia) were considered a single infection, whereas concurrent diagnoses of different infections at the same or different anatomical sites (e.g. rectal gonorrhoea and rectal chlamydia) were considered multiple infections. For those included in the any STI outcome, we calculated the number and proportion of participants diagnosed with zero, one to four, and five or more STIs during follow-up, and the attributable proportion of all STI diagnosed among each group.

Study period and trend analyses period

Overall incidence rates per 100 person-years (100py) during the observation period (1st January 2016 to 31st December 2019) were calculated for chlamydia, gonorrhoea, infectious (primary, secondary or early [<2 years] latent) syphilis and any STI. For trend analyses, incidence rates per 100-person years were calculated and plotted for each calendar half-year (six-monthly) period from July 2016 to December 2019, and defined as the number of infections divided by the total person-time accumulated. January-June 2016 was excluded from trend estimates as the small amount of follow-up time in this period inflated the incidence estimates.

Tests for non-linearity and sensitivity analysis

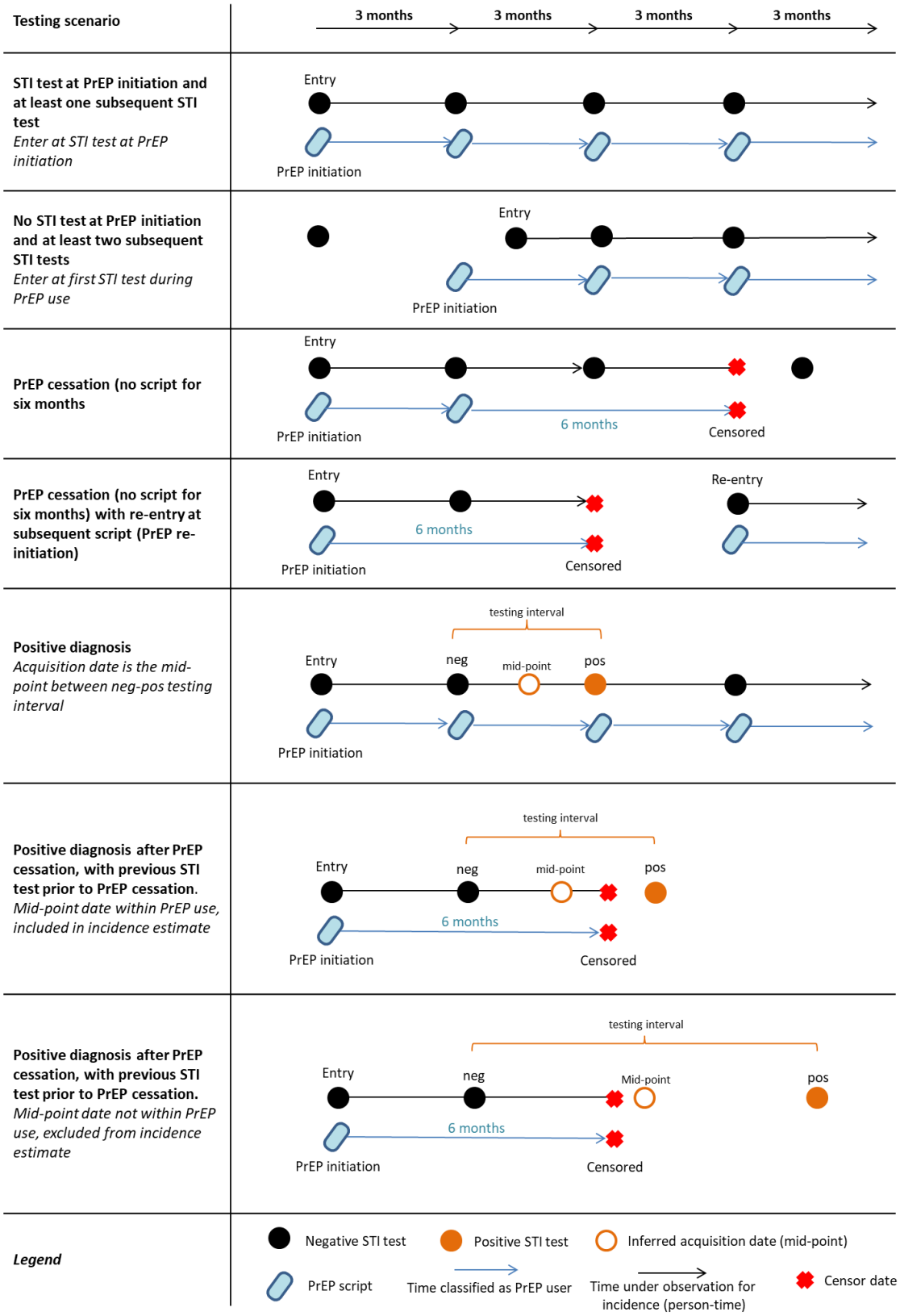
For all trend analysis, sensitivity analyses were performed to test the assumption of linearity for each trend across the study period by including an interaction term between time (calendar half-

year) and itself, with an interaction coefficient with significance $p<0.05$ indicating deviation from linearity. Where non-linearity was detected, piecewise negative binomial regression was used to examine trends into two periods, split at the median value of calendar half-year (before January-June 2018 and from January-June 2018 onwards).

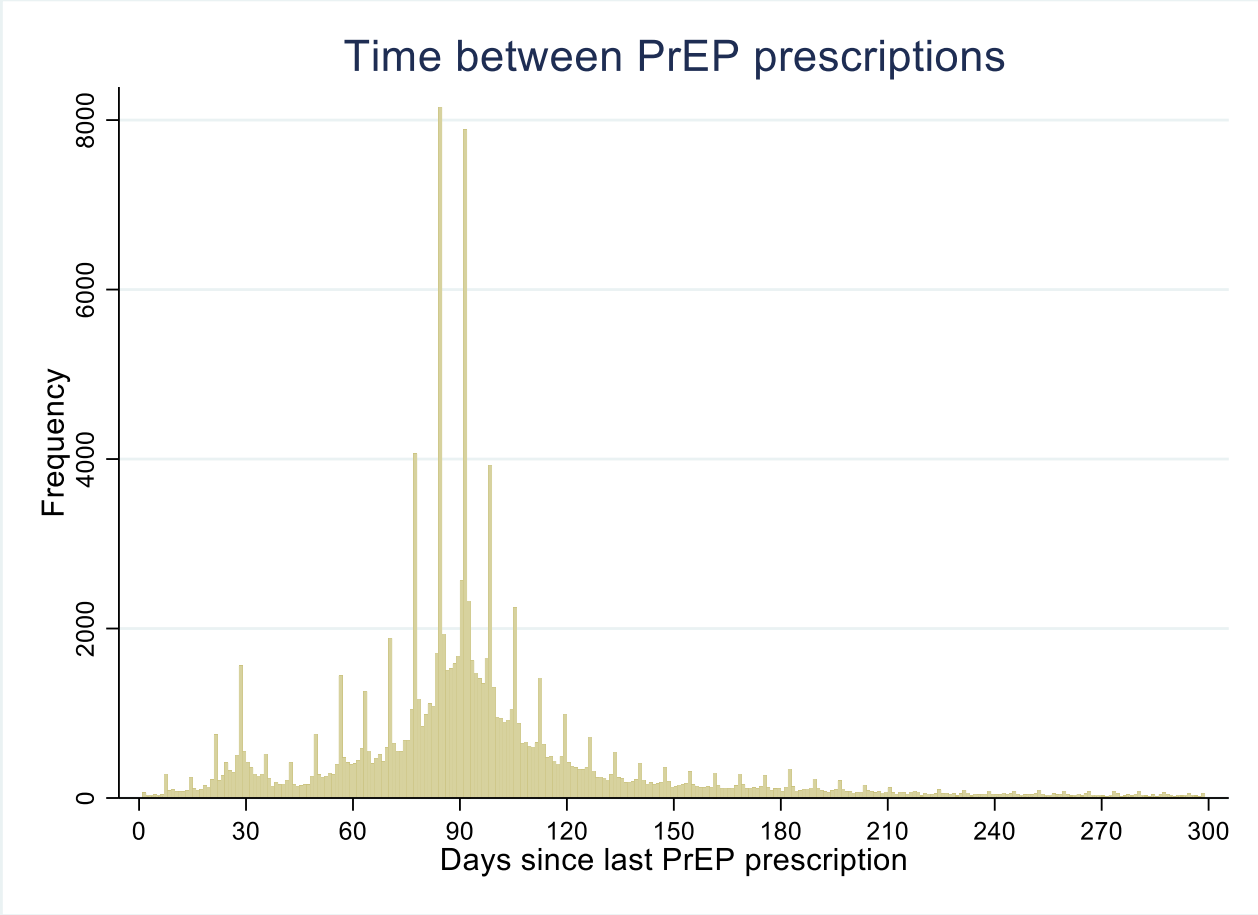
Secondary analysis of STI incidence per 6 months of PrEP use (time measured in days since PrEP initiation)

In the secondary analysis measuring STI incidence in 6-month intervals from PrEP initiation, we calculated incidence rates for each STI outcome in 6-monthly intervals of PrEP use since PrEP initiation, and overall incidence rates for each initiation year-cohort (i.e. individuals initiating PrEP in 2016, 2017, 2018, and 2019 separately). *For individuals initiating PrEP in 2016, 2017, 2018 and 2019, analyses included 42 months, 30 months, 18 months, and 6 months of PrEP use, respectively.*

A1.2: PrEP prescribing and testing scenarios and time at risk for calculating STI incidence using repeat testing methods



A1.3: Histogram of time between PrEP prescriptions during the study period

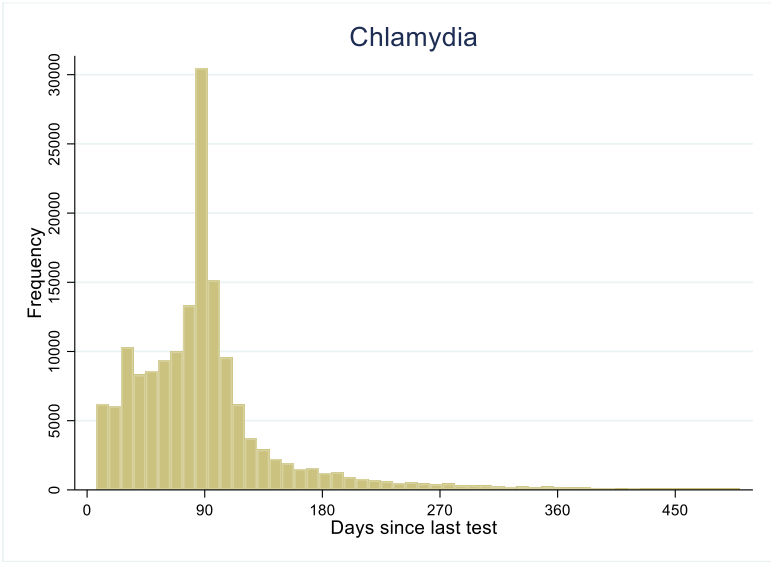


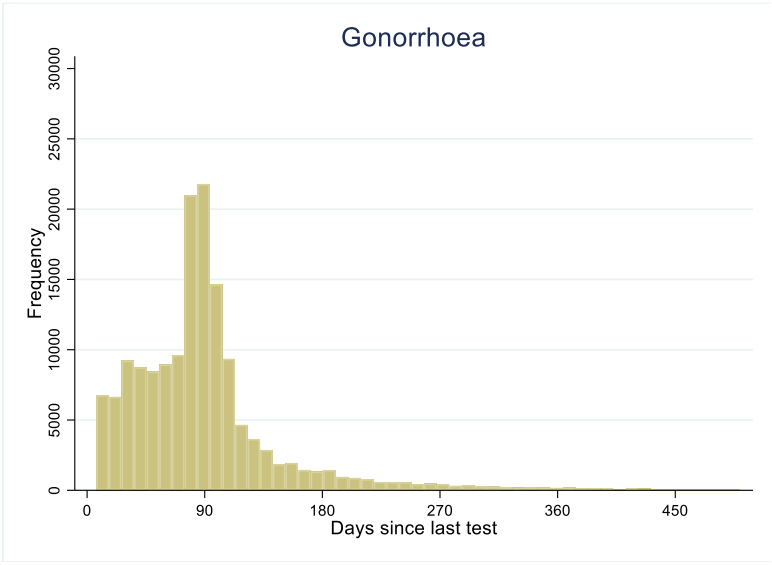
A1.4: Cumulative number of PrEP prescriptions prescribed within 3, 4 and 6 months of last prescription

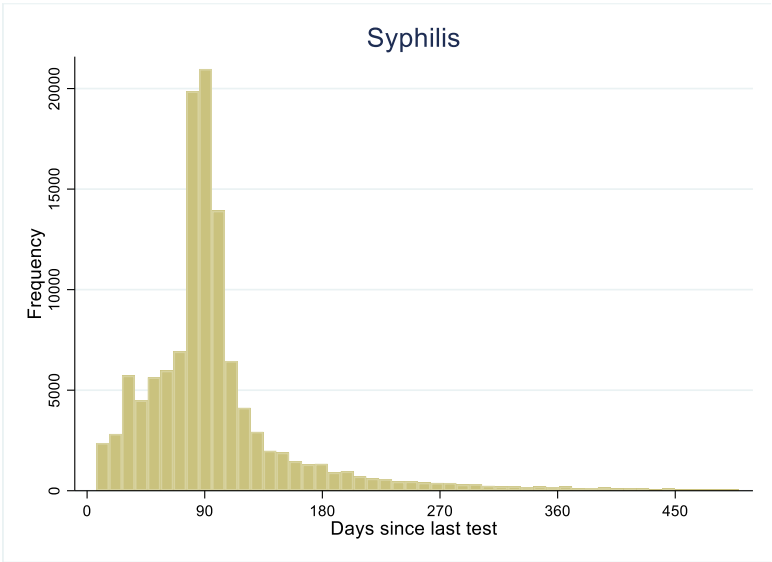
Total subsequent PrEP prescriptions during study period = 123,586 (Not including individuals' first PrEP prescription)

	Within 90 days	Within 120 days	Within 185 days
N PrEP prescriptions (%)	66,203 (53.6)	98,420 (79.6)	111,319 (90.1)

A1.5: Histograms of number of days since last test per test among PrEP users 2016-2019







A1.6: Number of tests and mean and median time since last test for all test events during the study period

	Chlamydia	Gonorrhoea	Syphilis
Number of tests	160,778	155,861	120,875
Mean days since last test (SD)	97.7 (91.2)	97.5 (91.2)	107.1 (95.8)
Median days since last test (IQR)	84 (55 – 104)	84 (54 – 104)	90 (70 – 108)
90th percentile time since last test	161	162	174

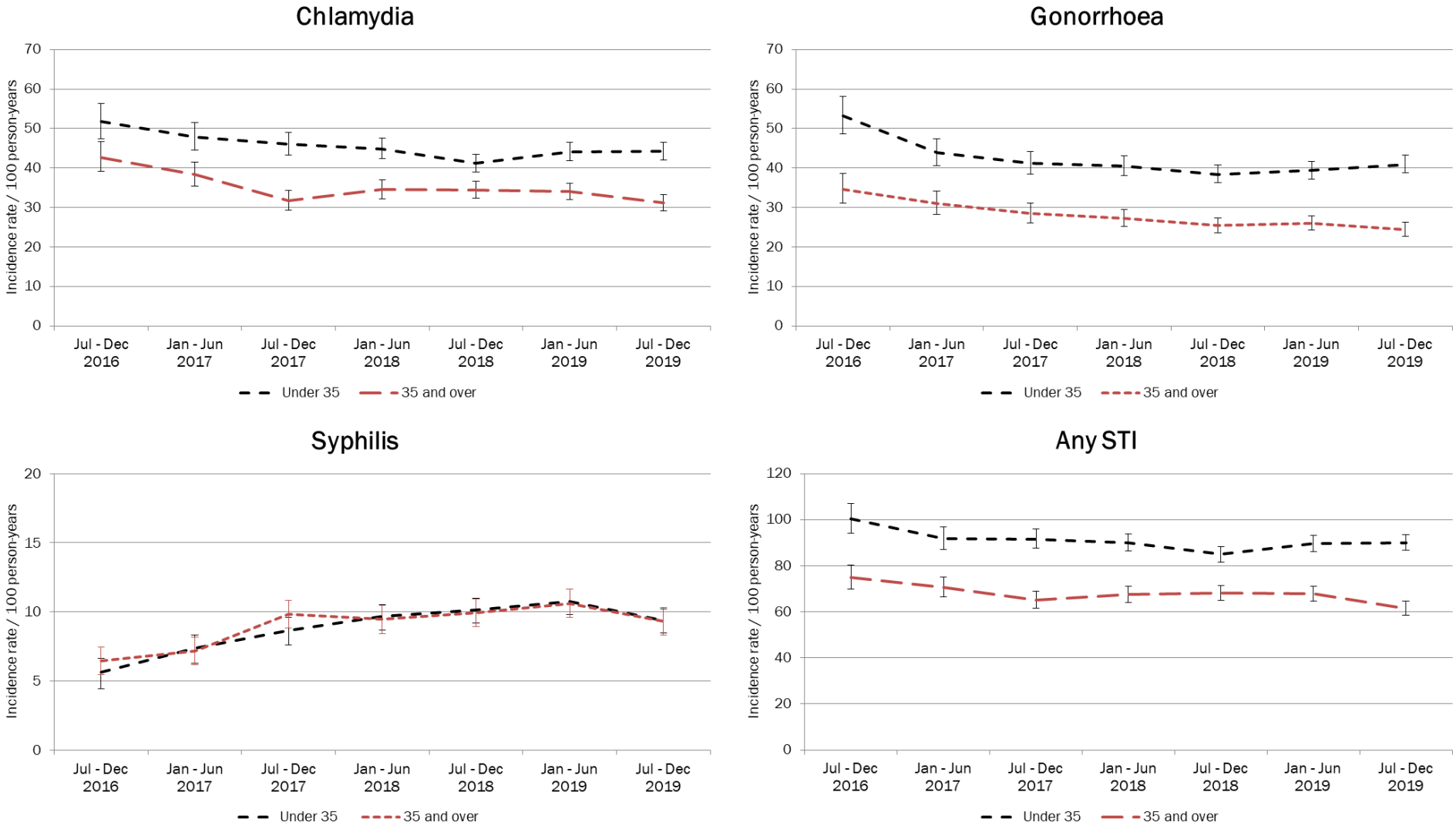
A1.7: Mean person-years of follow-up disaggregated by year of PrEP initiation for primary incidence analyses.

		Chlamydia	Gonorrhoea	Syphilis	Any STI
Year of PrEP initiation	Person-years at risk				
2016	Total	12415.4	11429.8	10418.1	11248.5
	Mean (SD)	2.0 (1.3)	1.9 (1.1)	1.8 (1.1)	2.3 (1.2)
2017	Total	7117.9	6947.8	6096.8	6490.5
	Mean (SD)	1.3 (0.8)	1.2 (0.8)	1.2 (0.8)	1.3 (0.8)
2018	Total	4882.6	4907.9	4183.7	4378.1
	Mean (SD)	0.8 (0.5)	0.8 (0.5)	0.8 (0.5)	0.9 (0.5)
2019	Total	1575.1	1573.1	1280.2	1282.5
	Mean (SD)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Total	Total	25,991.2	24,858.7	21,978.9	23399.8
	Mean (SD)	1.17 (0.95)	1.14 (0.93)	1.14 (0.94)	1.27 (0.99)

A1.8: Entry, exit, PrEP censorship and PrEP re-entry rates across each time period

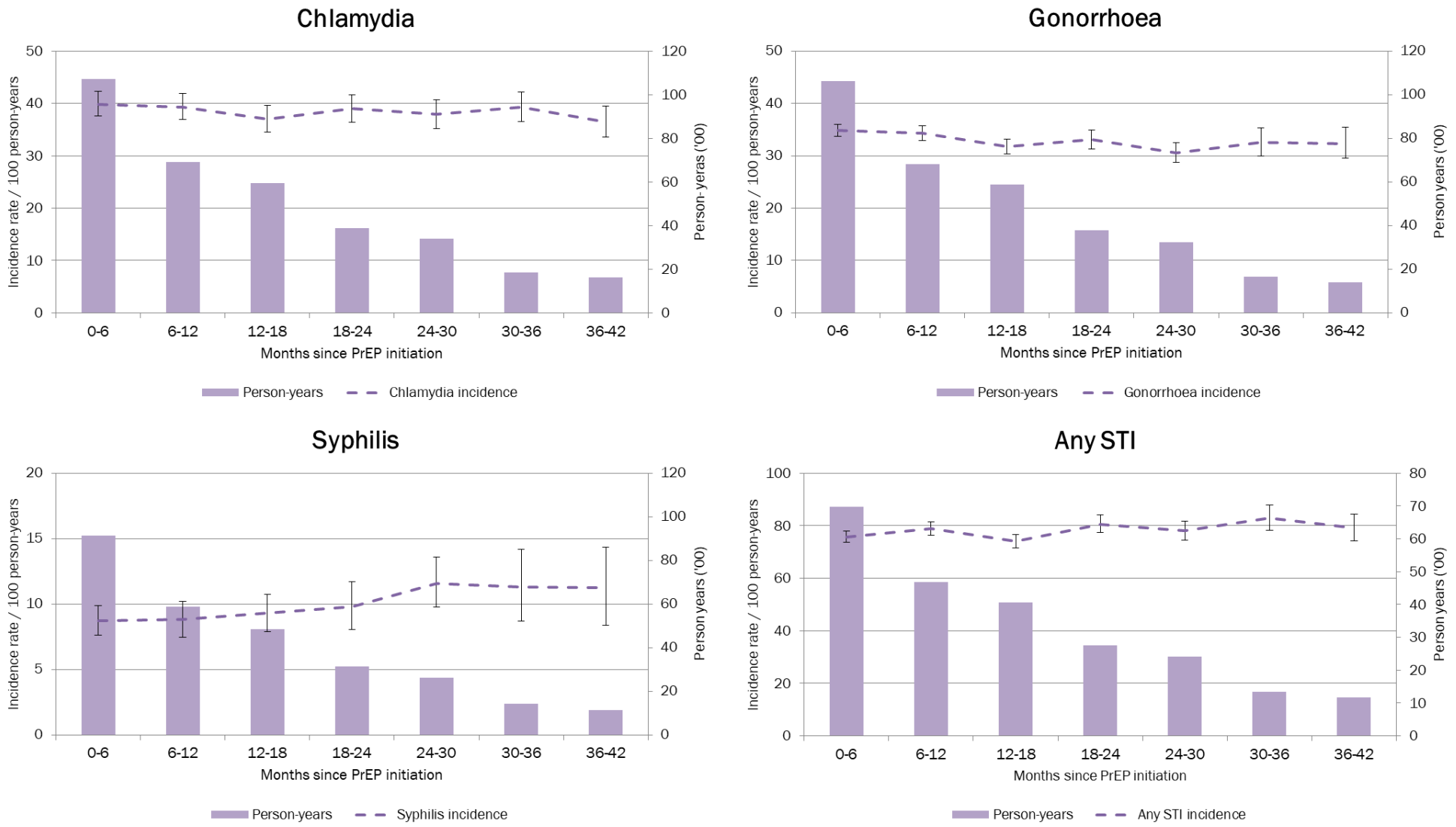
		Jan-Jun 2016	Jul-Dec 2016	Jan-Jun 2017	Jul-Dec 2017	Jan-Jun 2018	Jul-Dec 2018	Jan-Jun 2019	Jul-Dec 2019
Chlamydia	Number contributing person-time	2506	5877	7751	9572	11430	12627	12564	12086
	Enter date for each individual	2506	3554	2677	2990	3082	2778	2436	2011
	Final censorship date for each individual	134	511	873	1072	1790	2688	2880	12086
	Number censored (final or gap start) due to 4 months since previous PrEP script	314	1451	2382	2854	3472	5683	5696	5374
	Number re-entered following break in PrEP and subsequent PrEP prescription	43	468	1030	1568	2070	2980	3381	3562
Gonorrhoea	Number contributing person-time	2487	5674	7458	9388	11382	12621	12574	12107
	Enter date for each individual	2487	3355	2529	3016	3154	2826	2455	2023
	Final censorship date for each individual	123	467	826	1013	1765	2670	2874	12107
	Number censored (final or gap start) due to 4 months since previous PrEP script	307	1406	2323	2783	3437	5667	5683	5376
	Number re-entered following break in PrEP and subsequent PrEP prescription	43	458	1006	1556	2065	2977	3388	3558
Syphilis	Number contributing person-time	2267	5208	6875	8411	9907	10782	10438	9699
	Enter date for each individual	2267	3115	2435	2635	2734	2426	2013	1637
	Final censorship date for each individual	126	525	862	1110	1734	2521	2681	9699
	Number censored (final or gap start) due to 4 months since previous PrEP script	274	1275	2099	2560	3094	5072	4924	4536
	Number re-entered following break in PrEP and subsequent PrEP prescription	35	408	895	1377	1820	2660	2934	3098
Any STI	Number contributing person-time	2243	5180	6887	8484	10141	11114	10834	10170
	Enter date for each individual	2243	3079	2355	2555	2665	2305	1865	1416
	Final censorship date for each individual	91	375	684	873	1523	2335	2432	10170
	Number censored (final or gap start) due to 4 months since previous PrEP script	258	1199	2002	2431	2996	4981	4807	4407
	Number re-entered following break in PrEP and subsequent PrEP prescription	35	396	876	1355	1804	2632	2903	3044

A1.9: Half-yearly incidence of (a) chlamydia, (b) gonorrhoea, (c) syphilis and (d) any STI among GBM using PrEP, July 2016 to December 2019, by age group.



Vertical lines represent 95% confidence intervals.

A1.10: Six-monthly incidence of (a) chlamydia, (b) gonorrhoea, (c) syphilis and (d) any STI, by months since PrEP initiation



Vertical lines represent 95% confidence intervals. Bars represent person-years of follow-up accrued in each period (right axis).

A1.11: Distribution of participants and STI diagnoses by number of infections per participants during follow-up for the any STI outcome

	Number of participants	Number of STI diagnoses	Proportion of participants (N=18,483)	Proportion of all STIs diagnosed (N=20,116)
No STIs	10260	0	55.5%	0.0%
1 STI	3723	3723	20.1%	18.5%
2 STIs	1832	3664	9.9%	18.2%
3 STIs	1003	3009	5.4%	15.0%
4 STIs	616	2464	3.3%	12.2%
5 or more STIs	1049	7256	5.7%	36.1%
Total	18483	20116	100%	100.0%

A1.12: Tests for non-linearity and piecewise negative binomial regression for non-linear trends

Outcome	Time period interaction term coefficient	Interaction term p-value	Trend segment 1 Jul-Dec 2016 – Jul-Dec 2017		Trend segment 2 Jan-Jun 2018 – Jul-Dec 2019	
			IRR* (95% CI)	p-value	IRR* (95% CI)	p-value
Primary analysis						
Chlamydia - any site	1.009	0.002	0.910 (0.875 – 0.947)	<0.001	0.991 (0.971 – 1.010)	0.359
Chlamydia - rectal	1.010	0.002	0.918 (0.876 – 0.961)	<0.001	0.999 (0.976 – 1.023)	0.960
Chlamydia – urogenital	1.008	0.146				
Chlamydia - oropharyngeal	0.991	0.356				
Chlamydia – Under 35	1.011	0.004	0.945 (0.895 – 0.998)	0.043	1.007 (0.980 – 1.034)	0.610
Chlamydia – 35 and over	1.007	0.078				
Gonorrhoea - any site	1.014	<0.001	0.897 (0.856 – 0.940)	<0.001	0.995 (0.973 – 1.018)	0.670
Gonorrhoea - rectal	1.012	0.005	0.910 (0.854 – 0.970)	0.004	0.996 (0.966 – 1.027)	0.820
Gonorrhoea - urogenital	1.008	0.404				
Gonorrhoea - oropharyngeal	1.017	<0.001	0.869 (0.815 – 0.927)	<0.001	1.004 (0.973 – 1.035)	0.820
Gonorrhoea – Under 35	1.018	<0.001	0.882 (0.830 – 0.937)	<0.001	1.010 (0.982 – 1.040)	0.463
Gonorrhoea – 35 and over	1.009	0.086				
Syphilis	0.971	<0.001	1.240 (1.122 – 1.370)	<0.001	0.999 (0.960 – 1.040	0.969
Syphilis – Under 35	0.969	0.001	1.226 (1.066 – 1.409)	0.004	0.997 (0.944 – 1.053)	0.918
Syphilis – 35 and over	0.973	0.003	1.256 (1.088 – 1.450)	0.002	1.002 (0.945 – 1.061)	0.956
Any STI	1.004	0.094				

- any site						
Any STI – Under 35	1.008	0.006	0.953 (0.925 – 0.983)	0.002	0.992 (0.977 – 1.007)	0.287
Any STI – 35 and over	0.999	0.874				
			Secondary analysis			
Chlamydia – all (unadjusted)	1.003	0.334				
Chlamydia – all (adjusted)	1.002	0.454				
Chlamydia – 2016 initiates	1.001	0.817				
Chlamydia – 2017 initiates	1.002	0.827				
Chlamydia – 2018 initiates	1.005	0.919				
Gonorrhoea – all (unadjusted)	1.007	0.052				
Gonorrhoea – all (adjusted)	1.006	0.088				
Gonorrhoea – 2016 initiates	1.008	0.058				
Gonorrhoea – 2017 initiates	0.997	0.831				
Gonorrhoea – 2018 initiates	0.929	0.162				
Syphilis – all (unadjusted)	1.001	0.852				
Syphilis – all (adjusted)	1.001	0.882				
Syphilis – 2016 initiates	0.991	0.231				
Syphilis – 2017 initiates	1.017	0.394				
Syphilis – 2018 initiates	0.959	0.649				
Any STI – all (unadjusted)	1.000	0.882				
Any STI	0.999	0.611				

– all (adjusted)		
Any STI – 2016 initiates	0.998	0.464
Any STI – 2017 initiates	0.997	0.737
Any STI – 2018 initiates	0.917	0.051

A1.13: Association with time on PrEP with incidence, by year of PrEP initiation

	Year initiated PrEP	Trend^ IRR* (95% CI)	p-value
Chlamydia	2016	.99 (.97 - 1.00)	0.071
	2017	1.00 (.97 - 1.03)	0.986
	2018	1.01 (.96 - 1.07)	0.647
Gonorrhoea	2016	.98 (.96 - .99)	0.001
	2017	1.00 (.97 - 1.03)	0.882
	2018	.95 (.89 - 1.01)	0.119
Syphilis	2016	1.08 (1.05 - 1.12)	0.000
	2017	1.08 (1.02 - 1.15)	0.011
	2018	.96 (.84 - 1.09)	0.522
Any STI[#]	2016	1.00 (.99 - 1.01)	0.953
	2017	.99 (.97 - 1.02)	0.456
	2018	1.01 (.96 - 1.07)	0.591

IR=Incidence Rate
IRR=Incidence Rate Ratio, *average change per six months of PrEP use, included as continuous variable in negative binomial model.
No non-linearity detected (Supplementary Table 6)
^Observation period and trend-analysis is over 42 months (2016), 30 months (2017) and 18 months (2018) of PrEP use.
#Any STI analysis only includes individuals with at least 2 tests for each infection (chlamydia, gonorrhoea and syphilis)

Sensitivity Analysis 1: Censoring individuals at 6-months after final PrEP script

A1.14 Incidence rate and trend estimates among all PrEP users between 2016-2019 from primary analysis – Using 6 months since last PrEP prescription as censorship criteria.

		Study period				Trend Jul-Dec 2016 – Jul-Dec 2019	
		N	Person-years	Diagnoses	IR (95% CI) / 100py	IRR[a] (95% CI)	p-value
Chlamydia	Any site	22341	33206.0	13223	39.8 (39.1 - 40.5)	.98 (.97 - .99)	<0.0001
Site	Rectal	21466	31988.8	9847	30.8 (30.2 - 31.4)	.98 (.97 - .99)	0.0023
	Urogenital	21322	32026.7	3608	11.3 (10.9 - 11.6)	.98 (.96 - 1.00)	0.031
	Oropharyngeal	20344	30555.4	1161	3.8 (3.6 - 4.0)	.95 (.92 - .99)	0.0064
Age group	Under 35	12295	16962.8	7643	45.1 (44.1 - 46.1)	.98 (.97 - .99)	0.0046
	Over 35	10046	16243.2	5580	34.4 (33.5 - 35.3)	.97 (.95 - .98)	<0.0001
Gonorrhoea	Any site	22189	31928.9	10978	34.4 (33.7 - 35.0)	.96 (.95 - .98)	<0.0001
Site	Rectal	21363	30828.5	6306	20.5 (20.0 - 21.0)	.97 (.95 - .98)	<0.0001
	Urogenital	19839	29002.6	1874	6.5 (6.2 - 6.8)	.97 (.94 - 1.01)	0.12
	Oropharyngeal	21647	31187.3	6024	19.3 (18.8 - 19.8)	.97 (.95 - .98)	0.00013
Age group	Under 35	12175	16459.2	6782	41.2 (40.2 - 42.2)	.97 (.96 - .99)	0.0004
	Over 35	10014	15469.7	4196	27.1 (26.3 - 28.0)	.95 (.93 - .97)	<0.0001
Syphilis		19570	27942.1	2590	9.3 (8.9 - 9.6)	1.06 (1.04 - 1.08)	<0.0001
Age group	Under 35	10734	14349.0	1330	9.3 (8.8 - 9.8)	1.07 (1.03 - 1.10)	<0.0001
	Over 35	8836	13593.1	1260	9.3 (8.8 - 9.8)	1.05 (1.01 - 1.09)	0.0018
Any STI[b]		18852	29970.7	23708	79.1 (78.1 - 80.1)	.99 (.98 - .99)	0.0014
Age group	Under 35	10406	15512.5	14018	90.4 (88.9 - 91.9)	.99 (.98 - 1.00)	0.050
	Over 35	8446	14458.2	9690	67.0 (65.7 - 68.4)	.98 (.97 - .99)	0.0021

IR=Incidence Rate

IRR=Incidence Rate Ratio,

[a]Average change per calendar half-year, half-year included as continuous variable in negative binomial model

[b]Any STI analysis only includes individuals with at least 2 tests for each infection (chlamydia, gonorrhoea and syphilis)

A1.15: Negative binomial regression models for association between STI incidence with year of PrEP initiation and time on PrEP from secondary analyses – Using 6 months since last PrEP prescription as censorship criteria.

		Year initiated PrEP	Diagnoses	Person-years	IR / 100py (95% CI)	Unadjusted IRR (95% CI)	p-value	aIRR (95% CI)	p-value
Chlamydia	Year	2016	6483	15885.8	40.8 (39.8 - 41.8)	-ref-		-ref-	
		2017	3758	9807.6	38.3 (37.1 - 39.6)	.94 (.89 - .99)	0.019	.91 (.86 - .96)	0.0013
		2018	2318	6639.2	34.9 (33.5 - 36.4)	.85 (.80 - .90)	<0.0001	.81 (.76 - .86)	<0.0001
		2019	742	1988.3	37.3 (34.7 - 40.1)	.92 (.84 - 1.00)	0.058	.85 (.78 - .94)	0.00075
	Time on PrEP (6m)[a]					.99 (.98 - 1.00)	0.076	.97 (.96 - .98)	<0.0001
Gonorrhoea		2016	5301	15035.5	35.3 (34.3 - 36.2)	-ref-		-ref-	
		2017	3153	9704.1	32.5 (31.4 - 33.6)	.92 (.86 - .98)	0.0088	.89 (.83 - .95)	0.00028
		2018	2035	6664.6	30.5 (29.2 - 31.9)	.86 (.80 - .92)	<0.0001	.80 (.75 - .86)	<0.0001
		2019	639	1987.9	32.1 (29.7 - 34.7)	.91 (.83 - 1.01)	0.074	.83 (.75 - .92)	0.00025
	Time on PrEP (6m)[a]					.98 (.97 - .99)	0.0016	.96 (.95 - .97)	<0.0001
Syphilis		2016	1310	13063.9	10.0 (9.5 - 10.6)	-ref-		-ref-	
		2017	761	8151.5	9.3 (8.7 - 10.0)	.93 (.81 - 1.07)	0.32	.97 (.85 - 1.12)	0.70
		2018	466	5456.3	8.5 (7.8 - 9.4)	.85 (.74 - .98)	0.030	.93 (.80 - 1.07)	0.31
		2019	129	1519.7	8.5 (7.1 - 10.1)	.85 (.69 - 1.03)	0.10	.96 (.78 - 1.18)	0.68
	Time on PrEP (6m)[a]					1.06 (1.03 - 1.08)	<0.0001	1.05 (1.02 - 1.08)	0.00020

Any STI[b]	2016	9844	11640.3	84.6 (82.9 - 86.3)	-ref-		-ref-	
	2017	4739	6516.7	72.7 (70.7 - 74.8)	.86 (.81 - .91)	<0.0001	.85 (.80 - .90)	<0.0001
	2018	2754	4117.8	66.9 (64.4 - 69.4)	.79 (.74 - .84)	<0.0001	.77 (.73 - .82)	<0.0001
	2019	777	1107.2	70.2 (65.4 - 75.3)	.83 (.76 - .91)	<0.0001	.81 (.74 - .88)	<0.0001
Time on PrEP (6m)[a]					1.01 (1.00 - 1.02)	0.051	.99 (.98 - 1.00)	0.012

IR=Incidence Rate IRR=Incidence Rate Ratio

[a] Average change per six months of PrEP use, included as continuous variable in negative binomial model.

[b] Any STI analysis only includes individuals with at least 2 tests for each infection (chlamydia, gonorrhoea and syphilis)

Sensitivity Analysis 2: Inclusion of a random-effect for clinic in negative binomial models

Negative binomial regression models in the primary analysis use robust variance estimators clustered by individual to account for correlation between observations within individuals. To explore the potential impact of correlation between observations within clinics, we performed a sensitivity analysis where we included clinic as a random-effect in mixed-effects negative binomial regression models. Given that individuals could move between clinics, and the ACCESS database links individuals across clinics, individuals were not completely nested within clinics. As such, in this sensitivity analysis including a random-effect for clinic, individual-clustering is not performed.

A1.16: Trend estimates and p-values from negative binomial regression models with random-effect for clinic

Outcome	Trend Jul-Dec 2016 – Jul-Dec 2019 IRR[a] (95% CI)	p-value
Primary Analysis		
Chlamydia - any site	0.989 (0.979 – 0.999)	0.035
Chlamydia - rectal	0.993 (0.981 – 1.001)	0.254
Chlamydia – urogenital	0.987 (0.986 – 1.008)	0.226
Chlamydia - oropharyngeal	0.971 (0.937 – 1.006)	0.106
Chlamydia– Under 35	0.997 (0.984 – 1.011)	0.712
Chlamydia – 35 and over	0.977 (0.962 – 0.992)	0.003
Gonorrhoea - any site	0.985 (0.973 – 0.996)	0.008
Gonorrhoea - rectal	0.989 (0.974 – 1.004)	0.159
Gonorrhoea - urogenital	0.978 (0.947 – 1.009)	0.161
Gonorrhoea - oropharyngeal	0.987 (0.972 – 1.003)	0.110
Gonorrhoea – Under 35	0.992 (0.977 – 1.007)	0.317
Gonorrhoea – 35 and over	0.969 (0.950 – 0.987)	0.001
Syphilis	1.073 (1.047 – 1.099)	<0.001
Syphilis – Under 35	1.088 (1.050 – 1.127)	<0.001
Syphilis – 35 and over	1.056 (1.021 – 1.093)	0.002
Any STI - any site	1.000 (0.993 – 1.009)	0.833
Any STI – Under 35	1.006 (0.996 – 1.016)	0.246
Any STI – 35 and over	0.992 (0.980 – 1.004)	0.100
Secondary Analysis	IRR[b] (95% CI)	p-value
Chlamydia – all (unadjusted)	1.017 (1.006 – 1.028)	0.002
Chlamydia – all (adjusted)	1.000 (0.989 – 1.012	0.889
Gonorrhoea – all (unadjusted)	1.006 (0.994 – 1.018)	0.346
Gonorrhoea – all (adjusted)	0.988 (0.977 – 1.000)	0.049

Syphilis – all (unadjusted)	1.108 (1.082 – 1.125)	<0.001
Syphilis – all (adjusted)	1.091 (1.062 – 1.120)	<0.001
Any STI – all (unadjusted)	1.027 (1.018 – 1.036)	<0.001
Any STI – all (adjusted)	1.009 (1.000 – 1.019)	0.051

[a]Average change per calendar half-year, half-year included as continuous variable in negative binomial model
[b]Average change per six months of PrEP use, included as continuous variable in negative binomial model

Appendices

Appendix A2. Supplementary materials for Chapter 4

Syphilis testing, incidence, and reinfection among gay and bisexual men with and without HIV in Australia over a decade spanning HIV PrEP implementation: an analysis of surveillance data

Michael W. Traeger, Rebecca Guy, Caroline Taunton, Eric P.F. Chow, Jason Asselin, Allison Carter, Mark Bloch, Christopher K. Fairley, Anna McNulty, Vincent J. Cornelisse, Phillip Read, Louise Owen, Nathan Ryder, David J. Templeton, Darryl O'Donnell, Basil Donovan, Margaret E. Hellard*, Mark A. Stoové*

*Co-senior authors

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A2.1: Person-years-at-risk and number of syphilis tests and infections from 2012-2021, by HIV and PrEP status

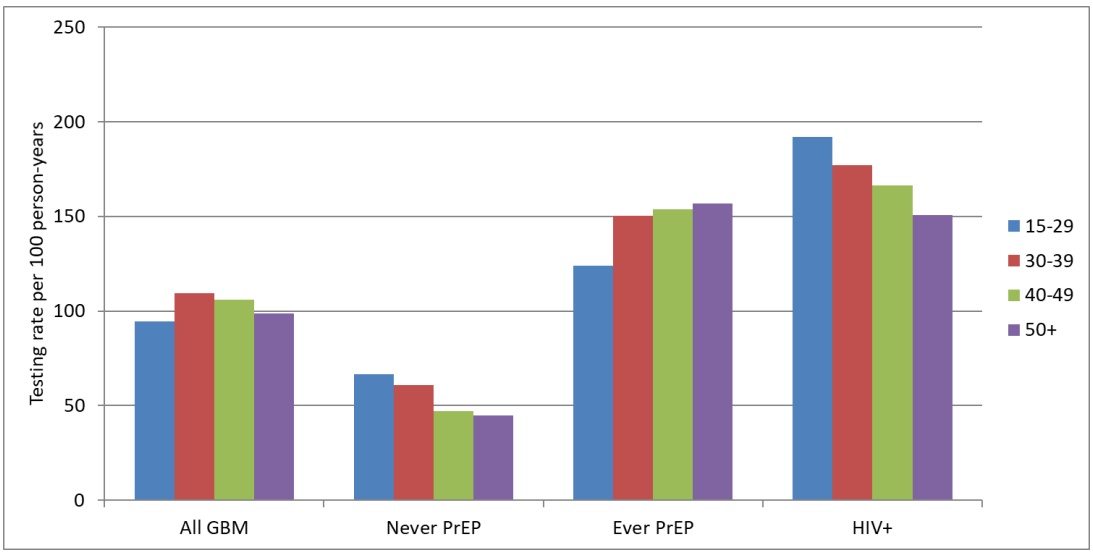
	Testing rate				Incidence rate			
	All GBM	Never PrEP users	Ever PrEP users	HIV+ GBM	All GBM	Never PrEP users	Ever PrEP users	HIV+ GBM
Number of individuals included in analysis	121013	86433	34847	13188	75577	39743	26925	10659
Total person-years during observation period	574,151	290,017	195,476	88,658	343,287	138,008	136,165	69,114
Overall rate / 100py from 2012-2021	102.4 (102.1 - 102.7)	55.5 (55.2 - 55.8)	144.7 (144.2 - 145.3)	162.5 (161.7 - 163.4)	4 (4 - 4.1)	1.9 (1.8 - 2)	4.2 (4.1 - 4.3)	8 (7.7 - 8.2)
Mean person-years (SD)	4.7	4.4	5.6	6.7	4.5	0.3	5.1	6.5
Median person-years (IQR)	4.3	3.7	5.6	7.8	4.0	2.8	4.8	7.3
Number of outcome events (tests or diagnoses)	587967	160991	282889	144087	13858	2607	5756	5495
Mean number of outcome events per person (SD)	4.9	3.5	8.1	10.9	0.2	0.1	0.2	0.5
Median number of outcome events per person (IQR)	2.0	1.0	5.0	9.0	0.0	0.0	0.0	0.0

A2.2: Syphilis testing rate per 100 person-years by HIV/PrEP status, year and age group.

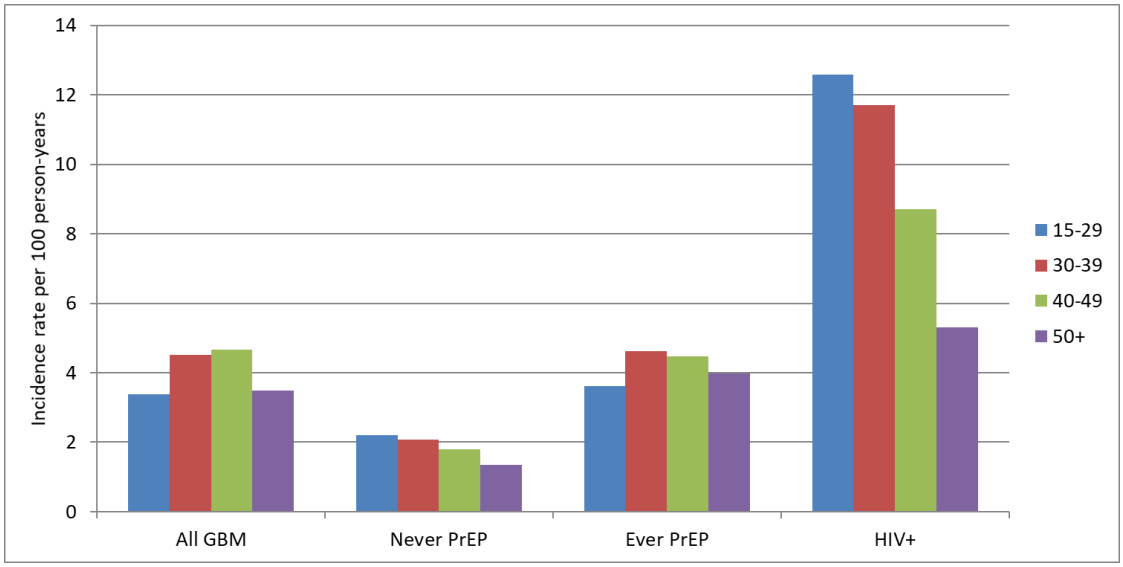
	Syphilis testing rate per 100 person-years (95% confidence interval)			
	All GBM	Never PrEP	Ever PrEP	HIV+
Total				
Year				
2012	69.1 (68.4 - 69.9)	42.9 (42.2 - 43.7)	67.9 (66.4 - 69.4)	176.3 (173.3 - 179.4)
2013	72.6 (71.9 - 73.3)	46 (45.3 - 46.8)	75.5 (74 - 77)	172.8 (169.9 - 175.7)
2014	75.7 (75.0 - 76.4)	48.4 (47.7 - 49.2)	81 (79.6 - 82.4)	172.5 (169.7 - 175.4)
2015	82.3 (81.6 - 83.1)	51.5 (50.7 - 52.2)	97.8 (96.3 - 99.2)	170.4 (167.6 - 173.1)
2016	100.6 (99.8 - 101.3)	54.7 (54 - 55.5)	148 (146.3 - 149.7)	165.6 (162.9 - 168.2)
2017	115.6 (114.8 - 116.4)	58.3 (57.5 - 59.2)	178.3 (176.6 - 180)	163 (160.5 - 165.6)
2018	124.0 (123.1 - 124.8)	63.9 (63 - 64.8)	185.4 (183.7 - 187.1)	160.6 (158.1 - 163.1)
2019	131.7 (130.8 - 132.6)	71.5 (70.5 - 72.5)	184.5 (182.8 - 186.2)	166.2 (163.7 - 168.8)
2020	109.8 (108.9 - 110.7)	55.2 (54.3 - 56.2)	149.3 (147.8 - 150.9)	137.2 (134.8 - 139.5)
2021	133.0 (132.0 - 134.1)	71.1 (69.8 - 72.4)	176.3 (174.5 - 178.1)	147.7 (145.2 - 150.2)
Age group				
15-29	94.5 (94.0 - 95.0)	66.7 (66.1 - 67.3)	124.1 (123.1 - 125)	192 (188.2 - 195.8)
30-39	109.5 (109.0 - 110.0)	60.9 (60.4 - 61.4)	150.5 (149.6 - 151.4)	177.1 (175.1 - 179.1)
40-49	106.0 (105.5 - 106.6)	47.2 (46.6 - 47.7)	153.6 (152.4 - 154.8)	166.5 (164.9 - 168)
50+	98.6 (98.0 - 99.1)	44.9 (44.4 - 45.4)	156.9 (155.5 - 158.3)	150.6 (149.4 - 151.8)

A2.3: Syphilis incidence rate per 100 person-years by HIV/PrEP status, year and age group.

	Syphilis incidence rate per 100 person-years (95% confidence interval)			
	All GBM	Never PrEP	Ever PrEP	HIV+
Year				
2012	2.6 (2.4 - 2.8)	1.6 (1.4 - 1.8)	1.6 (1.3 - 1.9)	6.3 (5.7 - 7.0)
2013	3.0 (2.8 - 3.2)	1.6 (1.4 - 1.8)	2.1 (1.8 - 2.4)	7.5 (6.8 - 8.2)
2014	3.4 (3.2 - 3.6)	1.9 (1.7 - 2.1)	2.5 (2.2 - 2.8)	8.4 (7.8 - 9.2)
2015	3.7 (3.5 - 3.9)	1.8 (1.6 - 2.0)	2.9 (2.6 - 3.2)	9.5 (8.8 - 10.3)
2016	3.5 (3.3 - 3.7)	1.7 (1.5 - 1.9)	3.5 (3.2 - 3.8)	7.8 (7.2 - 8.5)
2017	3.9 (3.7 - 4.1)	1.8 (1.6 - 2.0)	4.4 (4.1 - 4.8)	7.6 (7.0 - 8.2)
2018	4.2 (4.0 - 4.4)	1.8 (1.6 - 2.0)	4.7 (4.4 – 5.0)	8.2 (7.5 - 8.8)
2019	5.2 (5.0 - 5.5)	2.1 (1.9 - 2.4)	6.1 (5.7 - 6.4)	8.6 (8.0 - 9.3)
2020	4.6 (4.4 - 4.8)	2.2 (2.0 - 2.6)	5.0 (4.6 - 5.3)	6.8 (6.3 - 7.5)
2021	5.9 (5.7 - 6.2)	3.3 (2.9 - 3.8)	6.0 (5.6 - 6.4)	8.6 (7.9 - 9.3)
Age group				
15-29	3.4 (3.2 - 3.5)	2.2 (2.1 - 2.4)	3.6 (3.4 - 3.8)	12.6 (11.5 - 13.7)
30-39	4.5 (4.4 - 4.7)	2.1 (1.9 - 2.2)	4.6 (4.4 - 4.8)	11.7 (11.1 - 12.3)
40-49	4.7 (4.5 - 4.8)	1.8 (1.6 – 2.0)	4.5 (4.2 - 4.7)	8.7 (8.3 - 9.1)
50+	3.5 (3.4 - 3.6)	1.3 (1.2 - 1.5)	4.0 (3.7 - 4.3)	5.3 (5.0 - 5.6)



A2.4: Rate of syphilis testing/100py across entire observation period (2012-2021), by HIV/PrEP status and age group



A2.5: Syphilis incidence/100py across entire observation period (2012-2021), by HIV/PrEP status and age group

A2.6: Algorithm for syphilis detection in ACCESS

New cases of infectious syphilis were identified by the validated ACCESS algorithm which defines a new case of infectious syphilis (primary, secondary, early latent) as a test event with;

(1) a positive *Treponema pallidum* nucleic acid test result, or

(2) evidence of treponemal seroconversion within a two year period with a confirmatory treponemal result, or

(3) evidence of treponemal seroconversion within a two year period with a confirmatory non-treponemal result, or

(4) a fourfold or greater rise in non-treponemal titre within a two-year period, or

(5) a positive syphilis IgM with an additional reactive treponemal result, or

(6) a non-treponemal titre of $\geq$16 with no prior reactive syphilis serology or

(7) or a non-treponemal titre =8 and a reactive treponemal result with no prior reactive syphilis serology.

The algorithm has an estimated sensitivity of 84.3% and specificity of 99.8% in validation

Appendices

Appendix A3. Supplementary materials for Chapter 5

Incidence and prevalence of hepatitis C among HIV-negative gay and bisexual men using HIV pre-exposure prophylaxis (PrEP): a systematic review and meta-analysis

Michael W. Traeger, Brendan L. Harney, Rachel Sacks-Davis, Daniela K van Santen, Vincent Cornelisse, Edwina J. Wright, Margaret E. Hellard, Joseph S. Doyle, Mark A. Stoové

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A3.1: Search syntax

MEDLINE and EMBASE (OVID)

exp hepatitis C/ or exp Hepatitis C virus/ or hepatitis c.mp. or HCV.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

(PrEP or pre$exposure prophylaxis or pre$exposure chemo or truvada or tenofovir or TDF).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

(MSM or men who have sex with men or GBM or gay men or bisexual or homosexual or men having sex with men).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

1 and 2 and 3

Limit 4 to yr="2010-Current"

PubMed

(hepatitis c OR HCV) AND (PrEP or pre$exposure prophylaxis or pre$exposure chemo or truvada or tenofovir or TDF) AND (MSM or men who have sex with men or GBM or gay men or bisexual or homosexual or men having sex with men)

A3.2: Dates of broad access to direct-acting antiviral treatments for hepatitis C in included countries, and corresponding sources

Guiding analysis: Marshall AD, Cunningham EB, Nielsen S, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. *The Lancet Gastroenterology & Hepatology.* 2018;3(2):125-133. https://www.thelancet.com/journals/langas/article/PIIS2468-1253(17)30284-4/references

Country	HIV access availability	Broad / universal access date	Primary source excerpt	Citations
Australia		Mar-16	From Wade et al [1]; On 1 March 2016, the Australian government funded DAA for all Australians with hepatitis C infection [1]. To increase access to hepatitis C treatment, the government enabled all medical practitioners to prescribe pharmaceutical benefits scheme (PBS) funded DAA, although medical practitioners without experience in the management of hepatitis C were required to prescribe *in consultation* with a specialist gastroenterologist, hepatologist or infectious diseases physician experienced in the management of hepatitis C [2].	[1] Wade, AJ, McCormack, A, Roder, C, et al. Aiming for elimination: Outcomes of a consultation pathway supporting regional general practitioners to prescribe direct-acting antiviral therapy for hepatitis C. *J Viral Hepat*. 2018; 25: 1089–1098. https://doi.org/10.1111/jvh.12910 [2] Thompson AJ. Australian recommendations for the management of hepatitis C virus infection: a consensus statement. Med J Aust. 2016 Apr 18;204(7):268-72. doi: 10.5694/mja16.00106. PMID: 27078601. [3] Australian Government. General Statement for Drugs for the treatment of hepatitis C. In: Health Do, editor. http://www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c2017
Belgium	Jan 17	Jan-19	From Busschots et al [3]; Belgium based its 2015 guidelines for prescribing DAA therapy on the fibrosis stage, restricting it to patients with severe fibrosis or cirrhosis (F3–F4). Since January 2017 DAA therapy was reimbursable not only for patients starting treatment from the F2 fibrosis stage, but for all	[4] Busschots, D., Toghanian, S., Bielen, R. *et al.* Eliminating viral hepatitis C in Belgium: the micro-elimination approach. *BMC Infect Dis* 20, 181 (2020). https://doi.org/10.1186/s12879-020-4898-y [5] Antivirale geneesmiddelen tegen hepatitis C: vergoedingsvoorwaarden vanaf 1 januari 2019 - RIZIV.

			patients with risk factors or comorbidities such as hepatitis B virus (HBV)- or HIV-coinfection, haemophilia, and severe extrahepatic manifestations, as well as patients on dialysis or those on a transplant waiting list. Since the latest update in January 2019 HCV treatment is reimbursed for every patient regardless of the degree of fibrosis [5]. Currently, DAAs can be prescribed and initiated only by a gastroenterologist and are available only in a hospital pharmacy [6].	2019. https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/wijzigingen/Paginas/antivirale-hepatitisc-terugbetalingsvoorwaarden_20190101.aspx. [6] Antivirale geneesmiddelen tegen hepatitis C: vergoedingsvoorwaarden vanaf 1 januari 2017 - RIZIV. 2018. http://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/wijzigingen/Paginas/antiretrovirale_hepatitisc_terugbetalingsvoorwaarden_20170101.aspx#.Ww0_40iFNPY.
Canada (Quebec)		Jun-14	From Saeed et al [7]; For PLWH in Quebec, between June 2014-July 2015 and from July 2016 onwards there were no restrictions based on fibrosis stage. In Ontario and British Columbia, fibrosis restrictions were removed as of March 2017. There were never any sobriety restrictions for the reimbursement of DAAs in any province [8].	[7] Sahar Saeed, Erin Strumpf, Erica E M Moodie, Leo Wong, Joseph Cox, Sharon Walmsley, Mark Tyndall, Curtis Cooper, Brian Conway, Mark Hull, Valerie Martel-Laferriere, John Gill, Alexander Wong, Marie-Louise Vachon, Marina B Klein, Canadian Coinfection Cohort Study Investigators, Eliminating Structural Barriers: The Impact of Unrestricted Access on Hepatitis C Treatment Uptake Among People Living With Human Immunodeficiency Virus, *Clinical Infectious Diseases*, Volume 71, Issue 2, 15 July 2020, Pages 363–371, https://doi.org/10.1093/cid/ciz833
Canada (Ontario / BC)		Mar-17	In Quebec, in 2014, simeprevir and sofosbuvir were unrestricted for patients living with HCV. Although HIV infection was a listed restriction, coinfected patients were usually granted access on a case-by-case basis through the “patient d’exception” process. As of 2016, people coinfected with HIV and HCV were considered a priority population and sofosbuvir/ledipasvir and ombitasvir/paritaprevir/ritonavir dasabuvir were available without fibrosis stage restrictions; sofosbuvir/velpatasvir was available without restrictions from 2017. In British Columbia and Ontario, in 2017, after the pan-Canadian	[8] Marshall, Alison D., et al. "Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study." *Canadian Medical Association Open Access Journal* 4.4 (2016): E605-E614.

			Pharmaceutical Alliance used collective bargaining to reduce DAA drug prices across Canada, provinces removed fibrosis stage restrictions as a criterion for treatment reimbursement. No sobriety restrictions were present in Canada. Abbreviations: BC, British Columbia; ON, Ontario; QC, Quebec.	
France	Nov 2014	April 2017	From Pol et al [9] In France, following the recommendations of the Haute Autorité de Santé (HAS), [10] a prioritized access policy to DAAs was initially enforced. From November 2014 to June 2016, access to DAAs was initially restricted to patients with severe liver disease (cirrhosis) or extrahepatic disease (HIV, cryoglobulinemia and B-cell lymphoma), [11] The prioritized access was then extended in June 2016 to patients with stage F2 fibrosis and patients with a high risk of transmission (inmates, drug users and pregnant women). [12] Additionally, during the prioritized access period, DAAs could only be prescribed in hospital settings after a multidisciplinary concertation. Eventually, in April 2017, following the evolution of the HAS recommendations, [13] a universal access policy replaced the prioritized access policy: DAAs became available for all CHC patients, and prescriptions were made possible outside of the hospital by specialists in ambulatory care. Consecutively, in March 2018, DAAs were offered in all retail pharmacies, and in May 2019, every physician was granted the ability to prescribe pangenotypic second-generation DAAs.	[9] Pol S, Fouad F, Lemaitre M, et al. Impact of extending direct antiviral agents (DAA) availability in France: an observational cohort study (2015-2019) of data from French administrative healthcare databases (SNDS). *Lancet Reg Health Eur.* 2022;13:100281. [10] Haute Autorité de Santé. Recommandation du Collège de la HAS, prise en charge de l'hépatite C par les médicaments anti-viraux à action directe (AAD). Jul, 2014. https://www.has-sante.fr/upload/docs/application/pdf/201407/hepatite_c_prise_en_charge_anti_viraux_aad.pdf [11] Journal Officiel de la République Française. Arrêté du 18 novembre 2014 relatif aux conditions de prise en charge de spécialités pharmaceutiques disposant d'une autorisation de mise sur le marché inscrites sur la liste visée à l'article L. 5126-4 du code de la santé publique. NOR: AFSS1426759A ELI. 18 novembre 2014. https://www.legifrance.gouv.fr/eli/arrete/2014/11/18/AFSS1426759A/jo/texte [12] Journal Officiel de la République Française. Arrêté du 10 juin 2016 relatif aux conditions de prise en charge de spécialités pharmaceutiques disposant d'une autorisation de mise sur le marché inscrites sur la liste visée à l'article L. 5126-4 du code de la santé publique. NOR:

				AFSS1613575A ELI. https://www.legifrance.gouv.fr/eli/arrete/2016/6/10/AFSS1613575A/jo/texte [13] Haute Autorité de Santé. Recommandation du Collège de la HAS, pris en charge de l'hépatite C par les médicaments antiviraux d'action directe (AA), élargissement du périmètre de remboursemnet. https://www.has-sante.fr/portail/upload/docs/application/pdf/201612/recommandation_college_hepatite_c.pdf
Netherlands		Nov-15	From Isfordink et al [14] As of November 2015, unrestricted DAA access is available in the Netherlands. [15] DAAs are fully reimbursed by Dutch healthcare insurance, with exception of the yearly obligatory deductible excess of €385. Healthcare insurance is obligated for people residing in the Netherlands.	[14] Isfordink CJ, Brakenhoff SM, van Dijk M, et al. Hepatitis C elimination in the Netherlands (CELINE): study protocol for nationwide retrieval of lost to follow-up patients with chronic hepatitis C. *BMJ Open Gastroenterol*. 2020;7(1):e000396. Published 2020 Apr 12. doi:10.1136/bmjgast-2020-000396 [15] Ekpanyapong S, Reddy KR. Hepatitis C virus therapy in advanced liver disease: outcomes and challenges. *United European Gastroenterol J* 2019;7:642–50. 10.1177/2050640619840149
Spain		Jun-17		Limited access: [16] Campillo-Artero C, Garcia-Armesto S, Bernal-Delgado E. The merry-go-round of approval, pricing and reimbursement of drugs against the Hepatitis C virus infection in Spain. Health Policy. 2016 Sep;120(9):975-81. doi: 10.1016/j.healthpol.2016.07.005. Epub 2016 Jul 16. PMID: 27460522. Broad access:

				[17] Corma-Gomez A, Pineda JA. Hepatitis C virus infection in Spain: Challenges in the track to elimination. *Enferm Infecc Microbiol Clin (Engl Ed).* 2019;37(4):219-221. Also June 2017 here https://bmjopen.bmj.com/content/11/10/e053394 which refs Marshall et al. if need to simplify refs a bit.
UK		April-16	From Hepatitis C in England report 2022 [18] The recent reduction is largely due to the advent of new DAA treatments which became available via early access programmes in 2014 to 2015 and became more widely accessible from 2016 to 2017. The substantial fall in numbers of people with chronic HCV infection is largely due to improved access to direct-acting antivirals, with around 58,850 treatments taking place between tax years 2015 to 2016 and 2020 to 2021. NHS England commissioning data shows significant increases in the number of people accessing HCV treatment since 2015 as access to new DAA drugs increased in England.	[18] Harris HE, Costella A, Mandal S, Desai M, and contributors. Hepatitis C in England, 2022: Working to eliminate hepatitis C as a public health problem. Full report. March, 2022. UK Health Security Agency, London. Gradual approval of DAA treatments from January 2015 – Available from the NHS NICE. 'Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance TA330' 2015 https://www.nice.org.uk/guidance/ta330 NICE. 'Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA365]' 2015 https://www.nice.org.uk/guidance/ta365 NICE. 'Ledipasvir–sofosbuvir for treating chronic hepatitis

				C' 2015 https://www.nice.org.uk/guidance/ta363 NICE. 'Sofosbuvir–velpatasvir for treating chronic hepatitis C' 2017 https://www.nice.org.uk/guidance/ta430 NICE. 'Elbasvir–grazoprevir for treating chronic hepatitis C' 2016 https://www.nice.org.uk/guidance/TA413/chapter/2-The-technology
US		Jan-15	From CDC [19] Since 2015, many states have removed policy restrictions that prevented people living with hepatitis C from accessing treatment, and the new CDC treatment estimates show from 2014 to 2020, the proportion of claims for hepatitis C DAAs paid for by Medicaid increased by three-fold. **Full Report** Published February 16, 2022:Characteristics of persons treated for hepatitis c using national pharmacy claims data, United States, 2014-2020external icon [20]	[19] New estimates reveal declines in hepatitis C treatment in the U.S. between 2015 and 2020. US CDC. https://www.cdc.gov/nchhstp/newsroom/2021/2014-2020-hepatitis-c-treatment-estimates.html#Summary Full report: [20]Teshale EH, Roberts H, Gupta N, Jiles R. Characteristics of persons treated for hepatitis C using national pharmacy claims data, United States, 2014-2020. *Clin Infect Dis.* 2022. https://stateofhepc.org/resources/ 2017 report shows numerous states have resitctions based on liver disease
Slovenia		Jan-18	Elimination of hepatitis C in Slovenia (National Program) Webpage from Coalition for Global Hepatitis Elimination.	https://www.globalhep.org/programs/elimination-hepatitis-c-slovenia-national-program

			There are five hospital-based clinics for treatment of viral hepatitis regionally spread throughout the country. Historically all the currently recommended standard of care treatment options have been available, including the direct acting antivirals (DAAs), starting in 2014. Hepatitis C treatment is available and accessible for everyone. It is fully publicly funded by a national health insurance system and provided with no limitations except for one: it had to be prescribed by the nominated specialists for viral hepatitis (infectologists, hepatologists) according to the national guidelines. Restrictions to the use of DAAs were present according to the fibrosis stage only in the period 2014-2017 due to high prices.	

A3.3: Reported behavioural characteristics of study participants

Study	Project / Study / Clinic	Sexual behaviours of the PrEP cohort at baseline	Sexual behaviours reported for HCV cases	Drug use behaviours of the PrEP cohort at baseline	Drug use behaviours of the HCV cases
Aloysius et al 2017 [309]	InterPrEP	NR	NR	30% (191/641) reported recreational drug use in the p12m at baseline. IDU in p12m was reported in 61 participants (12%) at baseline and 42 participants (13%) during follow-up	NR
Amin et al 2021 [185]	EPIC-NSW Study	8042 (92.9%) participants reported RCAI with a casual partner in p3m at baseline	88% of HCV cases reported RCAI at baseline compared to 92.9% of non-cases (p=0.159)	1740 (20.1%) participants reported methamphetamine use in p3m at baseline	Of the 20 HCV incidence cases, 9 (45%) reported methamphetamine use at baseline, compared to 19.7% in those with HCV incident infections (IRR 2.7 [1.0-7.2] p=0.35). Of the 11/20 cases with available responses, 3 reported injecting methamphetamine during follow-up.
Ayerdi Aguirrebengoa et al 2021 [310]	Centre Sanitario Sandoval	At baseline, 85% used condoms usually (>50%) 10% occasionally (<50%) and 4.5% never. At 12 months, 30% used condoms usually, 50% occasionally and 20% never. Before PrEP, 32.7% (n=36) had 1–5 sexual partners per month, 47.3% (n = 52) 6–10, 15.5% (n = 17) 11–50 and 4.5% (n = 5) more than 50 per month. After PrEP, the 31.8% (n = 35) had 1–5 sexual partners per month, 40.0% (n = 44) 6–10, 24.5% (n = 27) 11–50 and 3.6% (n = 4) more than 50 sexual partners per month.	NR	59 (53.6%) reported chemsex, with a median number of sessions per year of 4 (IQR: 2–12). 2 participants reported IDU.	NR
Behanzin et al 2022 [478]	Community-based demonstration study	NR	NR	NR	NR
Cornelisse et al 2020 [311]	PrEPX Study	48.2% reported RCAI with casual partners in p3m at baseline. Of those with data, 61.5% reported any CAI in the p6m.	All HCV cases reported RCAI. 7/8 HCV cases reported group sex. 5/6 reported attending a SOPV. 2/6 cases reported receptive fisting. Authors report 5/8 HCV cases likely via sexual transmission.	4.9% reported current IDU at baseline. 13.5% reported methamphetamine use in p3m at baseline. Of those with follow-up data, 5.7% reported recent IDU during PrEP use. 9.9% reported ever IDU. 13.2% reported recent use of	7/8 HCV cases reported drug use during sex. 4/8 cases reported IDU. Authors report 3/8 cases likely via sharing injecting equipment.

				methamphetamines in the context of sex. 9.9% reported recent use of GHB in the context of sex.	
Cotte et al 2018 [179]	French Dat'AIDS cohort	NR	NR	NR	NR
Desai et al 2020 [312]	PROUD	Median [IQR] partner number p3m = 10 [5-20]. Median [IQR] number of CRAI partners in p3m = 2 [1-5].	NR	226/490 (47.6%) participants reported chemsex drug use in p3m at baseline (i.e. methamphetamine, GHB, mephedrone, ketamine)	NR
Gras et al 2020	ANRS IPERGAY PrEP	At baseline, median [IQR] number of partners in p2m was 17 [8-30] in HCV cases and 8 [5-16] in non-HCV cases (p=0.03). At baseline, median [IQR] number of sexual acts over p4m was 18 [12-20] in HCV cases and 10 [5-16] in non-HCV cases (p=0.02). At baseline, proportion reporting CRAI at last anal sex was 92% in HCV cases and 85% in non-HCV cases (p=0.70).		At baseline, proportion reporting chemsex during last sexual act was 57% in HCV cases and 11% in non-cases (p<0.001). At baseline, receptive fisting was 25% in HCV cases compared to 3% in non-HCV cases.	
Hamed et al 2018 [314]	Clinic Network in Newark	NR	NR	NR	NR
Harney et al 2021[a] [186]	ACCESS surveillance network	NR	NR	NR	NR
Hassan et al 2019 [315]	CCTG 595 PATH-PrEP	Anal sex in p1m at baseline was reported in 563/594 (95%) of non-cases and 3/5 (60%) of cases (p=1.00). No difference between non-cases and cases in median number of male sex partners (5 vs 3.5;p=0.39), median number of CRAI acts (1 vs 4.5; p0.34); or median number CIAI acts (2 vs 1;p=0.60).		At baseline use of heroin in p1m was reported in 15/594 (3%) of non-cases and 0/5 (0%) of cases (p=1.00). At baseline use of methamphetamine in p1m was reported in 92/594 (15%) of non-cases and 2/5 (40%) cases (p=0.071).	
Hoornenborg et al 2020 [180]	Amsterdam PrEP project	At follow-up visit: Median [IQR] RCAI acts in p3m: 10 [6-17] for cases 3 [0-11] for non-cases Number of HIV-positive partners in p3m: 76.9% for cases vs 51.1% for non-cases Sharing sex toys in p6m: 30% for cases vs 24.6% for non-cases Fisting without gloves in p6m: 30% for cases vs 24.9% for non-cases During follow-up, hazard ratio [95% CI] for incident HCV infection: Number of HIV-positive partners in p3m: 1.91 [0.81-4.33] Sharing sex toys in p6m: 1.64 [0.64-7.14] Fisting without gloves in p6m: 1.51 [0.59-3.90]		At follow-up visit: Sharing straws when snorting drugs p6m: 60% for cases vs 28.7% for non-cases IDU in p12m: 40% of cases vs 5.1% of non-cases Chemsex in p6m: 63.6% of cases vs 41.2% of non-cases During follow-up, hazard ratio [95% CI] for incident HCV infection: Sharing straws when snorting drugs in p6m: 2.62 (1.09-6.02) Injecting drug use in p12m: 4.69 (1.61-12.09) Chemsex inp6m: 2.02 (0.83-4.89)	
Lalley-Chareczko et al 2018 [316]	Philadelphia FIGHT clinic	At baseline: 40 (80%) reported inconsistent condom use 15 (60%) reported 4 or more partners in p6m 27 (54%) reported partner of unknown HIV status	NR	At baseline: 37 (74%) reported drug and/or alcohol use	NR
Mikati et al 2018 [317]	NYC Sexual Health Clinics	At baseline, median number of partners in p3m was 4	NR	At baseline, 10 (2.7%) participants reported IDU / chemsex (Meth or GHB) in p3m.	One HCV case reported IDU
Molina et al 2019 [181]	ANRS PREVENIR	At baseline, median [IQR] number of CAI acts in p1m was 2 [0-5] At baseline, median [IQR] number of partners in p3m was 10 [5-20]	NR	At baseline, 427 (13.9%) reported chemsex use at last intercourse	NR

Nguyen et al 2018 [318]	Clinique l'Actuel	NR	NR	NR	NR
Noret et al 2018	Saint-Louis Hospital	At baseline; Median [IQR] partner number in p3m: 10 [5-10] Median [IQR] number CAI acts in p1m: 4 [1-10] 557 (55.3%) participants reported CAI at last intercourse 315 (30.6%) participants reported RCAI at last intercourse	NR	At baseline; 437 (42.6%) participants reported chemsex in p1m 279 (27.5%) participants reported chemsex at last intercourse	NR
Pecavar		At baseline; 64 (92.8%) participants reported CAI in p12m Mean [range] number of anal sex acts with condom in p12m was 53 [0-200] Mean [range] number of CAI acts in p12m was 44 [0-100] Mean [range] number of oral sex acts in p12m was 56 [0-119]	NR	NR	NR
Ramiere et al 2019[b] [182]	Lyon University Hospital	NR	Of 24 cases; 19 (79.2%) reported participating in a sex party 12 (50%) reported fisting 19 (79.2%) reported participants in a sex party or fisting	NR	Of 24 cases: 13 (54.2%) reported IDU 17 (70.8%) reported nasal drug use 23 (95.8%) reported IDU or nasal drug use
Reyniers et al 2018[c] [321]	Belgian PrEP study				
Tabatabavakili et al 2022 [322]	University HIV Prevention Clinic	At baseline; 20 (25.7%) participants reported an HIV+ positive partner 102 (95.3%) participants reported multiple partners 85 (91.4%) participants reported inconsistent condom use	NR	At baseline; 10 (9.2%) participants reported history of methamphetamine use 2 (1.8%) participants reported history of IDU	1/2 cases reported IDU and methamphetamine use
Thompson et al 2022 [323]	BC PrEP Program	NR	NR	NR	NR
Volk et al 2015 [324]	Kaiser Permanente SF MC	NR	1/2 cases reported RCAI with multiple partners in a group sex setting	NR	0/2 cases reported IDU
Vuylesteke et al 2019[c] [325]	Belgian PrEP study	NR	NR	NR	NR

Footnote:

p1m = past 1 month; p3m = past 3 months; p6m = past 6 months; p12m = past 12 months

CAI = condomless anal intercourse; RCAI = receptive condomless anal intercourse; ICAI = insertive condomless anal intercourse

IDU = Injection drug use; SOPV = sex on premises venue; IQR = inter-quartile range

A3.4: Modified Newcastle-Ottawa quality assessment scale for cohort studies

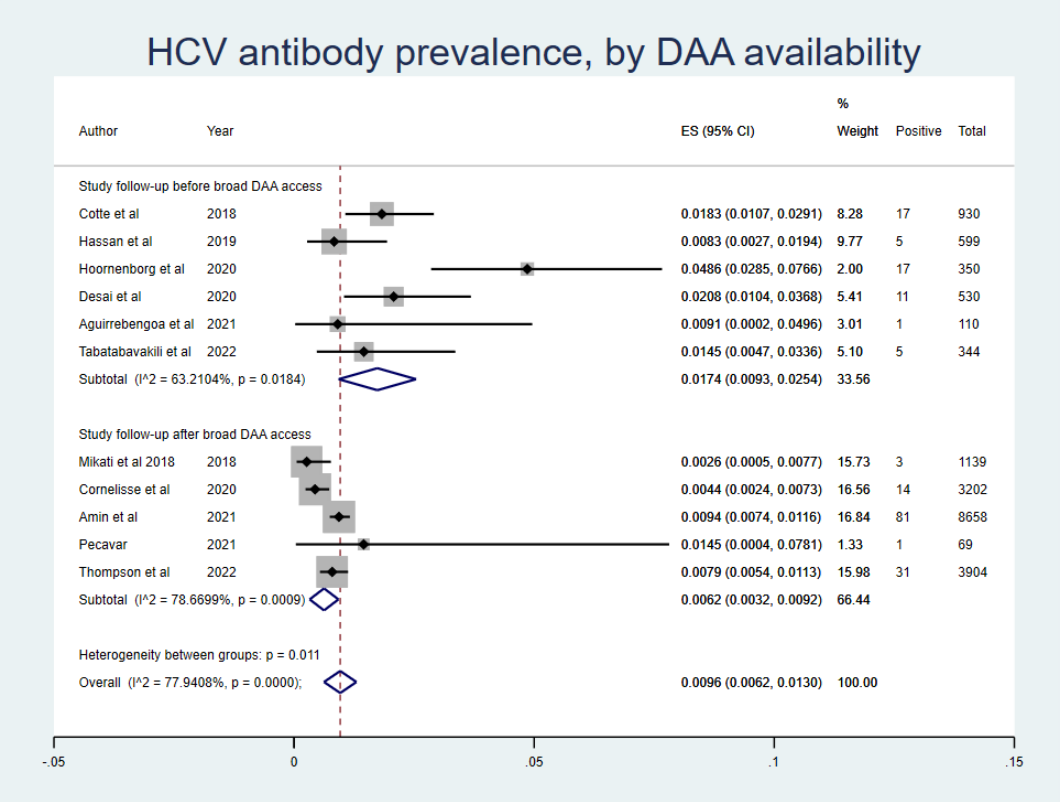
Selection	1) Representativeness of the cohort [1 score if a or b; zero score if c or d] a. Study population are truly representative of the average population of GBM using PrEP b. Study population are somewhat representative of GBM using PrEP * c. Study population are selective group of GBM using PrEP d. No description of the derivation of the cohort
	2) Clear definition of study population provided (i.e., GBM followed during period of PrEP use) [1 score if a; zero score if b] a. Yes * b. No
	3) Ascertainment of testing frequency interval in study population [1 score if a; zero score if b or c] a. Secure record (e.g. clinical record, record linkage) * b. Self-report c. No description
	4) Demonstration that outcome of interest was not present at start of study (all participants included in incidence analyses HCV negative at baseline) [1 score if a; zero score if b] a. Yes * b. No
Outcome	5) Assessment of outcome (HCV infection) [1 score if a or b; zero score if c or d] a. Independent blind assessment by HCV RNA test results * b. Record linkage * c. Self-report d. No description
	6) Confirmation of outcome (HCV infection) [1 score if a; zero score if b] a. HCV RNA confirmation test for new infection c. No description
	7) Was follow-up long enough for outcomes to occur [1 score if a; zero score if b or c] a. Yes (mean/median of follow-up longer than six months) * b. No

	c. Not reported
	8) Adequacy of follow up of cohort [1 score if a or b; zero score if c or d] a. Complete follow up – all participants accounted for * b. Participants lost to follow up unlikely to introduce bias (small number lost (<20%), or description provided of those lost) * c. >20% lost to follow-up and no description provided of those lost d. No statement

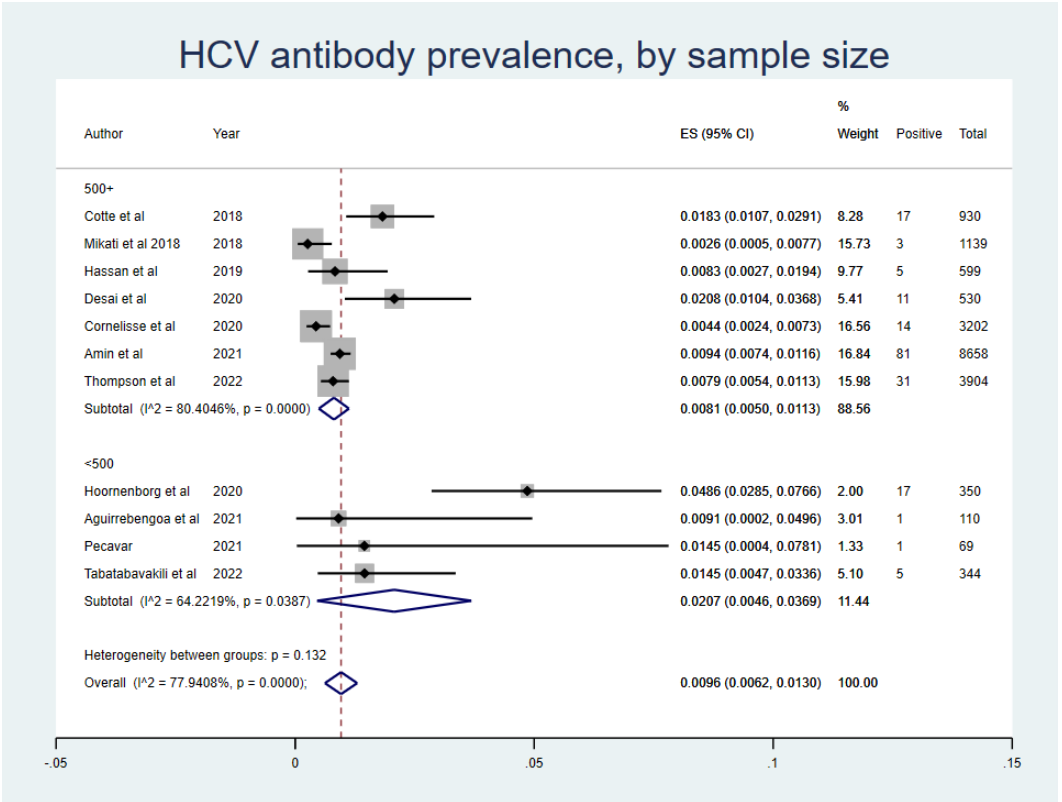
A3.5: Risk of bias scores of included studies

Study	1) Representativeness of the cohort	2) Clear definition of study population provided	3) Ascertainment of testing frequency interval in study population	4) Demonstration that outcome of interest was not present at start of study	5) Assessment of outcome	6) Confirmation of outcome	7) Was follow-up long enough for outcomes to occur	8) Adequacy of follow up of cohort	Total score (/8)
Aloysius et al 2017 [309]	0	1	0	0	1	0	0	0	2
Amin et al 2021 [185]	1	1	1	1	1	1	1	1	8
Ayerdi Aguirrebengoa et al 2021 [310]	1	1	1	1	1	0	0	1	6
Cornelisse et al 2020 [311]	1	1	1	1	1	1	1	1	8
Cotte et al 2018 [179]	1	1	1	1	1	1	1	1	8
Desai et al 2020 [312]	0	1	1	1	1	1	1	1	7
Gras et al 2020 [313]	0	1	1	1	1	1	1	1	7
Hamed et al 2018 [314]	0	1	0	0	0	0	0	0	1
Harney et al 2021 [186]	1	0	1	1	1	1	1	1	7
Hassan et al 2019 [315]	1	0	1	1	1	1	1	1	7
Hoornenborg et al 2020 [180]	1	1	1	1	1	1	1	1	8
Lalley-Chareczko et al 2018 [316]	0	1	0	0	0	0	0	0	1
Mikati et al 2018 [317]	0	1	0	0	1	1	0	0	3
Molina et al 2019 [181]	1	1	1	1	1	1	1	1	8
Nguyen et al 2018 [318]	0	1	0	1	1	1	1	1	6
Noret et al 2018 [319]	1	1	1	1	1	1	1	1	8
Pečavar et al 2021[320]	0	1	1	1	1	1	1	1	7
Ramiere et al 2019 [182]	1	0	1	1	1	1	1	1	7
Reyniers et al 2018 [321]	1	1	1	1	1	1	0	0	6
Tabatabavakili et al 2022 [322]	1	1	1	1	1	1	1	1	8
Thompson et al 2022 [323]	1	1	1	1	1	1	1	1	8
Volk et al 2015 [324]	0	0	1	1	0	0	0	0	2
Vuylesteke et al 2019 [325]	0	1	1	1	1	0	1	1	6

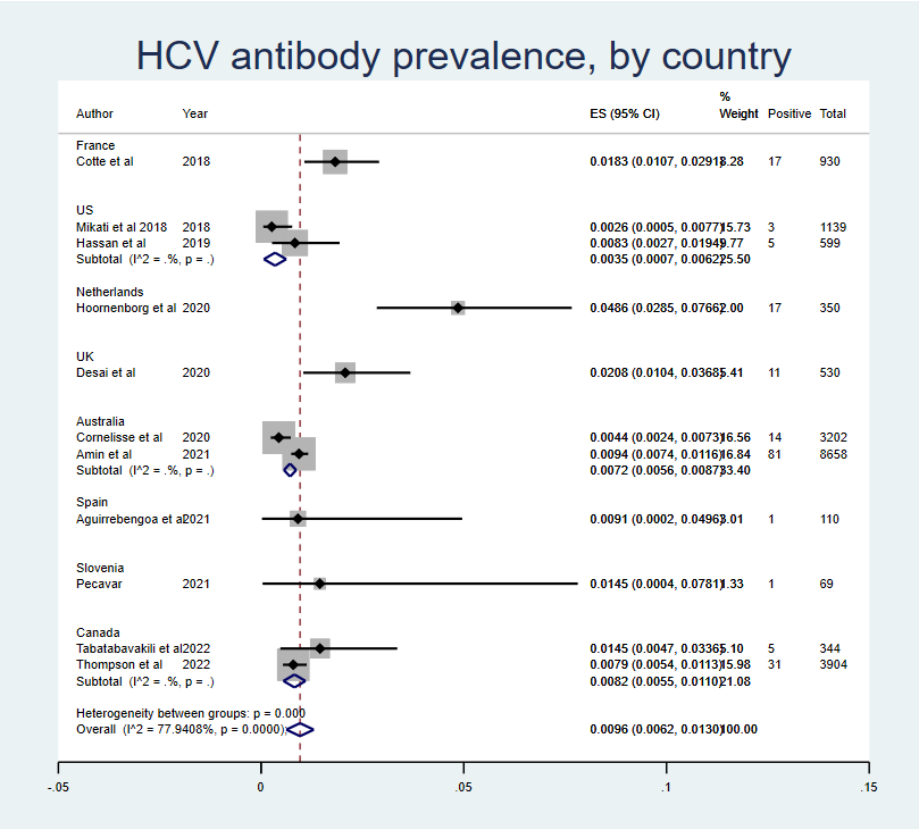
A3.6: HCV Ab prevalence by DAA availability



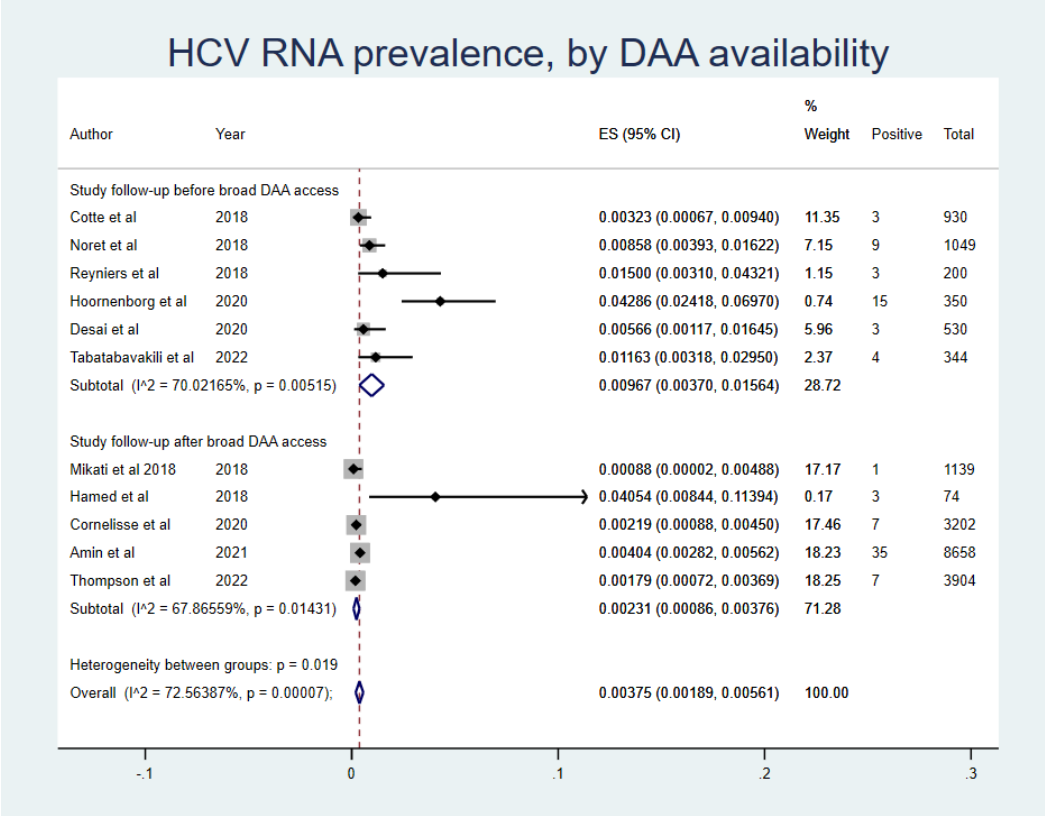
A3.7: HCV Ab prevalence by sample size



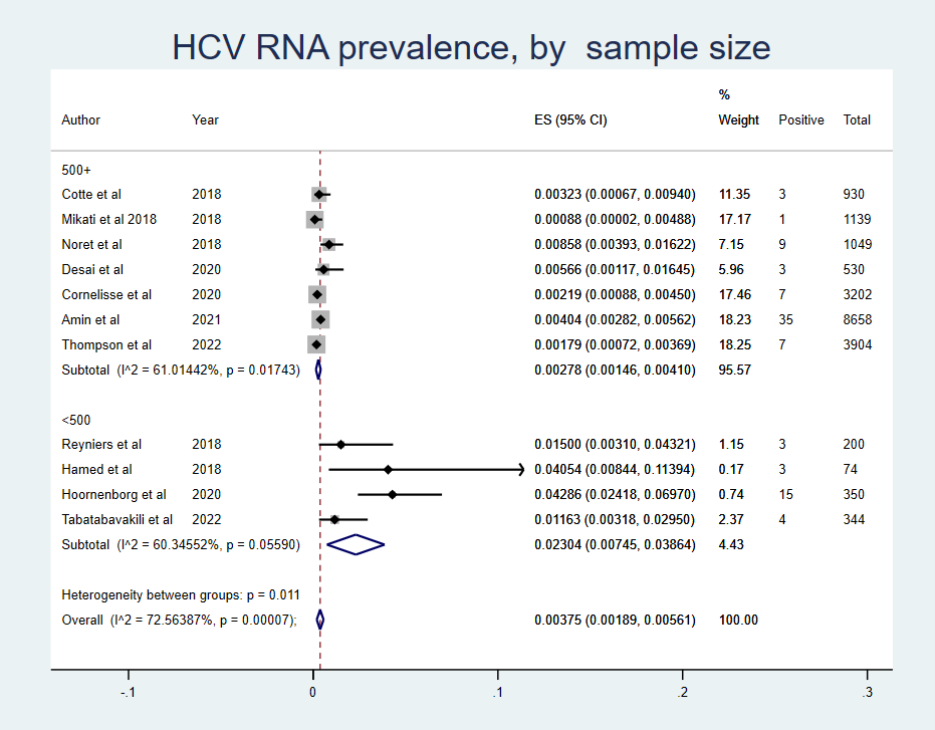
A3.8: HCV Ab prevalence by country



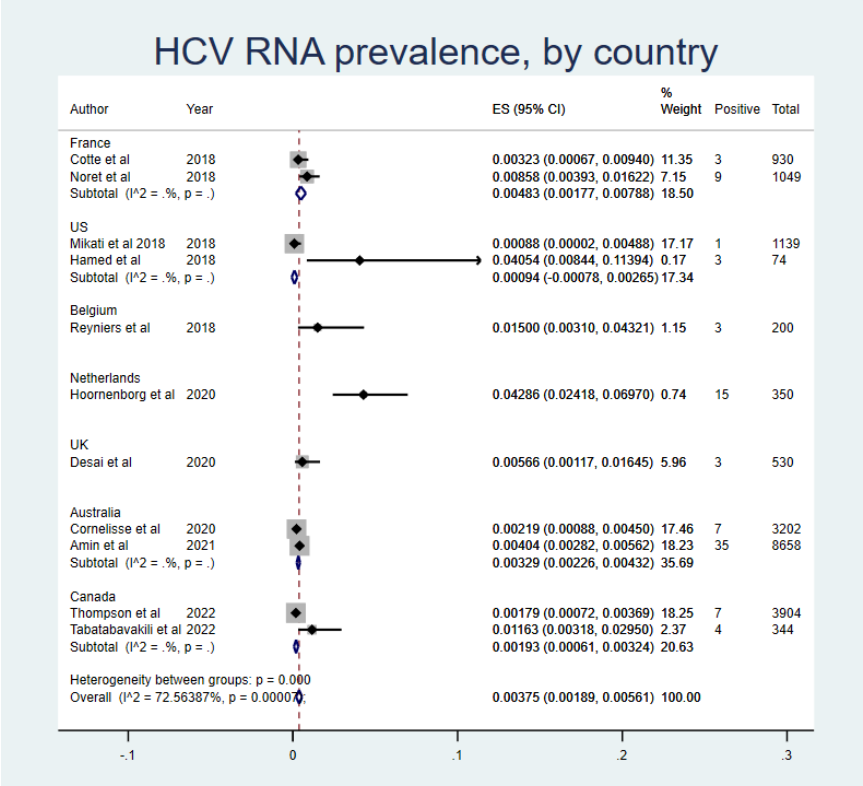
A3.9: HCV RNA prevalence by DAA availability



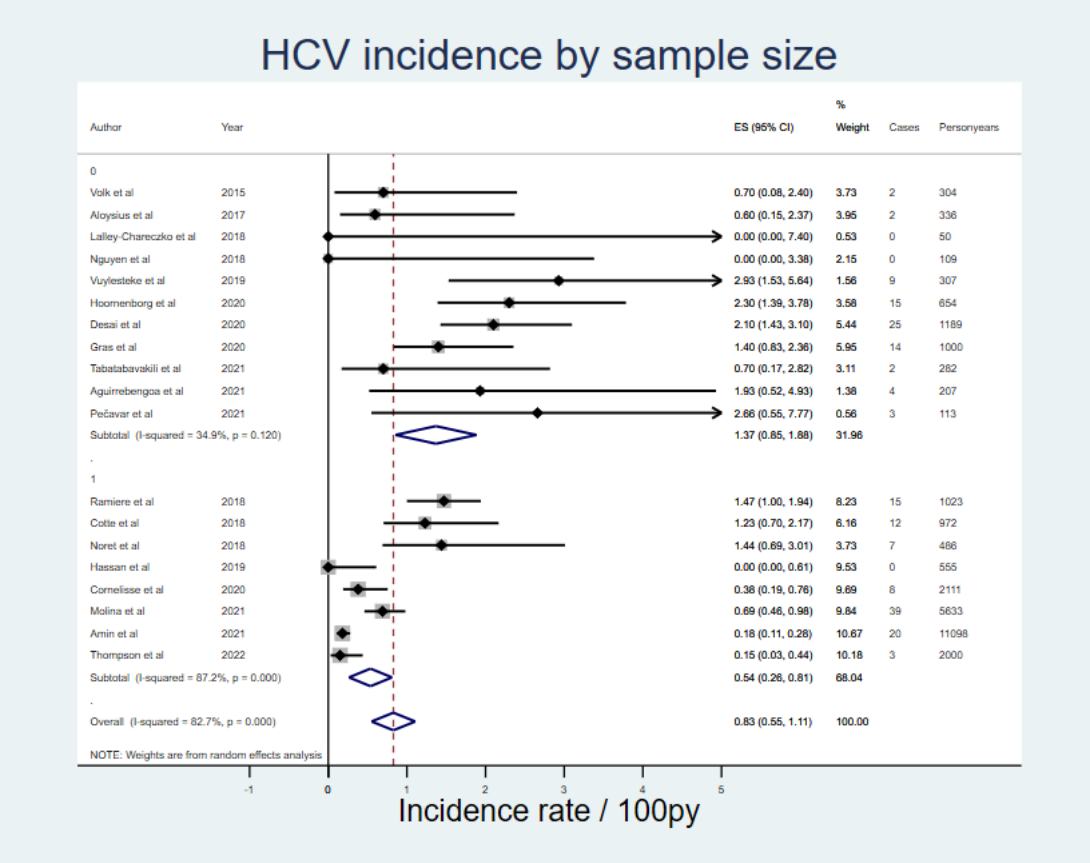
A3.10: HCV RNA prevalence by sample size



A3.11: HCV RNA prevalence by country



A3.12: HCV incidence by sample size



Appendix A4. Supplementary materials for Chapter 7

The potential impact of a gel-based point-of-sex intervention in reducing gonorrhoea incidence among gay and bisexual men: a modelling study

Michael W. Traeger, Tom Tidhar, Martin Holt, Chris Williams, Edwina J. Wright, Mark A. Stoové, Nick Scott*, Margaret E. Hellard*

*co-senior authors

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A4.1: Supplementary Table 1: Model parameters and references for parameters

Parameter	Value	Reference/comment
HIV parameters		
Effectiveness of latex condoms at preventing HIV	91%	Estimated condom effectiveness during anal sex between men in two prospective cohort studies [479]
Effectiveness of latex condoms at preventing gonorrhoea	75%	Conservative estimate (Supplementary Methods 4)
Effectiveness of PrEP at preventing HIV transmission	99%	US CDC PrEP effectiveness estimate [480]
Reduction in HIV infectiousness when on treatment	100%	Reduction in HIV transmission from Opposites Attract study [37]
Gonorrhoea parameters		
Duration of exposed stage for symptomatic individuals	5 days	[481]
Duration of treatment	7 days	Australian STI guidelines recommend abstaining from sex for 7 days post treatment [482]
Proportion of GBM with gonorrhoea who are symptomatic	29%	Calculated from ACCESS study data. Proportion diagnosed with either rectal infection only or including urethral infection, and corresponding probabilities of being symptomatic (Supplementary Methods 4)
Increased gonorrhoea risk for high-risk GBM	7.5	Estimated from the PrEPX study [67] (Supplementary Methods 6)
Proportion of GBM at high-risk of gonorrhoea	13%	
Gonorrhoea testing frequency		
HIV-negative GBM on PrEP	1/90 days	Australian PrEP guidelines recommend quarterly testing [75]
HIV-negative GBM not on PrEP	1/224 days	Previous analysis of Victorian GBM in ACCESS data [166]
HIV-positive GBM	1/133 days	Previous analysis of Victorian GBM in ACCESS data [166]
Sexual risk parameters		
Proportion of HIV serodiscordant sex acts (HIV-negative non-PrEP)	10%	Estimated from large cross-sectional survey of GBM [483]
Proportion of HIV serodiscordant sex acts (HIV-negative PrEP users)	17%	
Proportion of HIV serodiscordant sex act (HIV-positive)	34%	
Relative condom use of GBM on PrEP and HIV-positive GBM compared to HIV-negative GBM not on PrEP	0.3	Estimated from Melbourne Gay Community Period Survey 2019 [358]

A4.2: Supplementary Methods 1: Population sizes

The size of the GBM population living in Victoria in 2006 was estimated at 42,000 [484] and increased at a rate of 2.5% per year in line with Victorian population growth. The annual population size of GBM living with HIV in Victoria was estimated as the total GBM population multiplied by an HIV prevalence of 7.2% [485]. Annual HIV notifications among GBM were calibrated from 2010 to 2018, with 233, 194 and 155 HIV notifications in Victoria with male-to-male sex as the exposure category in 2016, 2017 and 2018 respectively ([486]; Supplementary Table 2). The annual number of HIV notifications from 2019 onwards was kept as constant at 155. The proportion of HIV-negative GBM in the model using PrEP between 2009 and 2019 was derived from routine behavioural surveillance of Australian gay and bisexual men [358] (Supplementary Table 3). PrEP became publically subsidised in April 2018, and the proportion of GBM in the model using PrEP was assumed to remain constant from 2019 onwards. Scenarios of further PrEP uptake post-2019 were explored in sensitivity analyses (Supplementary Table 5).

A4.3: Supplementary Methods 2: Gonorrhea testing rate

Gonorrhoea testing rate was estimated from data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) project. ACCESS is a government-funded, national STI surveillance network which routinely extracts de-identified clinical data from sexual health clinics and diagnostic laboratories in each Australian state and territory [243]. Gonorrhoea testing rate was a constant parameter for each subpopulation (HIV-negative on PrEP, HIV-negative not on PrEP, HIV-positive), and reflected the mean number of days between asymptomatic gonorrhoea tests among each subpopulation. Gonorrhea testing rate for GBM using PrEP in the model was every three months, as Australian PrEP guidelines outline quarterly testing for bacterial STIs for all GBM using PrEP [75]. The average testing frequency for HIV-negative GBM not using PrEP (1.6 tests per year) and HIV-positive GBM (2.7 tests per year) was estimated from previous analysis of ACCESS surveillance data [166].

A4.4: Supplementary Methods 3: Condom use

Condom use was included as a time-varying parameter for each subpopulation (HIV-negative on PrEP, HIV-negative not on PrEP, HIV-positive) which reflected the proportion of each population using condoms consistently with casual partners. Consistent condom use among HIV-negative non-PrEP users was estimated as the proportion of GBM in self-reported behavioural surveillance data reporting anal sex with casual partners in the last 6 months who always used a condom with casual partners, and steadily decreased from 44% in 2010 to 29% in 2019 [358, 487]. Consistent condom use among PrEP users and HIV-positive GBM was estimated to be 0.3 times that of HIV-negative GBM not on PrEP [277]. Although condom use is likely to continue to decrease among the GBM population in the future, condom use was held constant in the model from 2019 onwards, (except for reductions resulting from the introduction of the gel-PSI intervention, described below), in order to produce a conservative estimate of the benefit of gel-PSI introduction given the scenario of maintaining current levels of condom use. This was explored in sensitivity analysis.

The model population and equations were not explicitly stratified by condom use (non-condom user and condom users) as this would require significant assumptions to be made about different testing practices, sexual mixing and PrEP use among condom and non-condom users.

A4.5: Supplementary Methods 4: Condom effectiveness, gonorrhoea symptomatic rate and sexual mixing

Condom effectiveness: The effectiveness of condoms in reducing HIV transmission among GBM was taken from a study which estimated the per partner effectiveness of condoms using data from four cohorts of GBM to be 91% [488]. As we did not model site-specific gonorrhoea transmission, and as there are limited estimates for the effectiveness of condoms in reducing transmission risk of gonorrhoea in GBM, we chose to set effectiveness of condoms in reducing gonorrhoea transmission as 75%. This is likely an overestimate for the per partner effectiveness of condoms in reducing gonorrhoea transmission risk, however was chosen as a conservative estimate; different effectiveness levels were explored in sensitivity analyses.

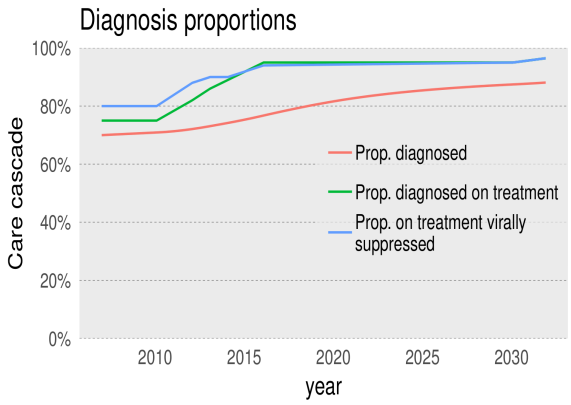
Gonorrhoea symptomatic rate: The proportion of gonorrhoea infections (any site) which were symptomatic was set as 39%, and was calculated using ACCESS data on site-specific rates of gonorrhoea among Victorian GBM and corresponding symptomatic rates [489, 490]. Given that we did not model site-specific gonorrhoea infections, the proportion of gonorrhea-infected individuals who were symptomatic in the model (39%) was estimated based on a combination of site-specific diagnosis data and the chance of infection being symptomatic at each site. The parameter was calculated as the proportion of GBM visiting Victorian sentinel surveillance sites in ACCESS diagnosed with gonorrhoea between 2016 and 2018 who had a urethral infection (24%) plus the proportion who had a rectal infection without urethral infection, each multiplied by the respective estimated chance of symptomatic presentation for infection at that site (89% for urethral infections [489], 24% for rectal infections [490]).

Sexual mixing: Sexual mixing was incorporated in the gonorrhoea model by including a parameter for each subpopulation (HIV-negative on PrEP, HIV-negative not on PrEP and HIV-positive) which represented the proportion of sex acts which were serodiscordant. Proportion of sex acts which were serodiscordant were estimated from a published study on sexual mixing among GBM [483] and were set at 17% for HIV-negative PrEP users, 10% for HIV-negative non-PrEP users and 35% for HIV-positive individuals (model equations are provided in the supplementary material). Sexual mixing in the gonorrhoea model was explored in sensitivity analysis. It was not necessary to include a sexual mixing paramter in the HIV model, as HIV tranmission could only occur between HIV-positive (non-virally supressed) and HIV-negative individuals. The force of HIV infection is influeced by: average condom use among HIV-negative population, PrEP coverage in the HIV-negative population, and HIV prevalence (excluding virally supressed individuals) among the entire population.

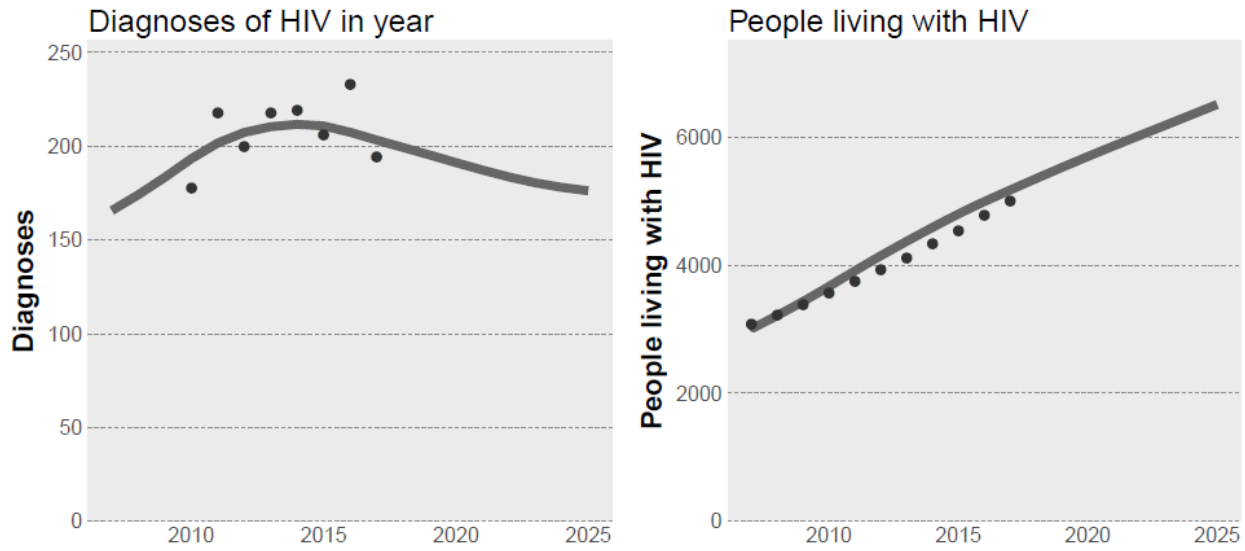
A4.6: Supplementary Methods 5: Gonorrhoea risk groups

We estimated the proportion of GBM belonging to the high and low gonorrhoea risk groups using data published from the PrEPX study, a large, multisite PrEP intervention study which ran from July 2016 to March 2018 and provided more than 4,200 Victorian GBM access to PrEP prior to public subsidy of PrEP in April 2018 [66]. Analysis of STI diagnoses among PrEPX participants found that STIs were highly concentrated among a subgroup of men experiencing repeat infections, with 53% of diagnoses concentrated among 13% of participants [67]. We considered participants diagnosed with two or more STIs during the PrEPX study (13%) as at high gonorrhoea-risk. To estimate the relative increase in force of infection for gonorrhoea in the high gonorrhoea-risk group compared to the low gonorrhoea-risk group in the model, we used the relative increase in the ratio of STI diagnoses to participants among the high-risk group in PrEPX (52% of STIs among 13% of participants) compared to the ratio of STI diagnoses to participants among the low-risk group in PrEPX (48% of STIs among 87% of participants). This equated to an increased risk factor of 7.5. This was also explored in sensitivity analyses.

A4.7: Supplementary Figure 1: Model inputs for the HIV care cascade



A4.8: Supplementary Figure 2: HIV model calibration

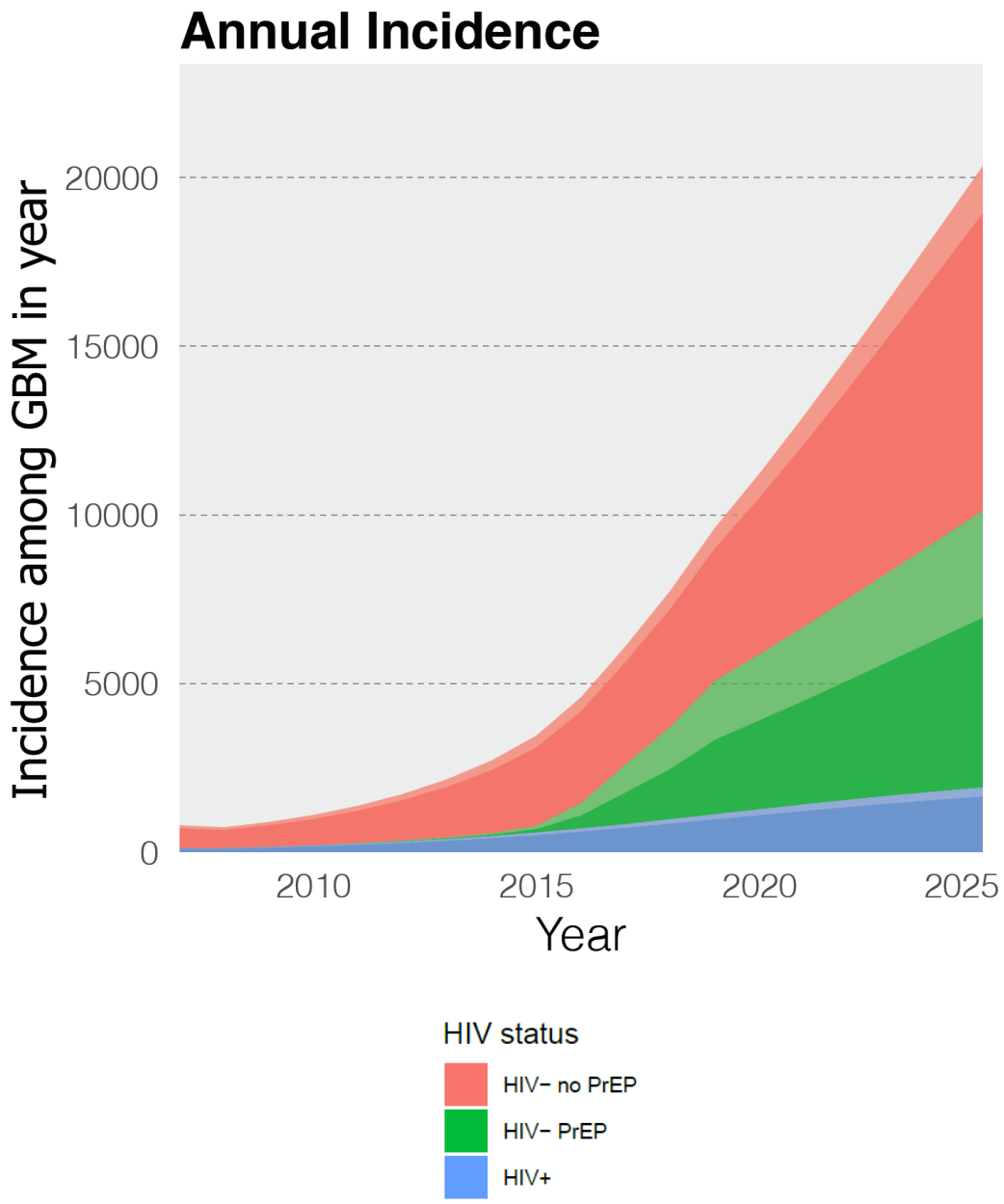


Left: annual HIV diagnoses among GBM in Victoria versus the calibrated model projections. Right: estimated HIV-positive GBM in Victoria versus the calibrated model projection.

Calibration of the HIV model to the data was reasonably accurate. Changes in diagnoses (left), including the slight decrease over the projection period (2019-2025), were largely driven by improvement to the care cascade (Supplementary Figure 1, left) and increasing PrEP coverage (Supplementary Figure 1, right), which led to a decreasing population-level viral load and suseptible population, and reduced number of incident cases.

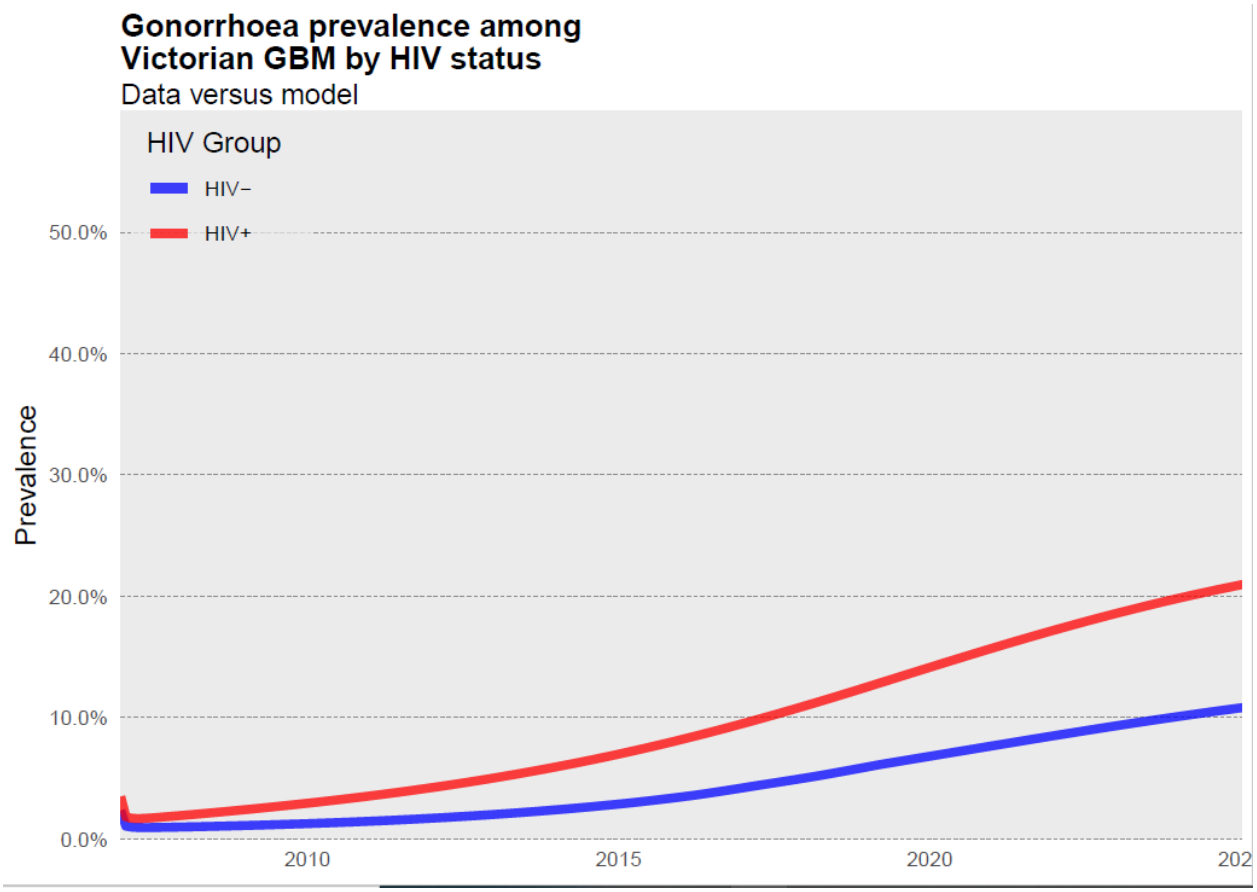
In Victoria, estimates suggest that HIV prevalence among GBM has remained stable over time (~7.2%), however the total GBM population size has been increasing, in line with general population growth. Therefore, the HIV model is dynamic, with force of infection calibrated to produce new HIV infections at a rate sufficient to maintain a stable HIV prevalence among an increasing population.

A4.9: Supplementary Figure 3. Projected gonorrhoea incidence among Victorian GBM from 2007 to 2025 by subpopulation



Dark-shaded areas reflect number of incidence infections attributable to those categorised as 'high gonorrhoea risk' in the model.

A4.10: Supplementary Figure 4: Projected gonorrhoea prevalence by HIV status



A4.11: Supplementary Table 2: HIV model calibration data

YEAR	VICTORIAN GBM POPULATION SIZE[a]	ANNUAL HIV DIAGNOSES[b]	TOTAL GBM WITH HIV[c]
2007	42714		3075
2008	44850		3229
2009	47092		3391
2010	49447	178	3560
2011	51919	218	3738
2012	54515	200	3925
2013	57241	218	4121
2014	60103	219	4327
2015	63108	206	4544
2016	66263	233	4771
2017	69577	194	5010

[a] Estimated to be 42,000 in Victoria in 2006 [484], assuming annual growth rate of 5%

[b] Victorian Department of Health notification data [486] (number of notified cases of HIV by exposure category "male-to-male sex")

[c] Calculated based on estimated average 7.2% HIV prevalence among GBM [121, 486]

A4.12: Supplementary Table 3: Proportion of HIV-negative GBM classified as PrEP users.

YEAR	PROPORTTION OF HIV-NEGATIVE GBM CLASSIFIED AS PREP USERS[a]
2007	0%
2008	0%
2009	0%
2010	0%
2011	0%
2012	0%
2013	0%
2014	0%
2015	1.9%
2016	5.7%
2017	17.9%
2018	21.8%
2019	30.4%

[a]Taken from the Gay Community Periodic Survey: Melbourne 2019[358]

A4.13: Supplementary Table 4: Gonorrhoea model calibration data

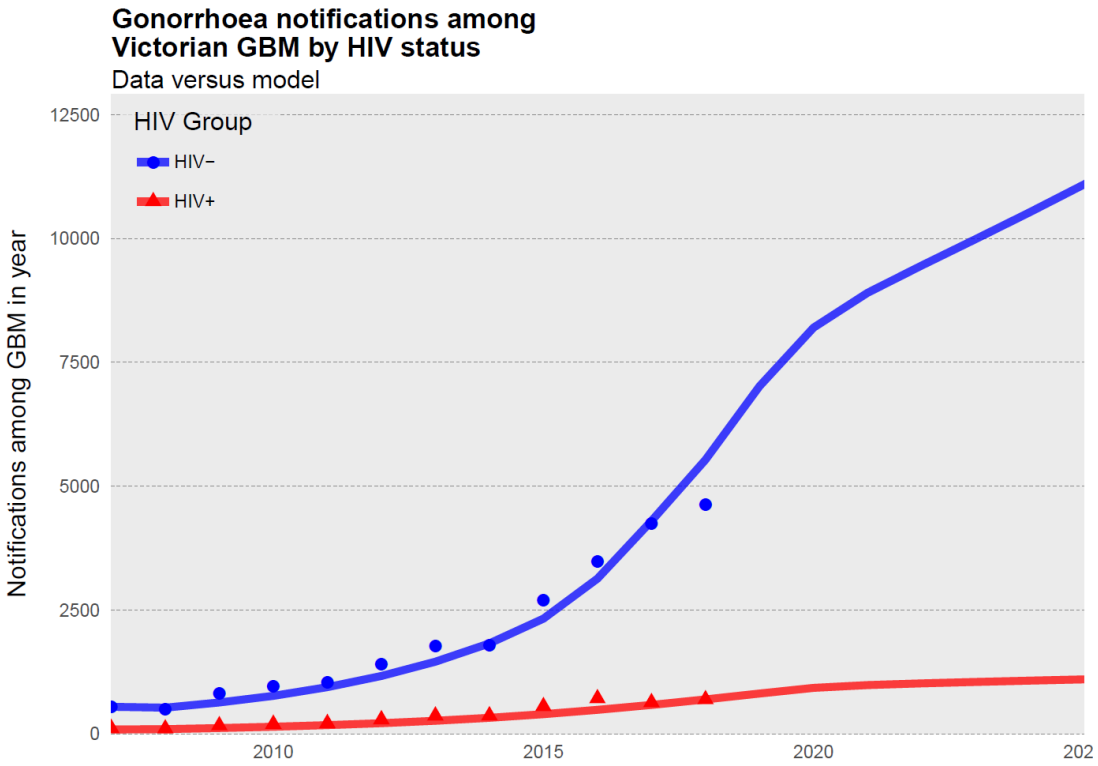
YEAR	ANNUAL GONORRHOEA NOTIFICATIONS AMONG GBM IN VICTORIA[a]	ANNUAL GONORRHOEA DIAGNOSES AMONG HIV-NEGATIVE [b]	ANNUAL GONORRHOEA DIAGNOSES AMONG HIV-POSITIVE [b]
2007	989	545	112
2008	927	511	105
2009	1491	822	168
2010	1755	968	198
2011	1885	1039	213
2012	2561	1412	289
2013	3234	1783	365
2014	3266	1801	369
2015	4902	2702	554
2016	6321	3485	714
2017	7352	4248	635
2018	8026	4638	693

[a] Taken from the National Notifiable Diseases Surveillance System, available from the Australian Government Department of Health website. Adjusted for the proportion of notifications that were among males (81%)[491], the proportion of notifications among males where the men reported sex with other men as a risk factor (82%)[491]

[b] Estimated from the proportion of notifications that were among people with HIV (17%) [492].

A4.14: Supplementary Figure 5: Sensitivity analysis (force of infection) model fit

Annual gonorrhoea notifications among gay and bisexual men in Victoria (dots) versus calibrated model projections (lines) for HIV-negative (blue) and HIV-positive (red) gay and bisexual men, with force of infection held constant from 2018 onwards, rather than being dynamic and dependent on gonorrhoea prevalence. Note that increases in notifications are driven by increases in population size.



A4.15: Supplementary Table 5: Sensitivity analysis (force of infection) results

Cumulative gonorrhoea incidence among Victorian GBM from 2020 to 2025 across different model scenarios of uptake of a gel-based point-of-sex intervention according to HIV-status, PrEP use and condom use, with force of infection held constant from 2018 onwards.

	Scenario	Cumulative incidence 2020 - 2025	Difference in cumulative incidence to status quo	Relative reduction in cumulative incidence
	Status quo (no gel-PSI uptake)	73780		
a	Uptake in all subpopulations up to 50% threshold*	51204	-22576	-31%
b	50% of condom users downgrade and 50% of non-condom users upgrade	65788	-7992	-11%
c	All condom users downgrade to gel-PSI	78167	4387	6%
d	All PrEP users switch to gel-PSI	66090	-7690	-10%
e	50% of PrEP users and HIV-positive GBM switch to gel-PSI	69136	-4644	-6%
f	50% of non-PrEP users switch to gel-PSI	70360	-3420	-5%

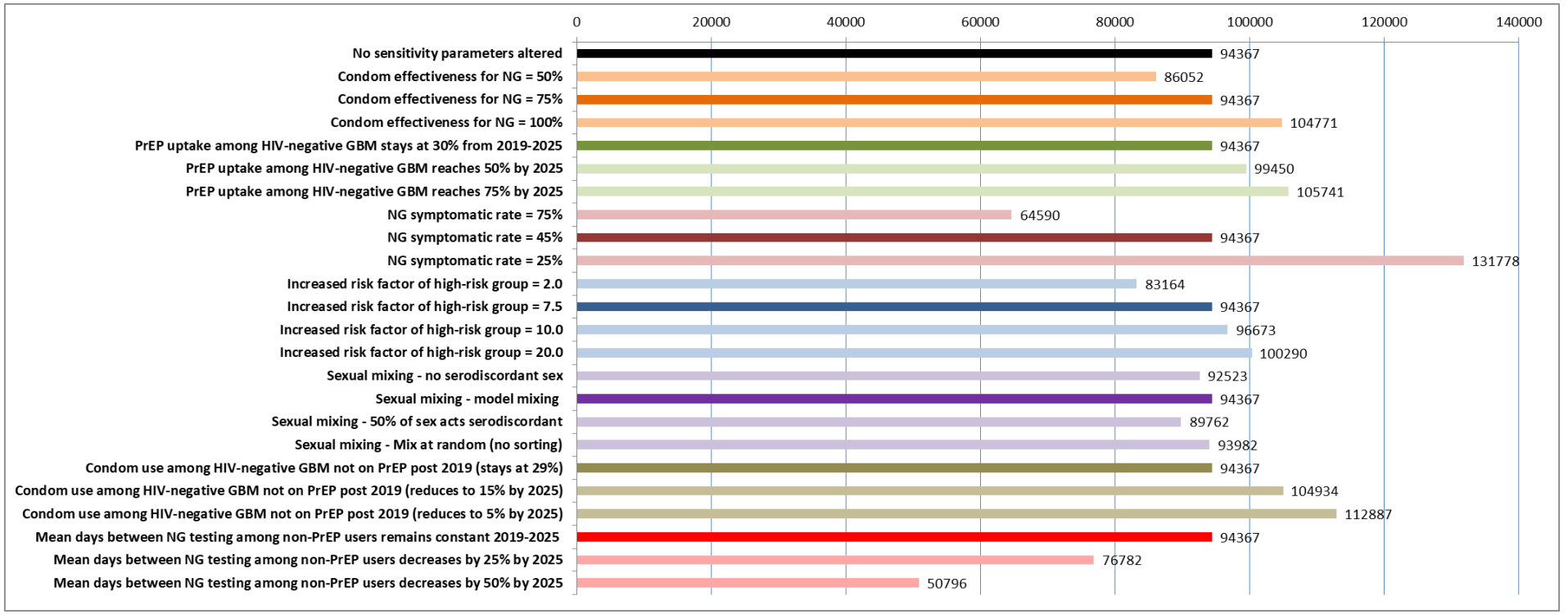
A4.16: Supplementary Table 6. Sensitivity analysis (parameters) results

Changes in projected cumulative gonorrhoea notifications among Victorian GBM from 2018-2025 and relative reduction in gonorrhoea notifications with gel-PSI uptake by varying values for models parameters included in sensitivity analysis.

Parameter	Parameter estimate used in model	Sensitivity value	Cumulative gonorrhoea notifications 2020-2025 (no gel-PSI uptake)	Cumulative gonorrhoea notifications 2018-2025 (Model Scenario B: 50% gel-PSI uptake and 40% gel-PSI efficacy)	Difference in cumulative notifications	Proportion reduction
No sensitivity parameters altered			94367	72559	-21808	-23.11
Condom effectiveness for gonorrhoea	75%	50%	86052[a]	63558	-22494	-26.14
Condom effectiveness for gonorrhoea	75%	100%	104771[a]	84389	-20382	-19.45
PrEP coverage among HIV-negative GBM from 2020 to2025	30%	50% at 2025	99450	75014	-24436	-24.57
PrEP coverage among HIV-negative GBM from 2020 to2025	30%	75% at 2025	105741	77881	-27860	-26.35
NG symptomatic rate	45%	25%	131778	102789	-28989	-22.00
NG symptomatic rate	45%	75%	64590	48969	-15621	-24.18
Increased risk factor of high-risk group	7.5	2	83164	63177	-19987	-24.03
Increased risk factor of high-risk group	7.5	10	96673	74951	-21722	-22.47
Increased risk factor of high-risk group	7.5	20	100290	79611	-20679	-20.62
Sexual mixing	Model mixing[b]	No serodiscordant sex acts	92523	71447	-21076	-22.78
Sexual mixing	Model mixing[b]	50% of sex acts serodiscordant	89762	68656	-21106	-23.51
Sexual mixing	Model mixing[b]	Mix at random (no serosorting)	93982	72574	-21408	-22.78
Condom use among HIV-negative GBM not on PrEP from 2020-2025[c]	Stays at 29%	Reduces to 15% by 2025	104934	77600	-27334	-26.05
Condom use among HIV-negative GBM not on PrEP from 2020-2025 [c]	Stays at 29%	Reduces to 5% by 2025	112887	81337	-31550	-27.95
Mean days between NG testing among non-PrEP users from 2020 to 2025	Model testing rates	Reduced by 25% by 2025	76782	57352	-19430	-25.31
Mean days between NG testing among non-PrEP users from 2020 to 2025	Model testing rates	Reduced by 50% by 2025	50796	36890	-13906	-27.38

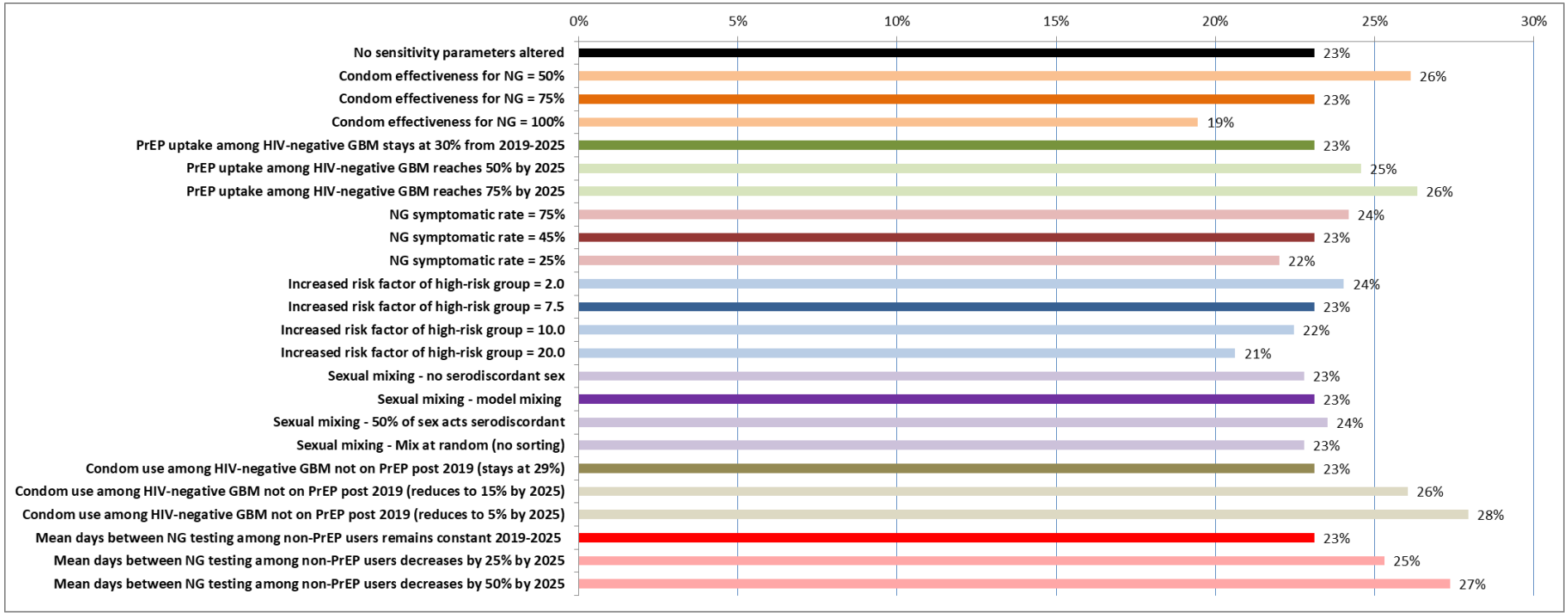
[a]Greater baseline projections for gonorrhoea incidence in sensitivity analysis with greater condom efficacy is a product of the method of calibration; with greater condom efficacy, the calibrated force of gonorrhoea infection is overestimated to fit the data points, leading to greater gonorrhoea incidence as condom use is decreased through the years 2020-2025 [b]Proportion of sex acts which were HIV serodiscordant were estimated as 17% for HIV-negative PrEP users, 10% for HIV-negative non-PrEP users and 35% for HIV-positive individuals [c]Consistent condom use among HIV-negative GBM on PrEP and HIV-positive GBM was 0.3 times that of HIV-negative GBM not on PrEP

A4.17: Supplementary Figure 6: Sensitivity analysis, cumulative gonorrhoea incidence



Number of cumulative gonorrhoea infections among Victorian gay and bisexual men between 2020 to 2025 (inclusive) under the scenario of no uptake of a gel point-of-sex intervention by different variations of specific parameters included in the model. Dark bars reflect parameter values used in the main model. Other parameters are kept constant for each sensitivity analysis.

A4.18: Supplementary Figure 7: Sensitivity analysis, relative reduction in cumulative gonorrhoea incidence



Relative reduction in cumulative number of gonorrhoea infections among Victorian gay and bisexual men between 2020 to 2025 (inclusive) between model Scenario B (50% gel-PSI uptake among condom and non-condom users with a gel-PSI efficacy of 40% for gonorrhoea risk reduction) and the base scenario of no gel-PSI uptake, by different variations of specific parameters included in the model. Dark bars reflect parameter values used in the main model. Other parameters are kept constant for each sensitivity analysis.

A4.19: Supplementary Methods 6: Model equations

Define the following compartments and stratifications

t = time (implemented in monthly time steps)

$P(t)$ = total estimated GBM population size

$P^{+}(t), P^{-}(t), \widehat{P^{-}}(t)$ = total model population size for HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM respectively. Note that these are functions of time due to population growth.

$S^{+}(t), S^{-}(t), \widehat{S^{-}}(t)$ = total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) susceptible for gonorrhoea compartments

$E^{+}(t), E^{-}(t), \widehat{E^{-}}(t)$ = total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) exposed to gonorrhoea compartments

$Ia^{+}(t), Ia^{-}(t), \widehat{Ia^{-}}(t)$ = total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) infected with gonorrhoea, asymptomatic compartments

$T^{+}(t), T^{-}(t), \widehat{T^{-}}(t)$ = total size of the HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) treatment compartments

i = subscript to indicate whether or not someone is at low or high risk of gonorrhoea (i=0 for low and i=1 for high). Note that for the HIV-negative non-PrEP and HIV-positive groups, the high and low risk groups for gonorrhoea were the same.

Define the following parameters

$\beta_1 = 1/$ average duration of gonorrhoea exposed period (5 days)

β_2 = proportion of gonorrhoea cases that are symptomatic

$\beta_3 = 1/$ gonorrhoea treatment duration (7 days)

$\tau_i^{+}, \tau_i^{-}, \widehat{\tau_i}$ =1/average time between tests for HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM.

$\gamma^{+}, \gamma^{-}, \widehat{\gamma}$ =fraction of HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM are at high risk for gonorrhoea

δ =relative reduction in the risk of HIV infection for people with viral suppression

δ_P =relative reduction in the risk of HIV infection for people on PrEP

D(t) = fraction of people with HIV who are virally supressed

μ = 1/average time at risk (assumed to be 50 years; 15-64 year olds)

α_1 = proportion of HIV serodiscordant sex acts among HIV-negative non-PrEP GBM

α_2 = proportion of HIV serodiscordant sex acts occurring among HIV-negative PrEP GBM

α_3 = proportion of HIV serodiscordant sex acts occurring among HIV-positive GBM

Γ_i = additional risk factor for GBM at high-risk of gonorrhoea. Note that $\Gamma_i = 1$ if i=0 (low risk is the reference)

$c^{+}, c^{-}, \widehat{c^{-}}$ = average condom use among HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM

$g^+, g^-, \widehat{g^-}$ = average gel-based prevention use among HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM

ϵ_c = effectiveness of condoms

ϵ_g = effectiveness of gel-based prevention at preventing gonorrhoea

Force of infection

Let λ_{HIV} be the proportionality constant (determined in the calibration procedure) for the force of HIV infection. Then the force of infection for HIV among non-PrEP (Θ^-) and PrEP ($\widehat{\Theta^-}$) users is given by:

$$\Theta^- = \lambda_{HIV}(1 - \epsilon_c c^-)\frac{\left[(1-\delta)D(t) + \left(1 - D(t)\right)\right]P^+}{\left[P^+ + P^- + \widehat{P^-}\right]}$$

$$\widehat{\Theta^-} = \lambda_{HIV}\delta_P(1 - \epsilon_c \widehat{c^-})\frac{\left[(1-\delta)D(t) + \left(1 - D(t)\right)\right]P^+}{\left[P^+ + P^- + \widehat{P^-}\right]}$$

Let $\lambda^+, \lambda^-, \widehat{\lambda^-}$ be the proportionality constants (determined in the calibration procedure) for the force of gonorrhoea infection among HIV-positive, HIV-negative (no PrEP) and HIV-negative (PrEP) GBM respectively. The force of infection for gonorrhoea among these populations was modelled to account for condom use and mixing between HIV-positive and HIV-negative GBM populations:

$$\Phi_i^+ = \lambda^+\Gamma_i\left(1 - \epsilon_c c^+ - \epsilon_g g^+\right)\left(\alpha_3\frac{Ia^- + I\widehat{a^-}}{P^- + \widehat{P^-}} + (1-\alpha_3)\frac{Ia^+}{P^+}\right)$$

$$\Phi_i^- = \lambda^-\Gamma_i\left(1 - \epsilon_c c^- - \epsilon_g g^-\right)\left((1-\alpha_1)\frac{Ia^- + I\widehat{a^-}}{P^- + \widehat{P^-}} + \alpha_1\frac{Ia^+}{P^+}\right)$$

$$\widehat{\Phi_i^-} = \widehat{\lambda^-}\Gamma_i\left(1 - \epsilon_c \widehat{c^-} - \epsilon_g \widehat{g^-}\right)\left((1-\alpha_2)\frac{Ia^- + I\widehat{a^-}}{P^- + \widehat{P^-}} + \alpha_2\frac{Ia^+}{P^+}\right)$$

HIV-positive GBM differential equations

$$\frac{dS_i^+}{dt} = \Theta^- S_i^- + \widehat{\Theta^-}\widehat{S_i^-} - \Phi_i^+ S_i^+ + \beta_3 T_i^+ - \mu S_i^+$$

$$\frac{dE_i^+}{dt} = \Theta^- E_i^- + \widehat{\Theta^-}\widehat{E_i^-} + \Phi_i^+ S_i^+ - \beta_1 E_i^+ - \mu E_i^+$$

$$\frac{dIa_i^+}{dt} = \Theta^- Ia_i^- + \widehat{\Theta^-}\widehat{Ia_i^-} + \beta_1(1-\beta_2)E_i^+ - \tau_i^+ Ia_i^+ - \mu Ia_i^+$$

$$\frac{dT_i^+}{dt} = \Theta^- T_i^- + \widehat{\Theta^-}\widehat{T_i^-} + \beta_1\beta_2 E_i^+ + \tau_i^+ Ia_i^+ - \beta_3 T_i^+ - \mu T_i^+$$

HIV-negative (no PrEP) GBM differential equations

$$\frac{dS_i^-}{dt} = \frac{dP(t)}{dt} - \Theta^- S_i^- - \Phi_i^- S_i^- + \beta_3 T_i^- - \mu S_i^-$$

$$\frac{dE_i^-}{dt} = -\Theta^- E_i^- + \Phi_i^- S_i^- - \beta_1 E_i^- - \mu E_i^-$$

$$\frac{dIa_i^-}{dt} = -\Theta^- Ia_i^- + \beta_1(1-\beta_2)E_i^- - \tau_i^- Ia_i^- - \mu Ia_i^-$$

$$\frac{dT_i^-}{dt} = -\Theta^- T_i^- + \beta_1\beta_2 E_i^- + \tau_i^- Ia_i^- - \beta_3 T_i^- - \mu T_i^-$$

HIV-negative (PrEP) GBM differential equations

$$\frac{d\widehat{S_i^-}}{dt} = -\widehat{\Theta^-}\widehat{S_i^-} - \Phi_i^-\widehat{S_i^-} + \beta_3\widehat{T_i^-} - \mu\widehat{S_i^-}$$

$$\frac{d\widehat{E_i^-}}{dt} = -\widehat{\Theta^-}\widehat{E_i^-} + \Phi_i^-\widehat{S_i^-} - \beta_1\widehat{E_i^-} - \mu\widehat{E_i^-}$$

$$\frac{d\widehat{Ia_i^-}}{dt} = -\widehat{\Theta^-}\widehat{Ia_i^-} + \beta_1(1-\beta_2)\widehat{E_i^-} - \widehat{\tau_i^-}\widehat{Ia_i^-} - \mu\widehat{Ia_i^-}$$

$$\frac{d\widehat{T_i^-}}{dt} = -\widehat{\Theta^-}\widehat{T_i^-} + \beta_1\beta_2\widehat{E_i^-} + \widehat{\tau_i^-}\widehat{Ia_i^-} - \beta_3\widehat{T_i^-} - \mu\widehat{T_i^-}$$

Appendix B Published thesis chapters in journal format

Appendix B1. Chapter 2 in *The Lancet Infectious Diseases*

Citation:

Traeger MW, Guy R, Asselin J, et al. Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Australia following nationwide PrEP implementation: an analysis of sentinel surveillance data. ***Lancet Infect Dis***. Aug 2022;22(8):1231-1241. doi:10.1016/S1473-3099(22)00175-X

Real-world trends in incidence of bacterial sexually transmissible infections among gay and bisexual men using HIV pre-exposure prophylaxis (PrEP) in Australia following nationwide PrEP implementation: an analysis of sentinel surveillance data

Michael W Traeger, Rebecca Guy, Jason Asselin, Prital Patel, Allison Carter, Edwina J Wright, Andrew Grulich, Hamish McManus, Christopher K Fairley, Eric P F Chow, Anna McNulty, Robert Finlayson, Charlotte Bell, Louise Owen, Lewis Marshall, Darren Russell, Darryl O'Donnell, Basil Donovan, Margaret E Hellard, Mark A Stoové*, on behalf of the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) Study Group†*

Summary

Background Although data from large implementation trials suggest that sexually transmissible infection (STI) risk increases among gay and bisexual men who initiate HIV pre-exposure prophylaxis (PrEP), there are few data on the trends in population-level STI incidence in the years following widespread PrEP implementation. We aimed to describe trends in bacterial STI incidence among gay and bisexual men using PrEP across Australia in the context of broad PrEP availability through Australia's subsidised medicines scheme.

Methods We analysed linked clinical data from HIV-negative gay and bisexual men aged 16 years or older who had been prescribed PrEP across a sentinel surveillance clinical network, including 37 clinics in Australia, between Jan 1, 2016, and Dec 31, 2019. Patients were included if they had STI testing at least twice during the observation period. Repeat testing methods were used to calculate chlamydia, gonorrhoea, syphilis, and any STI incidence rates during individuals' periods of PrEP use. Incidence rate ratios (IRRs) for estimated change in incidence per half calendar year (6-month) period were calculated using negative binomial regression. Secondary analyses compared STI incidence rates across individuals initiating PrEP in each year from 2016 to 2019, as well as by length of time using PrEP (per each additional 6 months of PrEP use).

Findings 22 730 men were included in the analyses. During the observation period, 11 351 chlamydia infections were diagnosed in 6630 (30·1%) of 22 034 men over 25 991·2 person-years of PrEP use (incidence rate 43·7 cases [95% CI 42·9–44·5] per 100 person-years). Chlamydia incidence decreased from 48·7 cases per 100 person-years in July–December, 2016, to 42·0 cases per 100 person-years in July–December, 2019 (IRR for estimated change per 6-month period 0·98 [95% CI 0·97–0·99]; p=0·0031). 9391 gonorrhoea infections were diagnosed in 5885 (26·9%) of 21 845 men over 24 858·7 person-years of PrEP use (incidence rate 37·8 cases [95% CI 37·0–38·5] per 100 person-years). Gonorrhoea incidence decreased from 45·5 cases per 100 person-years in July–December, 2016, to 37·2 cases per 100 person-years in July–December, 2019 (IRR 0·97 [95% CI 0·96–0·98]; p<0·0001). Declines in chlamydia and gonorrhoea incidence were most prominent in the first 18 months of observation and incidence was stable thereafter. 2062 syphilis infections were diagnosed in 1488 (7·7%) of 19 262 men over 21 978·9 person-years of PrEP use (incidence rate 9·4 cases [95% CI 9·0–9·8] per 100 person-years). Syphilis incidence increased from 6·2 cases per 100 person-years in July–December, 2016, to 9·8 cases per 100 person-years in July–December, 2019 (IRR 1·08 [95% CI 1·05–1·10]; p<0·0001).

Interpretation Chlamydia and gonorrhoea incidence among gay and bisexual men using PrEP were highest in the early months of PrEP implementation in Australia and stabilised at slightly lower rates thereafter following wider PrEP uptake. Lower prospective STI risk among people initiating PrEP in later years contributed to the observed trends in STI incidence. Widespread PrEP implementation can contribute to increased STI screening and detection.

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Introduction

Reductions in HIV diagnoses among populations of gay and bisexual men and other men who have sex with men have been observed following the implementation of HIV pre-exposure prophylaxis (PrEP) programmes in multiple countries, including Australia.[1] Implementation of PrEP has also led to considerable increases in testing for sexually transmissible infections (STIs) among gay

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*Contributed equally

†Members are listed in the appendix (p 19)

Burnet Institute, Melbourne, VIC, Australia (M W Traeger MSc, J Asselin MEpi, E J Wright PhD, Prof M E Hellard PhD, Prof M A Stoové PhD); **School of Public Health and Preventive Medicine** (M W Traeger, Prof M A Stoové) **and Department of Infectious Diseases, Alfred Health, Central Clinical School** (E J Wright, Prof C K Fairley PhD, Prof M E Hellard), **Monash University, Melbourne, VIC, Australia; Kirby Institute** (Prof R Guy PhD, P Patel PhD, A Carter PhD, Prof A Grulich PhD, H McManus PhD, Prof B Donovan MD), **Australian Human Rights Institute** (A Carter), **and School of Population Health** (A McNulty MMed), **UNSW Sydney, Sydney, NSW, Australia; Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada** (A Carter); **Peter Doherty Institute, Melbourne, VIC, Australia** (E J Wright, Prof M E Hellard); **Melbourne Sexual Health Centre, Alfred Health, Melbourne, VIC, Australia** (Prof C K Fairley, E P F Chow PhD); **Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global**

STI incidence outside of implementation and demonstration projects might help explain how PrEP uptake and the associated increase in STI testing is influencing trends in STI incidence.

PrEP was made widely available through primary care in Australia in April, 2018, at a highly subsidised price, via the Pharmaceutical Benefits Scheme, to be prescribed at visits once every 3 months alongside comprehensive HIV and STI testing. Previous modelling studies on the effect of high rates of STI screening with PrEP use on population-level gonorrhoea and chlamydia incidence among gay and bisexual men have shown varied findings,[6,7] with one study suggesting that 3-monthly STI testing among men using PrEP would not be enough to reduce gonorrhoea prevalence among gay and bisexual men.[7] However, an Australian modelling study suggested that increased PrEP coverage might result in declines in new syphilis cases through increased STI testing.[8]

Increasing notifications of STIs among gay and bisexual men in Australia and internationally, especially in the context of more widespread PrEP use, suggests increasing transmission of STIs. However, notification data are influenced by changes in testing rates and might miss some nuances only captured by incidence trend estimates. Furthermore, PrEP uptake in Australia has been gradual, and the changing composition of the population using PrEP over time, especially between those enrolled in early implementation studies and those who accessed PrEP when it was more widely available, might influence incidence trend estimates.

We aimed to estimate population-level incidence rates of bacterial STIs among gay and bisexual men using PrEP in Australia in the context of broad PrEP availability through large demonstration studies and Australia's subsidised medicines scheme. We also aimed to explore the association between length of time taking PrEP and individual-level STI incidence, how STI risk differs among gay and bisexual men initiating PrEP at different times, and how these factors influence overall trend estimates.

Methods

Study design and participants

We analysed routinely collected surveillance data from a large network of sentinel clinics across Australia. 37 clinics (19 sexual health clinics [including multiclinic and outreach services] and 18 general practice clinics) participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) system were included in the study. The ACCESS protocol has been previously published.[9] Briefly, retrospective patient data (demographics, pathology reports, and electronic prescriptions) were deidentified and extracted from patient management systems of participating services using the specialised data extraction software suite GHRANITE. Participants' data were linked within and across services using a highly sensitive linkage algorithm, which utilised probabilistic and deidentifying linkage keys generated from patient identifiers created before data were extracted.[10]

HIV-negative cisgender and transgender gay and bisexual men aged 16 years or older who had attended an ACCESS service and had been prescribed PrEP during the observation period from Jan 1, 2016, to Dec 31, 2019, were eligible for inclusion in the analyses. Patients were included if they had STI testing at least twice during the observation period, as we used repeat testing methods to estimate STI incidence.[11]

Ethics approval was provided by the human research ethics committees at Alfred Hospital (248/17), Central Australia (CA-19-3355), Northern Territory Department of Health and Menzies School of Health (08/47), University of Tasmania (H0016971), Aboriginal Health and Medical Research Council (1099/15), AIDS Council of New South Wales (2015/14), Victorian AIDS Council and Thorne Harbour Health (VAC REP 15/003), Western Australian Aboriginal Health Ethics Committee (885), and St Vincent's Hospital (08/051). As our study analysed deidentified data collected under the auspices of public health surveillance, individual patient consent was not required. Individuals were able to opt out of the surveillance system at will.

Procedures

Data were extracted up to June 30, 2021, to reduce the effects of right-censoring bias on inflating incidence estimates in the final 6 months of the observation period.[12] Our analysis was censored before 2020 because restrictions were implemented following the COVID-19 pandemic that greatly influenced PrEP use and sexual behaviour among Australian gay and bisexual men,[13,14] which made it difficult to compare trends during this period.

Individuals' person-time at risk began at the date of their first PrEP prescription if they had an STI test on the same date (or within the previous 7 days), or from their first STI test after PrEP prescription. Individuals contributed person-time until they were censored at their last STI test before data extraction, or Dec 31, 2019, whichever occurred first. Individuals who did not receive another PrEP prescription within 4 months of a previous PrEP prescription were considered to have ceased PrEP use and were censored at 4 months after their last PrEP prescription (4 months was chosen on the basis of the distribution of days between PrEP prescriptions; appendix p 5). These participants were able to be re-entered into the analysis if they received a subsequent PrEP prescription, with person-time recommencing at their subsequent STI test after the prescription.

Statistical analysis

For all STI tests conducted among participants within the observation period, we calculated the median and 90th percentile number of days since the participant's

	Participants (n=22 730)
Age at PrEP initiation, years	
Mean (SD)	36·4 (11·0)
Median (IQR)	34 (28–43)
16–29	7155 (31·5%)
30–39	7923 (34·9%)
40–49	4494 (19·8%)
≥50	3158 (13·9%)
Year of PrEP initiation	
2016	6494 (28·6%)
2017	5789 (25·5%)
2018	6027 (26·5%)
2019	4420 (19·4%)
Clinic type at PrEP initiation	
General practice	13 601 (59·8%)
Sexual health clinic	9129 (40·2%)
Clinic state at PrEP initiation	
New South Wales	11 633 (51·2%)
Victoria	6701 (29·5%)
Queensland	1247 (5·5%)
South Australia	1245 (5·5%)
Australian Capital Territory	825 (3·6%)
Western Australia	805 (3·5%)
Tasmania	262 (1·2%)
Northern Territory	12 (0·1%)

Data are n (%) unless otherwise stated. PrEP=HIV pre-exposure prophylaxis.

Table 1: **Participant characteristics**

	Chlamydia	Gonorrhoea	Syphilis	Any STI*
Person-years at risk				
Total	25 991·2	24 858·7	21 978·9	23 399·8
Mean (SD)	1·17 (0·95)	1·14 (0·93)	1·14 (0·94)	1·27 (0·99)
Diagnoses				
Total diagnoses	11 351	9391	2062	20 116
Individuals included	22 034	21 845	19 262	18 483
Individuals diagnosed	6630 (30·1%)	5885 (26·9%)	1488 (7·7%)	8223 (44·5%)
Number of diagnoses among individuals with ≥1 STI, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	2 (1–3)

Data are n or n (%) unless otherwise stated. STI=sexually transmissible infection. *Any STI analysis only includes participants who had at least two tests for each infection (chlamydia, gonorrhoea, and syphilis).

Table 2: **Follow-up time and number of STI diagnoses**

previous test. Overall incidence rates per 100 person-years during the observation period were calculated for chlamydia, gonorrhoea, infectious (primary, secondary, or early [<2 years] latent) syphilis, and any STI. Results were disaggregated by anatomical site (rectal, pharyngeal, or urogenital) and age group fixed at cohort entry (approximating median split <35 years *vs* ≥35 years). For the any STI outcome, we calculated the number and proportion of participants diagnosed with none, one to four, and five or more STIs during follow-up, and the attributable proportion of all STIs diagnosed among each group.

For trend analyses, incidence rates per 100 person-years were calculated and plotted for each half calendar year (6-month) period from July, 2016, to December, 2019, and were calculated as the number of incident infections divided by the total person-time accumulated. A series of negative binomial regression models (one for each respective STI outcome) with robust variance estimators clustered by individual were used to test for trends across the study period. In each model, time—a continuous variable representing half calendar years from July–December, 2016, to July–December, 2019—was included as the single independent variable. Incidence rate ratios (IRRs) represent the estimated change in incidence rate per each half calendar year (6 months) across the study period. Tests of non-linearity were performed for each trend analysis; where non-linearity was detected, piecewise negative binomial regression was used to examine trends in two periods, split at the median value of half calendar years (before January–June, 2018, *vs* from January–June, 2018, onwards; appendix p 3). Additional sensitivity analyses were performed—namely, including clinic as a random effect in mixed-effects negative binomial regression models (appendix p 18) and using 6 months (rather than 4 months) since previous PrEP prescription as the cutoff time for censorship (appendix p 16).

To describe STI risk among gay and bisexual men initiating PrEP in different years, we performed a secondary analysis of incidence trends, where time was measured in days since participants' PrEP initiation, rather than calendar time. We calculated incidence rates for each STI outcome in 6-monthly intervals of PrEP use since PrEP initiation, and overall incidence rates for each group by year of PrEP initiation (ie, participants initiating PrEP in 2016, 2017, 2018, and 2019). Multivariable negative binomial regression was used to compare STI incidence among participants initiating PrEP in different years, and to calculate the association between time on PrEP (per 6-month increase) and STI incidence, adjusted for year of PrEP initiation. In these models, independent covariates were time on PrEP (continuous, 6-month intervals) and year of PrEP initiation (categorical). Separate negative binomial regression models were used to test for associations between time on PrEP and STI incidence for each group by year of PrEP initiation (those initiating PrEP in 2019 were excluded as at least 12 months of follow-up were needed to test for trend). Additional information on statistical methodology is provided in the appendix (pp 2–3). All analyses were performed using Stata (version 15.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Individuals included	Person-years at risk	Diagnoses	Incidence rate per 100 person-years (95% CI)	IRR* (95% CI)	p value
Chlamydia						
Total	22 034	25 991·2	11 351	43·7 (42·9–44·5)	0·98 (0·97–0·99)†	0·0031
Rectal	21 121	25 251·0	8449	33·5 (32·8–34·2)	0·99 (0·98–0·99)†	0·049
Urogenital	21 001	25 064·9	3116	12·4 (12·0–12·9)	0·99 (0·97–1·01)	0·22
Pharyngeal	19 921	24 153·7	982	4·1 (3·8–4·3)	0·96 (0·93–1·00)	0·030
Age <35 years	12 103	12 753·0	6372	50·0 (48·8–51·2)	0·99 (0·98–1·01)†	0·44
Age ≥35 years	9931	13 238·2	4979	37·6 (36·6–38·7)	0·97 (0·96–0·99)	0·0003
Gonorrhoea						
Total	21 845	24 858·7	9391	37·8 (37·0–38·5)	0·97 (0·96–0·98)†	<0·0001
Rectal	20 984	24 184·2	5420	22·4 (21·8–23·0)	0·98 (0·96–0·99)†	0·0030
Urogenital	19 467	22 909·4	1569	6·8 (6·5–7·2)	0·97 (0·94–1·00)	0·079
Pharyngeal	21 261	24 399·7	5126	21·0 (20·4–21·6)	0·97 (0·96–0·99)†	0·0015
Age <35 years	11 958	12 305·8	5691	46·2 (45·1–47·5)	0·98 (0·97–1·00)†	0·045
Age ≥35 years	9887	12 552·9	3700	29·5 (28·5–30·4)	0·96 (0·94–0·98)	<0·0001
Syphilis						
Total	19 262	21 978·9	2062	9·4 (9·0–9·8)	1·08 (1·05–1·10)†	<0·0001
Age <35 years	10 544	10 897·1	1008	9·3 (8·7–9·8)	1·09 (1·05–1·13)†	<0·0001
Age ≥35 years	8718	11 081·8	1054	9·5 (9·0–10·1)	1·06 (1·03–1·10)†	0·0004
Any STI‡						
Total	18 483	23 399·8	20 116	86·0 (84·8–87·2)	0·99 (0·99–1·00)	0·17
Age <35 years	10 173	11 642·2	11 612	99·7 (97·9–101·6)	1·00 (0·99–1·01)	0·91
Age ≥35 years	8310	11 757·5	8504	72·3 (70·8–73·9)	0·99 (0·97–1·00)	0·036

Data are n unless otherwise stated. IRR=incidence rate ratio. STI=sexually transmissible infection. *Estimated change per half calendar year (6-month period) from July–December, 2016, to July–December, 2019; half calendar year included as continuous variable in negative binomial model. †Non-linearity detected, piecewise negative binomial regression performed (reported in appendix p 13). ‡Any STI analysis only includes participants who had at least two tests for each infection (chlamydia, gonorrhoea, and syphilis).

Table 3: **Incidence rates and trend estimates**

Results

22 730 men were included in the analyses (table 1). A total of 160 778 chlamydia tests, 155 861 gonorrhoea tests, and 120 875 syphilis tests were done during the observation period. The median time between tests was 84 days (IQR 55–104) for chlamydia tests, 84 days (54–104) for gonorrhoea tests, and 90 days (70–108) for syphilis tests (appendix pp 6–7).

During the observation period, 11 351 chlamydia infections were diagnosed in 6630 (30·1%) of 22 034 men over 25 991·2 person-years of PrEP use (table 2). The overall incidence rate of chlamydia was 43·7 cases (95% CI 42·9–44·5) per 100 person-years (table 3). 9391 gonorrhoea infections were diagnosed in 5885 (26·9%) of 21 845 men over 24 858·7 person-years of PrEP use (table 2). The overall incidence rate of gonorrhoea was 37·8 cases (95% CI 37·0–38·5) per 100 person-years (table 3). 2062 syphilis infections were diagnosed in 1488 (7·7%) of 19 262 men over 21 978·9 person-years of PrEP use (table 2). The overall incidence rate of syphilis was 9·4 cases (95% CI 9·0–9·8) per 100 person-years (table 3).

Among the 18 483 individuals who contributed to the any STI outcome determination, there were 20 116 diagnoses of any STI over 23 399·8 person-years (mean follow-up 1·27 years [SD 0·99]; table 2); participants who initiated PrEP in 2016 were followed-up for a mean of 2·3 years (SD 1·2; median 2·4 years, IQR 1·0–3·2). 8223 (44·5%) of 18 483 men were diagnosed with any STI during the observation period; the median number of STI diagnoses per individual was two (IQR 1–3), and 1049 (5·7%) men were diagnosed with five or more STIs, which accounted for 7256 (36·1%) of 20 116 infections diagnosed (figure 1, appendix p 12).

Chlamydia incidence decreased from 48·7 cases per 100 person-years in July–December, 2016, to 42·0 cases per 100 person-years in July–December, 2019 (IRR 0·98, 95% CI 0·97–0·99; p=0·0031; figure 2, table 3). However, the decline was non-linear, with the greatest decline during the first 18 months of observation; chlamydia incidence reached 42·7 cases per 100 person-years in July–December, 2017, and remained relatively stable thereafter. Gonorrhoea incidence decreased from 45·5 cases per 100 person-years in July–December, 2016, to 37·2 cases per 100 person-years in July–December, 2019 (IRR 0·97, 95% CI 0·96–0·98; p<0·0001). Similar to chlamydia, the decline was non-linear, with the greatest decline during the first 18 months of observation; gonorrhoea incidence fell to 38·7 cases per 100 person-years in July–December, 2018, and remained relatively

stable thereafter. Infectious syphilis incidence increased during the observation period, from 6·2 cases per 100 person-years in July–December, 2016, to 9·8 cases per 100 person-years in July–December, 2019 (IRR 1·08, 95% CI 1·05–1·10; p<0·0001); the increase in syphilis incidence was greatest during the first 18 months of observation (1·25, 1·08–1·49; p<0·0001; figure 2, table 3).

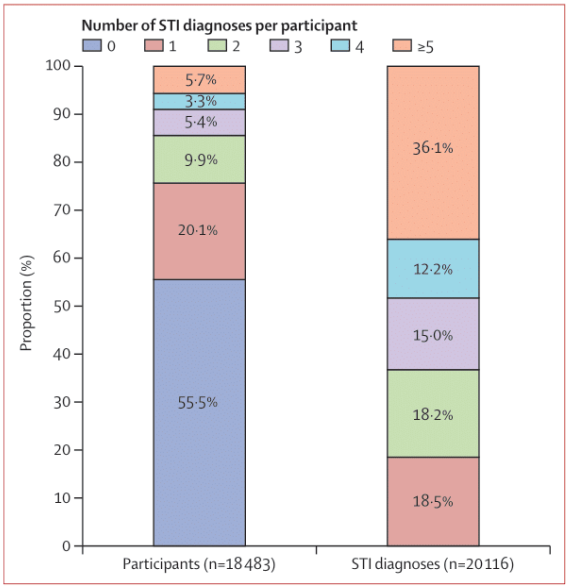

Figure 1: **Number of STI diagnoses per participant during PrEP use and distribution of all STI diagnoses**
PrEP=HIV pre-exposure prophylaxis. STI=sexually transmissible infection.

In secondary analysis of incidence trends measured in days since PrEP initiation, chlamydia incidence did not change with increased time on PrEP (IRR for estimated change per 6 months of PrEP use 1·01, 95% CI 1·00–1·02; p=0·098). After adjusting for year of PrEP initiation, time on PrEP was not associated with chlamydia incidence (adjusted IRR 0·99, 0·98–1·00; p=0·14; figure 3, table 4). Gonorrhoea incidence did not change with increased time on PrEP (IRR 1·00, 0·99–1·01; p=0·99). After adjusting for year of PrEP initiation, longer time on PrEP (each additional 6 months) was associated with a slight decrease in gonorrhoea incidence (adjusted IRR 0·98, 0·97–0·99; p=0·0016). Each additional 6 months of PrEP use was associated with a modest increase in syphilis incidence (IRR 1·08, 1·06–1·11; p<0·0001). After adjusting for year of PrEP initiation, longer time on PrEP was still associated with an increase in syphilis incidence (adjusted IRR 1·08, 1·05–1·11; p<0·0001; figure 3, table 4).

In the secondary analysis of incidence trends disaggregated by year of PrEP initiation, time on PrEP was only associated with a decrease in gonorrhoea incidence in participants who initiated PrEP in 2016, and an increase in syphilis incidence among those who initiated PrEP in 2016 and 2017 (appendix p 15). Extending the censorship cutoff for PrEP use to 6 months since the previous prescription led to slightly decreased

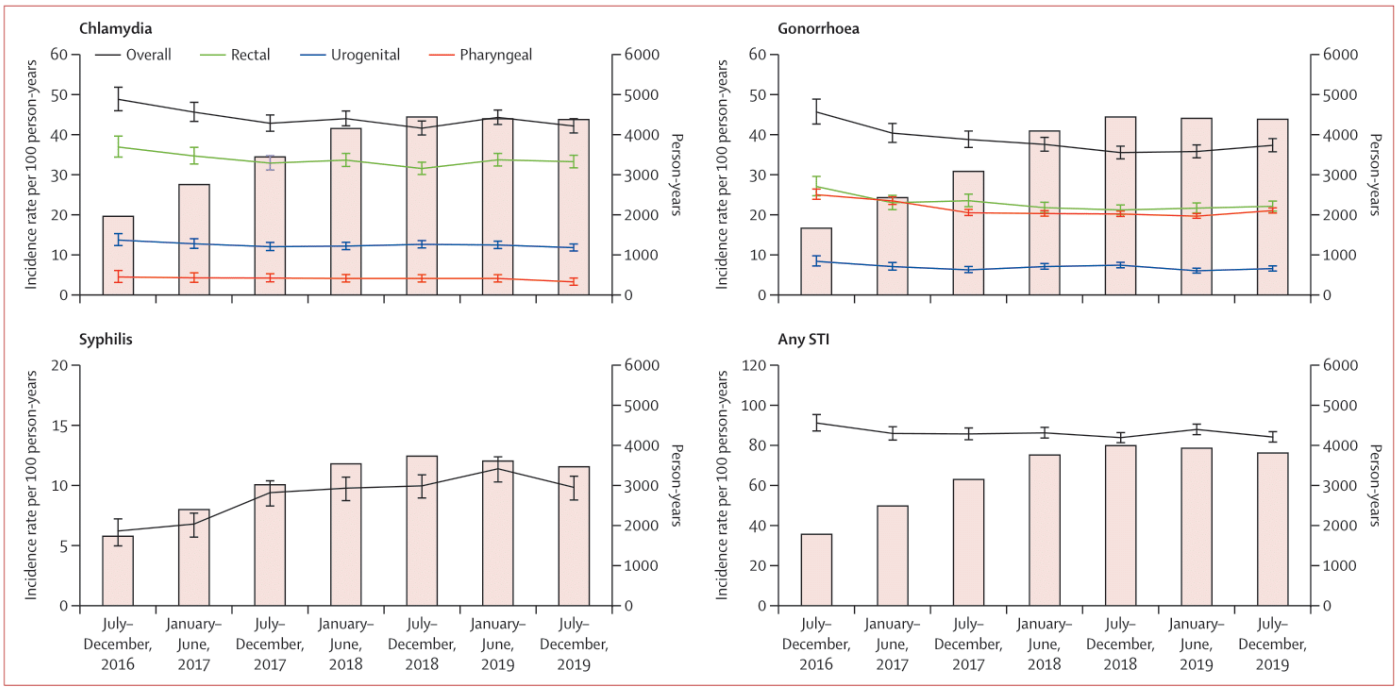

Figure 2: **STI incidence rates by calendar half year, from July–December, 2016, to July–December, 2019**
Error bars represent 95% CIs. Bars represent person-years of follow-up accrued in each period (right axis). Trends disaggregated by age group are shown in the appendix (p 10). STI=sexually transmissible infection.

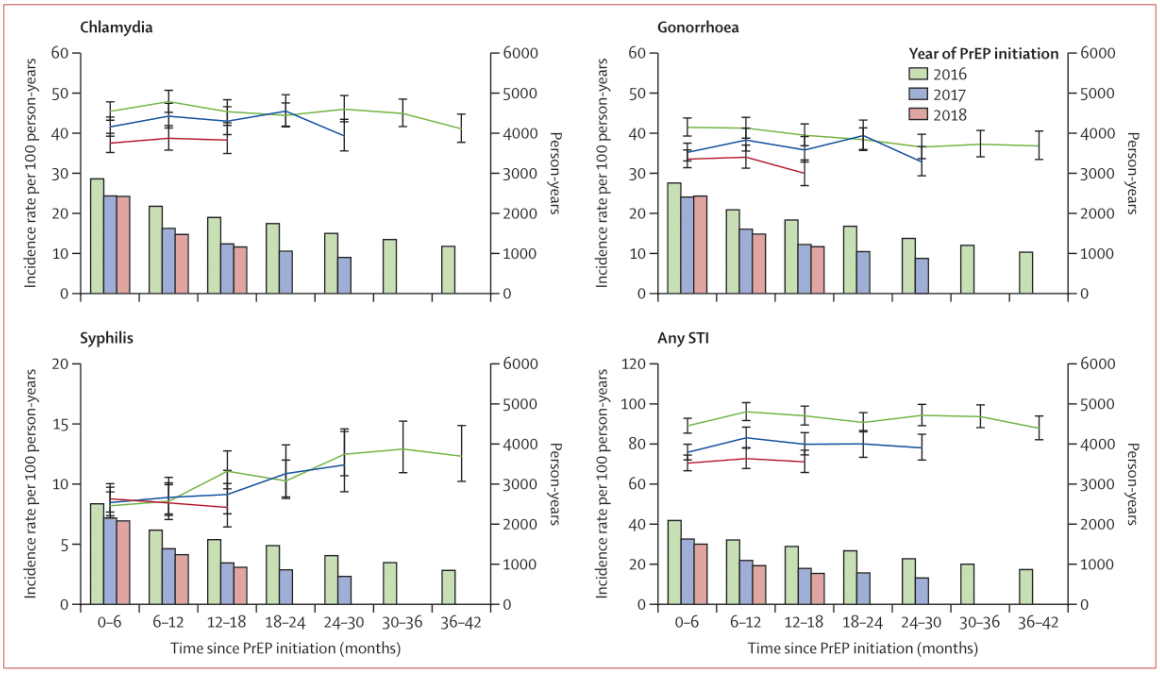

Figure 3: **6-monthly STI incidence rates, by time since PrEP initiation and by year of PrEP initiation**
Error bars represent 95% CIs. Bars represent person-years of follow-up accrued in each period (right axis). Incidence trends aggregated for all gay and bisexual men using PrEP are shown in the appendix (p 11). STI=sexually transmissible infection. PrEP=HIV pre-exposure prophylaxis.

overall incidence rate estimates for each outcome (appendix pp 16–17); however, the trends were similar to those in the primary analysis.

Discussion

To our knowledge, this is the largest cohort of gay and bisexual men using PrEP in which STI incidence rate estimates have been reported internationally. The large sample size in this study provided high precision in our estimates and statistical power to detect relatively small changes over time; significant trends should be interpreted with this in mind. Our analysis suggests that chlamydia and gonorrhoea incidence were high among gay and bisexual men using PrEP, particularly in the early months of nationwide PrEP implementation. Chlamydia and gonorrhoea incidence slightly declined in the years following broad access to PrEP in Australia, and seemed to stabilise later on in the study period. By contrast with chlamydia and gonorrhoea, syphilis incidence continued to increase among gay and bisexual men using PrEP during the study period. Approximately half (8223 [44·5%] of 18 483) of all participants using PrEP were diagnosed with any STI during the study period, and 5·7% of participants were diagnosed with five or more STIs, which accounted for more than one-third of all infections diagnosed. These data represent real-world, population-level incidence estimates of bacterial STIs following high and prolonged uptake of PrEP among gay and bisexual men and reinforce that gay and bisexual men using PrEP are a priority population for bacterial STIs.

There are several possible reasons for the observed trends showing a decline then stabilisation in the incidence of chlamydia and gonorrhoea. Changes in the cohort population over time, driven by the observed lower prospective STI risk of people initiating PrEP in later years, are likely to have influenced the incidence trends. The criteria for prescribing PrEP evolved during our observation period, with early PrEP demonstration studies requiring specific risk-based criteria to be met for enrolment, and less stringent criteria used for prescribing following the listing of PrEP on the Pharmaceutical Benefits Scheme in 2018. It is also possible that the high testing frequency among people using PrEP in Australia is affecting STI transmission through greater detection and shorter infection duration. The median time between tests for all STIs in our cohort closely reflected the recommended 3-monthly interval for STI testing among people using PrEP,[15] with 90% of all chlamydia and gonorrhoea tests occurring within 162 days of the previous test and 90% of all syphilis tests occurring within 174 days of the previous test. However, the effects of maintaining high STI testing rates on the incidence of STIs among people using PrEP are complex and multifaceted. Increased screening for STIs leads to greater likelihood of detecting an infection earlier, and therefore increases the rate of diagnosis and treatment of asymptomatic STIs among people using PrEP. More timely detection and treatment of bacterial STIs shortens the duration of infection, reducing the number of onward transmissions. However, shorter duration of infection, in

	Diagnoses	Person-years at risk	Incidence rate per 100 person-years (95% CI)	Unadjusted IRR (95% CI)	Unadjusted p value	Adjusted IRR (95% CI)	Adjusted p value
Chlamydia							
Year							
2016	5749	12 688·9	45·3 (44·2–46·5)	1 (ref)	..	1 (ref)	..
2017	3089	7236·0	42·7 (41·2–44·2)	0·94 (0·89–0·99)	0·031	0·93 (0·88–0·99)	0·016
2018	1921	5052·7	38·0 (36·4–39·8)	0·84 (0·79–0·89)	<0·0001	0·83 (0·78–0·88)	<0·0001
2019	652	1693·8	38·5 (35·6–41·6)	0·85 (0·78–0·93)	0·0002	0·83 (0·76–0·91)	<0·0001
Time on PrEP*	..	..	..	1·01 (1·00–1·02)	0·098	0·99 (0·98–1·00)	0·14
Gonorrhoea							
Year							
2016	4693	11 942·3	39·3 (38·2–40·4)	1 (ref)	..	1 (ref)	..
2017	2592	7138·5	36·3 (34·9–37·7)	0·92 (0·86–0·98)	0·011	0·90 (0·85–0·96)	0·0020
2018	1667	5076·2	32·8 (31·3–34·5)	0·83 (0·78–0·89)	<0·0001	0·80 (0·75–0·86)	<0·0001
2019	562	1692·6	33·2 (30·6–36·1)	0·84 (0·77–0·93)	0·0052	0·80 (0·72–0·89)	<0·0001
Time on PrEP*	..	..	..	1·00 (0·99–1·01)	0·99	0·98 (0·97–0·99)	0·0016
Syphilis							
Year							
2016	1080	10 514·2	10·3 (9·7–10·9)	1 (ref)	..	1 (ref)	..
2017	572	6110·7	9·4 (8·6–10·2)	0·91 (0·78–1·06)	0·23	0·98 (0·84–1·14)	0·80
2018	360	4230·6	8·5 (7·7–9·4)	0·83 (0·71–0·97)	0·016	0·94 (0·81–1·11)	0·48
2019	104	1312·9	7·9 (6·5–9·6)	0·77 (0·62–0·96)	0·020	0·93 (0·74–1·17)	0·53
Time on PrEP*	..	..	..	1·08 (1·06–1·11)	<0·0001	1·08 (1·05–1·11)	<0·0001
Any STI†							
Year							
2016	8722	9459·5	92·2 (90·3–94·2)	1 (ref)	..	1 (ref)	..
2017	4087	5041·3	81·1 (78·6–83·6)	0·88 (0·83–0·93)	<0·0001	0·88 (0·83–0·93)	<0·0001
2018	2345	3224·3	72·7 (69·8–75·7)	0·79 (0·74–0·84)	<0·0001	0·80 (0·75–0·85)	<0·0001
2019	708	975·3	72·6 (67·4–78·1)	0·79 (0·72–0·86)	<0·0001	0·80 (0·73–0·87)	<0·0001
Time on PrEP*	..	..	..	1·03 (1·02–1·04)	<0·0001	1·00 (0·99–1·02)	0·34

Data are n unless otherwise stated. For individuals initiating PrEP in 2016, 2017, 2018, and 2019, analyses included 42 months, 30 months, 18 months, and 6 months of PrEP use, respectively. No non-linearity in IRRs was detected (appendix pp 13–14). STI=sexually transmissible infection. PrEP=HIV pre-exposure prophylaxis. IRR=incidence rate ratio. *Estimated change per 6 months of PrEP use, included as continuous variable in negative binomial model. †Any STI analysis only includes participants who had at least two tests for each infection (chlamydia, gonorrhoea, and syphilis).

Table 4: **Negative binomial regression models for STI incidence by year of PrEP initiation and time on PrEP**

turn, means individuals become susceptible to new infections faster.

In addition to the effects of increased testing, PrEP roll-out is likely to have contributed to substantial changes in both the size and constituents of sexual networks among gay and bisexual men. Data suggest that gay and bisexual men using PrEP are more likely to have condomless sex with other people using PrEP compared with gay and bisexual men not using PrEP.[16] Given the relatively small number of people using PrEP in Australia in 2016, high rates of chlamydia and gonorrhoea in the first year of PrEP roll-out might reflect a high rate of homogenous mixing within relatively small sexual networks of early adopters of PrEP who had a high baseline risk for STIs. As PrEP use expanded in 2017 and 2018, sexual networks are likely to have also expanded, leading to more disassortative mixing between early adopters of PrEP with higher risk and individuals with lower risk who initiated PrEP in later years, leading to a diffusion of STIs among a wider network. This heterogeneous mixing between early adopters and later adopters of PrEP might partly explain the observed chlamydia and gonorrhoea incidence declines in gay and bisexual men using PrEP, and the declines in gonorrhoea incidence among participants who initiated PrEP in 2016 in our subgroup analysis by time on PrEP.

The divergent steady increase in syphilis incidence might also have emerged as a result of changing sexual networks, in this case due to the increasing likelihood of HIV serodiscordant sex. Routinely collected bio-behavioural data from gay and bisexual men in Australia show decreases in serosorting among both HIV-negative gay and bisexual men and gay and bisexual men living with HIV during our study period.[17] Increases in serodiscordant sex might have had a greater effect on syphilis transmission, given that syphilis diagnoses in Australia were much higher among gay and bisexual men living with HIV than among HIV-negative gay and

bisexual men during our study period.[18] An Australian survey conducted in 2018 showed that 48% of gay and bisexual men using PrEP reported being comfortable having condomless sex with gay and bisexual men living with HIV who had an undetectable viral load, compared with only 6% of gay and bisexual men not using PrEP. However, 78% of gay and bisexual men using PrEP reported being comfortable having condomless sex with other people using PrEP.[16] These data suggest that, among gay and bisexual men using PrEP, comfort in having condomless sex with gay and bisexual men living with HIV might have evolved slower than comfort in having condomless sex with other gay and bisexual men using PrEP, potentially explaining the gradual increase in syphilis incidence among gay and bisexual men using PrEP in the years after PrEP implementation, compared with relatively stable trends in chlamydia and gonorrhoea incidence. Separate analysis of data from the ACCESS network suggests that there has been an increase in syphilis incidence among gay and bisexual men living with HIV from 2017 onwards.[19]

In addition to high-frequency STI testing, other interventions are required to drive down gonorrhoea and chlamydia incidence and to curtail the rise in syphilis incidence among gay and bisexual men using PrEP. As with previously reported data from gay and bisexual men using PrEP in Victoria, Australia,[5] our data suggest that STI diagnoses remain highly skewed, with about 6% of individuals accounting for more than one-third (36%) of all STIs diagnoses. Gay and bisexual men who have repeat and concurrent STIs might be prime candidates for novel biomedical prevention strategies. There is growing interest in Australia in the use of doxycycline prophylaxis for the prevention of STIs, with a study published in 2019 showing that 9·9% (95% CI 8·1–11·8) of people using PrEP attending a large sexual health centre in Melbourne reported using doxycycline prophylaxis in the previous month.[20] Daily and event-driven doxycycline use have been shown to reduce rates of chlamydia and syphilis incidence,[21,22] and although it is not currently approved or recommended for STI prophylaxis in Australia, doctors can prescribe doxycycline off-label. A large study of doxycycline for the prevention of syphilis is ongoing in Australia.[23] In addition, there are future prospects for vaccines for bacterial STIs, including an ongoing randomised controlled trial of a meningococcal B vaccine (Bexsero) for gonorrhoea prevention.[24] In addition to novel biomedical prevention strategies, new models of partner notification (including community-led or peer-led models) and testing (self-testing or home-based testing) might be highly acceptable among people using PrEP and be effective in reducing STI transmission.

Our findings have implications for other countries currently implementing or planning to implement PrEP programmes at scale. These data show that incorporating a PrEP programme into existing clinical services and achieving high (3-monthly) STI testing rates can be accomplished. In this context, PrEP implementation reduces HIV diagnoses,[1] leading to cost-benefits in the long-term, and our analyses suggest that concerns around exponentially increasing rates of STI transmission following wide-scale PrEP implementation have not materialised in gay and bisexual men in Australia. Instances of stigma and hesitancy among practitioners to prescribe PrEP to individuals due to fear of increased STI acquisition risk, especially in the USA,[25] are likely to have hindered progress towards achieving optimal PrEP coverage. Our analysis adds to the body of evidence showing that comprehensive and frequent STI screening of gay and bisexual men using PrEP might have benefits for STI transmission at the population level. Other benefits of PrEP use, including reduced HIV-related anxiety and increased pleasure,[26] should also be considered.

Our analysis has a number of notable strengths, including the high PrEP coverage and large national cohort size. We estimate that our analyses captured approximately 70% of the 32 831 people dispensed publicly funded PrEP in Australia between 2016 and 2019.[27] Other strengths of this study include long periods of follow-up with frequent testing, and data linkage between ACCESS clinics, which allowed us to follow individuals who transferred care between clinics involved in ACCESS and reduced loss to follow-up.

Several limitations of our analysis should be noted. First, individuals attending the ACCESS network might not be representative of all gay and bisexual men using PrEP across Australia. However, the included clinical services specialise in the care of gay and bisexual men and are responsible for a large share of HIV treatment,[28] and we captured a large proportion of gay and bisexual men using PrEP in Australia. Second, individuals might have accessed PrEP or STI testing, and therefore been diagnosed with an STI, at a service outside of the ACCESS network. However, given the short intervals between the tests included in this analysis (median 84–90 days), the effect of external testing is likely to have been minimal; individuals were censored from this analysis if they did not return for PrEP within 4 months of the previous prescription. Third, for individuals attending general practice clinics, we relied on an algorithm of rectal swab testing among male patients to infer status of gay and bisexual men, which might have misclassified some patients. Fourth, we were not able to definitively define periods of PrEP use, but rather inferred PrEP use on the basis of the date of the most recent prescription. It is possible that some gay and bisexual men received their PrEP prescription but did not initiate PrEP, or were using PrEP intermittently. By including participants in our analyses until 4 months after their previous PrEP prescription, we believe we have captured a period of follow-up that is likely to reflect STI risk during PrEP use. Routinely collected

biobehavioural surveillance data suggest that event-driven PrEP use was low among Australian gay and bisexual men during our study period, with less than 10% of men using PrEP reporting non-daily use in 2019 and even fewer in earlier years.[29] Fifth, as the majority of these data were extracted from general practice clinics providing routine PrEP care, and as behavioural data are not routinely collected at these clinics, we were not able to include individual-level behavioural data or data on symptoms in our analyses. Finally, as only clinical testing data were extracted, and not data on STI treatments prescribed to participants, it could not be ensured that every STI was treated effectively and that all positive diagnoses were incident infections. However, the clinics included in this study are highly experienced in managing STIs and followed standard STI treatment guidelines. Australian STI testing guidelines for gay and bisexual men using PrEP did not change during the study period.

In this analysis of gay and bisexual men using PrEP in Australia, chlamydia and gonorrhoea incidence were highest during the first 18 months of PrEP implementation, and stabilised at slightly reduced incidence thereafter. The observed trends in STI incidence were influenced by lower prospective STI risk among gay and bisexual men initiating PrEP in later years after nationwide implementation, as well as slight declines in individual rates of some STIs following prolonged PrEP use and frequent STI testing. Although frequent testing of people using PrEP might be beneficial for population-level incidence of some STIs, changes in sexual networks of gay and bisexual men might be contributing to elevated STI incidence among some gay and bisexual men who use PrEP, and additional interventions aimed at interrupting transmission might be required to reduce STI transmission.

Contributors

MWT conceived the analysis. MWT, RG, and MAS contributed substantially to study conception, study design, and analysis and interpretation of the data. MWT, JA, and PP curated the data. MWT did the formal data analysis. HM provided methodological support. RG, JA, AC, BD, MEH, and MAS coordinated the ACCESS study and were responsible for acquisition of funding. EJW, MEH, and MAS provided academic supervision. CKF, EPFC, AM, RF, CB, LO, LM, and DR are ACCESS clinic investigators and contributed to data acquisition. MWT, JA, and MAS had full access to all the data in the study and verified the data. MWT led the manuscript preparation. All authors read and revised the manuscript critically for important intellectual content and approved the final version of the manuscript for publication.

Declaration of interests

MWT reports speakers' honoraria and investigator-initiated research grants from Gilead Sciences. RG reports research support funding from Gilead Sciences. CB reports honoraria from Gilead Sciences. EJW is the chair of the COVID-19 Taskforce of the Australasian Society of HIV, Viral Hepatitis, and Sexual Health Medicine, and reports investigator-initiated research funding from ViiV Healthcare, and consulting and travel fees from Gilead Sciences. AG reports research grants from Sequris and ViiV Healthcare, receipt of study drug from GlaxoSmithKline, and personal fees from Merck Sharp and Dohme. MEH reports investigator-initiated research grants from Gilead Sciences and Abbvie. MAS reports investigator-initiated research grants from Gilead Sciences and Abbvie and consulting fees from Gilead Sciences. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data included in this study cannot be shared publicly because of the sensitive nature of participant data anonymously extracted from participating clinical services. Access to deidentified data is available via the Burnet Institute, Melbourne, VIC, Australia, with approval from the Alfred Hospital Human Research Ethics Committee for researchers who meet the criteria for access to confidential data. The ACCESS study protocol has been published previously.

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Appendix B2. Chapter 5 in *AIDS and Behaviour*

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ORIGINAL PAPER

Latent Class Analysis of Sexual Behaviours and Attitudes to Sexually Transmitted Infections Among Gay and Bisexual Men Using PrEP

Michael W. Traeger[1,2] · Dean Murphy[3,4] · Kathleen E. Ryan[1,4] · Jason Asselin[1] · Vincent J. Cornelisse[3,4,5] · Anna L. Wilkinson[1,2] · Margaret E. Hellard[1,4,6] · Edwina J. Wright[1,4,6] · Mark A. Stoové[1,2,7]

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Abstract

Gay and bisexual men (GBM) who use pre-exposure prophylaxis (PrEP) are at increased risk of sexually transmitted infections (STIs) compared to those who don't use PrEP. Since the implementation of PrEP in Australia, it is possible that attitudes towards STIs have shifted in line with changes in risk and transmission dynamics in the context of increased screening. As the extent to which GBM utilise STI prevention strategies likely depends on their attitudes towards STIs and STI prevention, the aims of this study were to use latent class analysis (LCA) to classify GBM using PrEP on the basis of their attitudes towards STIs and reported risk behaviours, and examine how these categorisations relate to risk of STI acquisition. 1225 GBM who were previously enrolled in a PrEP implementation study (The PrEPX Study) completed a survey focused on sexual behaviours and attitudes towards STIs 1 year post-study follow-up. Data on chlamydia, gonorrhoea and syphilis testing and positivity were available through a sentinel network of participating study clinics. Using LCA, participants were allocated into four classes; Class 1, "Some concern and lowest risk"; Class 2, "Low concern and lower risk"; Class 3, " High concern and higher risk"; and Class 4, "Low concern and highest risk". The majority (78%) of participants were classified into Class 3 or Class 4, two groups which were distinguished by highly disparate attitudes towards STIs but with a similar proportion of participants diagnosed with a bacterial STI in the last 12 months (48% and 57%, respectively). Findings suggest that attitudes towards STIs among GBM using PrEP in Australia vary considerably, and this will likely influence their receptivity to different STI prevention strategies.

Keywords Pre-exposure prophylaxis · Sexually transmitted infections · Gay and bisexual men · Sexual behaviour · Latent class analysis

Introduction

In Australia, gay and bisexual men (GBM) are overrepresented in diagnoses of sexually transmitted infections (STIs), including gonorrhoea, chlamydia and syphilis [1]. Decades-long trends of increasing STI incidence among Australian GBM [1, 2] have coincided with steady declines in consistent condom use [3], and in recent years this decline has accelerated in association with the rapid uptake of HIV pre-exposure prophylaxis, PrEP [4]. Between June 2016 and April 2018, more than 20,000 Australian GBM accessed PrEP through implementation studies [5, 6]. Since the closure of these PrEP studies following PrEP becoming available through government subsidy on Australia's pharmaceutical benefits scheme (PBS) in April 2018 [7], more than 37,000 individuals have accessed PrEP via the PBS [8]. A previous analysis of a large cohort of GBM accessing PrEP

✉ Michael W. Traeger
michael.traeger@burnet.edu.au

1 Burnet Institute, 85 Commercial Road, Melbourne, VIC 3181, Australia

2 School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

3 The Kirby Institute, University of New South Wales, Sydney, NSW, Australia

4 Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, VIC, Australia

5 Kirketon Road Centre, NSW Health, Sydney, NSW, Australia

6 Peter Doherty Institute, University of Melbourne, Melbourne, VIC, Australia

7 School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia

via the PrEPX Study in Victoria, Australia found that STI incidence increased by 21% following PrEP initiation among those starting PrEP for the first time, and was high during PrEP use. Findings also highlighted that a relatively small proportion of PrEP users, among whom repeat infections were common, carried most of the burden of STI diagnoses [9].

The extent to which GBM utilise STI prevention strategies, and their preferences for different strategies, likely depends on their behaviour and perceived level of STI risk, as well as their attitudes towards STIs and STI prevention in general. Previous qualitative research has highlighted a degree of anxiety towards STIs among some GBM, with reports of experiencing stigma associated with STI infection common [10]. Research exploring attitudes towards STIs and STI prevention among Australian GBM found that, while most GBM were not overly concerned with being diagnosed with STIs, some reported feelings of shame, embarrassment and annoyance towards STIs [11]. A more recent study found that while the majority of participants described STIs as easy to manage and a natural part of sexual health, some still considered STIs a serious health issue, including having concerns around antimicrobial resistance [12]. These findings suggest that GBM are not homogenous in their attitudes towards and perceptions of STIs. GBM who use PrEP are at increased risk of STIs compared to those who don't use PrEP [13–15], and since the implementation of PrEP it is possible that attitudes towards STIs have shifted in line with changes in risk and transmission networks and the frequency with which STIs are acquired, diagnosed, and treated in the context of more frequent testing when attending clinics for PrEP prescribing.

Characterising and identifying people at various levels of risk for acquiring STIs can help inform targeted prevention or the development of screening and testing guidelines. Latent class analysis (LCA) is a statistical method commonly used to identify subgroups of individuals based on specific response patterns across multiple variables. LCA has been widely applied to data collected from GBM to identify GBM suitable for PrEP [16] and understand perceived barriers to PrEP uptake [17]; identify GBM at increased risk for STIs [18]; describe and categorise attitudes and perceptions towards biomedical HIV prevention [19] and the utilisation of different combination HIV prevention strategies [20]; identify behaviours associated with HIV risk [21]; and to explore associations between sexualised drug use behaviour and STI risk [22].

To our knowledge, no published research has utilised LCA to classify GBM according to their attitudes towards STIs and sexual behaviours, and explore associations with corresponding STI risk. Understanding how attitudes towards STIs vary among GBM using PrEP, and their potential influence on prevention strategies and behaviours, will help in the development and implementation of appropriately targeted interventions to reduce STI transmission. The aims of this study were to classify GBM who use PrEP on the basis of their attitudes towards STIs and their reported risk behaviours, and examine how these categorisations relate to risk of acquiring an STI.

Methods

Data were drawn from the Pre-exposure Prophylaxis Expanded (PrEPX) Study, a multisite, open-label PrEP implementation study. The PrEPX Study has been described in detail elsewhere [5, 9]. The PrEPX study enrolled participants from three Australian states, with enrolments commencing in July 2016 in Victoria, May 2017 in South Australia and in September 2017 in Tasmania. Participants were dispensed PrEP every 3 months until study closure (1st April 2018 in Victoria and 30th June 2018 in South Australia and Tasmania). PrEPX participants completed a clinician-guided survey at enrolment and were scheduled to return to study clinics every 3 months to receive a prescription for PrEP and undergo comprehensive STI screening.

A total of 5113 participants were enrolled in the PrEPX study across Victoria (n = 4275), South Australia (n = 656) and Tasmania (n = 182). All PrEPX participants were invited to complete an online survey in March 2019, approximately 1 year after PrEPX study visits ceased. In total, 1469 participants (28.9% of all participants) completed the follow-up survey, of which 1458 (99.3%) identified as non-heterosexual men (gay, bisexual or 'other' sexuality). For this analysis, we included the 1225 (84.0%) participants who reported they were still using PrEP at the time of 1-year follow-up survey completion. Included participants completed the survey between 19th March and 20th June 2019.

Enrollment and follow-up survey data were collected and managed using REDCap electronic data capture tools hosted at the Burnet Institute [23]. The online follow-up survey asked a range of behavioural, demographic, and attitudinal questions derived from a previous sexual health survey of young people [24]. Participants were asked about condom use, partner numbers, sexual positioning, frequency of drug use before or during sex including alcohol, methamphetamine, GHB, ecstasy, amyl/poppers, marijuana, speed and cocaine, whether participants had ever injected drugs and frequency of injecting drug use. Participants were also asked about how often they had discussed STI testing with partners before having sex (never, some of the time, about half of the time, most of the time, always).

Participants also answered eight items on attitudes towards STIs on a 5-point Likert scale. The questions and available responses are below:

1. I worry about getting an STI
2. Getting an STI is something I think about often
3. Getting an STI could seriously affect my health
4. Getting an STI is no big deal
5. I feel I am unlikely to get an STI
6. I can't picture myself getting an STI

1-Strongly disagree, 2-Disagree, 3-Neither Agree nor Disagree, 4-Agree, 5-Strongly Agree.

7. How important is it to you that you avoid STIs?
8. How important is it to you that you avoid passing on STIs to your sexual partners?

1-Very unimportant, 2-Somewhat unimportant, 3-Neither important or unimportant, 4-Somewhat important, 5-Very important.

Statistical Analyses

To explore potential for responder bias in the post-study follow-up survey, we compared baseline characteristics from enrolment surveys between those who completed the follow-up survey and were included in this analysis and those who did not using two-sided test of proportions for dichotomous variables and t-test for continuous variables.

Variables Considered for LCA

Variables included in the LCA included participant age in years (continuous), condom use with casual partners, number of casual partners (categorised into 0, 1–5, 6–10, 11–20, 21–50, > 50; to achieve an approximate even distribution of responses), reporting a regular sex partner (yes/no), sexual position during sex (insertive only, receptive only, both insertive and receptive), chemsex drug use defined as the use of methamphetamine or GHB (with or without other drugs) [25–27] during or before sex (yes/no), discussing STI testing with casual partners and the eight STI attitudinal items dichotomised into agree ('strongly agree' or 'somewhat agree') or not ('neither agree nor disagree', 'somewhat disagree' or 'strongly disagree'). Attitudinal items were included as dichotomous variables to both improve model fit and aid in interpretability; proportion in agreement with each attitude was deemed meaningful in assessing differences in attitudes across classes. Recall period for behavioural variables was last 6 months.

Latent Class Model

We assessed model fit based on models with between two and eight classes, and used Akaike information criterion (AIC), Bayesian information criterion (BIC), and model entropy [28], as well as interpretability, to assess the ideal number of classes. The minimum allowed class size was restricted to 5% of the sample. In order to ensure that maximum likelihood estimation converged on a global and not a local maximum, for each model under consideration, we reran the model 100 times with random starting points. For each draw of random starting points, each individual was randomly allocated to a class and an expectation maximization (EM) algorithm was used to select the starting class values which resulted in the highest log likelihood value after 100 EM iterations. We assumed convergence on a global maximum likelihood if at least 40% of solutions yielded the maximum value of the likelihood function [29]. Individuals were allocated to the class in which they had the highest posterior probability of class membership and average class probability was calculated for each class.

Once the ideal number of classes based on model fit and entropy was determined, we assessed whether the assumption of conditional independence was met in the final model by exploring correlation between included variables within classes. We conducted a conditional analysis by calculating Pearson's correlation coefficient for all variables within each class, with a correlation of 0.5 or greater within one or more classes indicating violation of the assumption of independence. During this process, we observed a high correlation between attitudinal items 7 (How important is it to you that you avoid STIs?) and 8 (How important is it to you that you avoid passing on STIs to your sexual partners?) within three classes. As such, item 8 was removed and the process of running the series of models with 2–8 classes was repeated. We also assessed each class qualitatively to see if any classes were similar across multiple variables. In most model permutations, the mean age of participants was very similar across each class (each within 2 years of the cohort mean), so age was removed from the model.

We report LCA results as class prevalence rates for each classification variable, i.e. distribution of responses across individuals in their respective allocated class. All statistical analyses were conducted in Stata version 15 (StataCorp) and latent class models were run using the gsem command [30].

STI Positivity

Participants who enrolled in the PrEPX study were monitored for STIs using linked data extracted from study clinics which were also participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) [31]. ACCESS uses specialised data extraction software installed behind patient management software at participating sexual health and general practice clinics to extract de-identified patient data [32]. For the purposes of the PrEPX study, participants consented to having their STI

testing data extracted via ACCESS and linked to their study data.

To explore how LCA classes related to risk of acquiring an STI, we calculated the proportion of participants with an available STI test result who tested positive for chlamydia, gonorrhoea and newly identified infectious [primary, secondary or early latent (< 2 years)] syphilis within each class. Test positivity was determined for any clinic visit in the 12-month period prior to date of survey completion and at their last clinic visit prior to completing the survey. To explore potential for selection bias associated with presenting for STI testing at ACCESS clinics, we compared characteristics between those with and without STI testing data available. Log-binomial regression was used to calculate prevalence ratios between each class of having a positive STI result within the past 12 for each STI outcome.

Results

Participant Characteristics and Survey Responses

Among the 1225 participants included in analyses, the mean age was 42.1 years and 94% identified as gay. Responses to behavioural questions in the follow-up survey are shown in Table 1. The distributions of participant responses to the eight STI attitudinal questions are shown in Table 2.

Based on enrolment survey responses, compared to PrEPX participants not included in the analysis, those included were older at enrolment (mean age, 39.7 years compared to 35.0 years; $P < 0.001$), less likely to have reported methamphetamine use in the 3 months prior to PrEPX study enrolment (9.1% compared to 12.4%; $P = 0.001$), more likely to have used PrEP prior to enrolment (30.7% compared to 22.1%; $P < 0.001$), and less likely to be report injecting drug use at enrolment (3.1% compared to 4.9%; $P = 0.009$). There was no difference between those included and not included in analyses on other enrolment survey responses, including reporting condomless receptive anal sex with a casual partner, reporting an STI diagnosis prior to enrolment, or reporting more than one episode of insertive condomless anal sex with a casual partner, in the 3 months prior to enrolment.

Latent Class Model

In addition to removing participant age from consideration in the LCA (see "Methods" section), item 8 (How important is it to you that you avoid passing on STIs to your sexual partners?) was removed due to high correlation with item 7 (How important is it to you that you avoid STIs?) within three classes (Pearson's correlation coefficient = 0.59, 0.64, and 0.69). Item 7 was retained over item 8 as it was deemed more relevant to the participant's attitudes towards avoiding STIs. In the final model specification, entropy was greatest in a model with three classes (0.74), AIC was lowest in a model with eight classes (22,284.7) and BIC was lowest a model with four classes (22,944.8, Table 3). As entropy was 0.62 in the 4-class model and decreased substantially with increasing classes thereafter, a model with four classes was selected and inspected for interpretability and conditional independence. Response patterns across classes were deemed reasonable and classes made interpretative sense in relation to distinguishing common attitudes across classes. The model satisfied the assumption of conditional independence (no correlation between variables within a class of greater than 0.5) and so a model with four classes was chosen for the final model. In the final model, the average posterior probabilities for class membership were 99% for Class 1, 81% for Class 2, 89% for Class 3 and 89% for Class 4 (Table 4).

Table 4 shows the distribution of variables included in the LCA across participants according to their allocated class. The latent class model revealed two smaller classes, Class 1 (9% of participants) and Class 2 (13%), and two larger classes, Class 3 (44%), Class 4 (35%). The four classes exhibited varying combinations of behaviors and perceived risk and concerns regarding STIs.

Class 1: 'Some concern and lowest risk'

GBM classified as belonging in Class 1 were most likely to report having a regular partner and the majority reported no casual partners in the past 6 months. Despite fewer reporting casual partners, GBM in Class 1 reported some concerns about STIs, indicating moderate levels of agreement for the item 'I worry about STIs' and the vast majority agreeing that 'STIs could seriously affect my health'.

Class 2: 'Low concern and lower risk'

GBM in Class 2 reported fewer casual partners than Classes 3 and 4, reported the highest proportion of insertive sex only with casual partners and the lowest level of chemsex drug use, but the proportion reporting never using condoms with casual partners was similar to Class 4. While some GBM in Class 2 still agreed they 'worry about STIs' and a large majority agreed that 'getting an STI could seriously affect their health' and wanted to avoid STIs, they had the lowest agreement with the item 'getting an STI is something I think about often'.

Class 3: 'High concern and higher risk'

Almost all of the GBM in Class 3 reported they 'worry about getting an STI', and GBM in Class 3 had the highest agreement with 'getting an STI is something I think about often'

Table 1 Participant characteristics and behaviours at time of follow-up survey

	n (N = 1225)	(%)
Age, years (mean, SD)	42.1 (11.1)	
Sexual identity		
Gay	1153	94.1
Bisexual	64	5.2
Other	8	0.7
Ever injected drugs		
No	1111	90.7
Yes	108	8.8
Prefer not to answer	6	0.5
Has regular partner	595	48.6
Number of casual partners in the last 6 months		
0	115	9.39
1–5	301	24.6
6–10	233	19.0
11–20	258	21.1
21–50	233	19.0
More than 50	85	6.9
Condom use with casual partners in the last 6 months[a]		
Never	437	39.4
Some of the time	451	40.6
About half the time	97	8.7
Most of the time	77	6.9
All of the time	33	3.0
No response	15	1.4
Drug use before or during sex in the last 6 months		
Methamphetamine	196	16.0
GHB	162	13.2
Alcohol	930	75.9
Ecstasy	209	17.1
Popper/amyl	878	71.7
Marijuana	274	22.4
Cocaine	185	15.1
Ketamine	101	8.2
Speed	56	4.6
Sexual positioning with casual partners in the last 6 months[a]		
Insertive/'top' only	220	19.8
Receptive/'bottom' only	169	15.2
Both insertive and receptive	708	63.8
No response	13	1.2
In the last 6 months, how often did you discuss STI testing with a casual partner?		
Never	296	24.2
Some of the time	439	35.8
About half of the time	151	12.3
Most of the time	215	17.6
Always	124	10.1

[a]Among those who reported a casual partner in the last 6 months (n = 1110)

Table 2 Participant responses to attitudinal questions in follow-up survey

	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree
	n (%)	n (%)	n (%)	n (%)	n (%)
Getting an STI could seriously affect my health	47 (3.8)	117 (9.6)	157 (12.8)	518 (42.3)	386 (31.5)
Getting an STI is no big deal	244 (19.9)	338 (27.6)	225 (18.4)	338 (27.6)	80 (6.5)
I feel I am unlikely to get an STI	236 (19.3)	478 (39)	319 (26)	145 (11.8)	47 (3.8)
I can't picture myself getting an STI	481 (39.3)	420 (34.3)	206 (16.8)	82 (6.7)	36 (2.9)
I worry about getting an STI	91 (7.4)	186 (15.2)	260 (21.2)	490 (40)	198 (16.2)
Getting an STI is something I think about often	135 (11)	272 (22.2)	340 (27.8)	344 (28.1)	134 (10.9)
	Very unimportant	Somewhat unimportant	Neither important or unimportant	Somewhat important	Very important
How important is it to you that you avoid STIs?	38 (3.1)	57 (4.7)	99 (8.1)	537 (43.8)	494 (40.3)
How important is it to you that you avoid passing on STIs to your partners?	49 (4)	18 (1.5)	30 (2.5)	294 (24)	834 (68.1)

Table 3 Model goodness of fit measures for models with two to eight classes

Classes	AIC	BIC	Entropy
2	23,272.3	23,512.6	0.68
3	22,643.8	23,001.6	0.74
4	**22,510.4**	**22,944.8**	**0.62**
5	22,420.6	22,967.5	0.46
6	22,345.7	23,005.0	0.28
7	22,317.5	23,073.9	0.26
8	22,284.7	23,158.6	0.39

Final model selection indicated in bold

and 'avoiding STIs is somewhat or very important'. A high proportion also agreed with the statement 'STIs could seriously affect my health'. GBM in Class 3 had more partners than those in Class 2, but fewer than in Class 4, and a moderate level of condom use. GBM in Class 3 were most likely to report discussing STIs with their casual partners most or all of the time in the past 6 months (35.4%).

Class 4: 'Low concern and highest risk'

GBM classified as belonging to Class 4 were least likely to agree they 'worry about STIs' or that they were concerned about avoiding STIs. GBM in Class 4 also reported the lowest agreement rate for the items; 'getting an STI could seriously affect my health', 'I feel I am unlikely to get an STI', and 'I can't picture myself getting an STI'. GBM in Class 4 reported higher numbers of casual partners than those in Classes 1–3, the lowest level of condom use, and more commonly reported both insertive and receptive sex with casual partners and chemsex drug use. GBM in Class 4 were least likely to report discussing STIs with their casual partners most or all of the time in the past 6 months (15.1%).

STI Positivity

A total of 957 participants (78% of those in the latent class model) were linked to a test result for chlamydia, gonorrhoea or syphilis at an ACCESS clinic in the 12 months prior to completing the survey (Table 5). Of these, 45.8% had at least one positive syphilis, chlamydia or gonorrhea result in this period. The proportion of those with a test result who had any positive STI diagnosis in the 12 months prior to survey completion was 18.8% in Class 1, 24.1% in Class 2, 48.2% in Class 3 and 56.7% in Class 4 (Fig. 1). At their most recent STI test (occurring a median of 53 days prior to survey completion), positivity for any STI was 2.4% in Class 1, 3.6% in Class 2, 14.8% in Class 3 and 23.0% in Class 4 (Fig. 2).

There was a significant difference in the prevalence of any STI in the past 12 months between each of the classes, except for between Classes 2 and 1 (PR = 1.28 [95% CI = 0.74–2.22]). The greatest difference in prevalence of any STI in the past 12 months was between Classes 4 and 1 (PR = 3.01 [95% CI = 1.92–4.73]). Between the two higher-risk classes (Classes 3 and 4), prevalence of any STI in the past 12 months was greater in Class 4 (PR = 1.18 [95% CI = 1.02–1.36]), with the largest relative

Table 4 Distribution of characteristics, behaviours and responses to attitudinal survey items according to class membership

	Class 1 N (%)	Class 2 N (%)	Class 3 N (%)	Class 4 N (%)
Total	114 (9.3)	158 (12.9)	537 (43.8)	416 (34.0)
Mean age (years)[a]	41.4	43.0	42.4	41.5
Number of casual partners in last 6 months				
0	107 (93.9)	0 (0)	3 (0.6)	5 (1.2)
1–5	5 (4.4)	108 (68.4)	159 (29.6)	29 (7)
6–10	2 (1.8)	41 (26)	122 (22.7)	68 (16.4)
11–20	0 (0)	5 (3.2)	131 (24.4)	122 (29.3)
21–50	0 (0)	2 (1.3)	100 (18.6)	131 (31.5)
> 50	0 (0)	2 (1.3)	22 (4.1)	61 (14.7)
Mean casual partner number in last 6 months[a]	0.1	8.9	17.9	32.8
Median casual partner number in last 6 months[a]	0.0	4.0	10.0	20.0
Condom use with casual partners in last 6 months				
No casual partners/no response	107 (93.9)	12 (7.6)	6 (1.1)	5 (1.2)
Always	5 (4.4)	7 (4.4)	21 (3.9)	0 (0)
Most of the time	0 (0)	10 (6.3)	59 (11)	8 (1.9)
About half the time	0 (0)	24 (15.2)	60 (11.2)	13 (3.1)
Some of the time	0 (0)	32 (20.3)	234 (43.6)	185 (44.5)
Never	2 (1.8)	73 (46.2)	157 (29.2)	205 (49.3)
Ever injected drugs	5 (4.5)	1 (0.6)	39 (7.3)	63 (15.2)
Chemsex drugs[b] before or during sex in the last 6 months	15 (13.2)	3 (1.9)	101 (18.8)	124 (29.8)
Has regular partner	79 (69.3)	69 (43.7)	267 (49.7)	180 (43.3)
Sexual position				
No casual partners/no response	108 (94.7)	10 (6.3)	5 (0.9)	5 (1.2)
Insertive only	0 (0)	67 (42.4)	105 (19.6)	48 (11.5)
Receptive only	2 (1.8)	31 (19.6)	99 (18.4)	37 (8.9)
Both insertive and receptive	4 (3.5)	50 (31.6)	328 (61.1)	326 (78.4)
I worry about getting an STI				
n (Agree or strongly agree)	57 (50.0)	58 (36.7)	522 (97.2)	51 (12.3)
Getting an STI is something I think about often				
n (Agree or strongly agree)	36 (31.6)	10 (6.3)	393 (73.2)	39 (9.4)
Getting an STI could seriously affect my health				
n (Agree or strongly agree)	99 (86.8)	131 (82.9)	461 (85.9)	213 (51.2)
Getting an STI is no big deal				
n (Agree or strongly agree)	26 (22.8)	40 (25.3)	112 (20.9)	240 (57.7)
I feel I am unlikely to get an STI				
n (Agree or strongly agree)	38 (33.3)	60 (38.0)	58 (10.8)	36 (8.7)
I can't picture myself getting an STI				
n (Agree or strongly agree)	23 (20.2)	32 (20.3)	49 (9.1)	14 (3.4)
How important is it to you that you avoid STIs?				
n (Important or very important)	107 (93.9)	140 (88.6)	518 (96.5)	266 (63.9)
In the last 6 months, how often did you discuss STI testing with a partner?				
n (Most of the time or all the time)	33 (29.0)	53 (33.5)	190 (35.4)	63 (15.1)

[a]Indicates variables that were not included in the latent class model, but which are reported here for each class

[b]Defined as use of either methamphetamine or GHB

Table 5 Proportion of participants with a linked test result in ACCESS within 12 months prior to survey completion and proportion positive by class membership

	Class 1	Class 2	Class 3	Class 4	Total
n in class (% of total sample)	114 (9.3)	158 (12.9)	537 (43.8)	416 (34.0)	1,225 (100)
Number with test present in ACCESS in last 12 months (% of class)					
Any STI test (gonorrhoea, syphilis or chlamydia)	85 (74.6)	112 (70.9)	425 (79.1)	335 (80.5)	957 (78.1)
Gonorrhoea or chlamydia test	85 (74.6)	111 (70.3)	424 (79.0)	334 (80.3)	954 (77.9)
Gonorrhoea test	85 (74.6)	111 (70.3)	424 (79.0)	334 (80.3)	954 (77.9)
Chlamydia test	85 (74.6)	111 (70.3)	424 (7.09)	334 (80.3)	954 (77.9)
Rectal NG or CT test	83 (72.8)	108 (68.4)	421 (78.4)	332 (79.8)	944 (77.1)
Urethral NG or CT test	85 (74.6)	111 (70.3)	422 (78.6)	333 (80.0)	951 (77.6)
Pharyngeal NG or CT test	85 (74.6)	111 (70.3)	422 (78.6)	334 (80.3)	952 (77.7)
Syphilis	81 (71.1)	100 (63.3)	401 (74.7)	321 (77.2)	903 (73.7)
Any positive result in the last 12 months (% of tested)					
Any STI (gonorrhoea, syphilis or chlamydia)	16 (18.8)	27 (24.1)	205 (48.2)	190 (56.7)	438 (45.8)
Gonorrhoea or chlamydia	16 (18.8)	26 (23.4)	197 (46.5)	180 (53.9)	416 (43.6)
Gonorrhoea	6 (7.1)	11 (9.9)	113 (26.7)	98 (29.3)	227 (23.8)
Chlamydia	12 (14.1)	16 (14.4)	142 (33.5)	133 (39.8)	303 (31.8)
Rectal (NG or CT)	14 (16.9)	17 (15.7)	136 (32.3)	138 (41.6)	305 (32.3)
Urethral (NG or CT)	8 (9.4)	13 (11.7)	80 (19.0)	68 (20.4)	169 (17.8)
Pharyngeal (NG or CT)	5 (5.9)	9 (8.1)	81 (19.2)	76 (22.8)	171 (18.0)
Syphilis	2 (2.5)	3 (3.0)	33 (8.2)	38 (11.8)	76 (8.4)
Positive result at the most recent test within 12 months (% of tested)					
Any STI (gonorrhoea, syphilis or chlamydia)	2 (2.4)	4 (3.6)	63 (14.8)	77 (23.0)	146 (15.3)
Gonorrhoea or chlamydia	1 (1.2)	3 (2.7)	58 (13.7)	67 (20.1)	128 (13.4)
Gonorrhoea	0 (0)	2 (1.8)	25 (5.9)	27 (8.1)	54 (5.7)
Chlamydia	1 (1.2)	2 (1.8)	37 (8.7)	44 (13.2)	84 (8.8)
Rectal (NG or CT)	1 (1.2)	3 (2.8)	43 (10.2)	46 (13.9)	93 (9.9)
Urethral (NG or CT)	2 (2.4)	1 (0.9)	22 (5.2)	24 (7.2)	49 (5.2)
Pharyngeal (NG or CT)	1 (1.2)	1 (0.9)	18 (4.3)	19 (5.7)	39 (4.1)
Syphilis	1 (1.2)	1 (1.0)	6 (1.5)	16 (5.0)	24 (2.7)

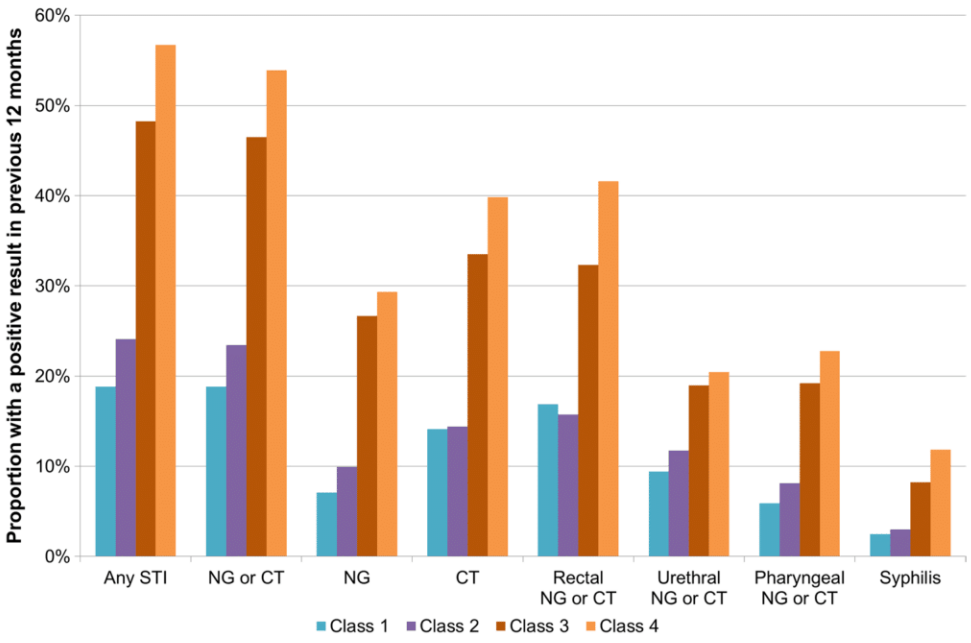

Fig. 1 Proportion of participants in each class with a positive test result within 12 months prior to survey completion

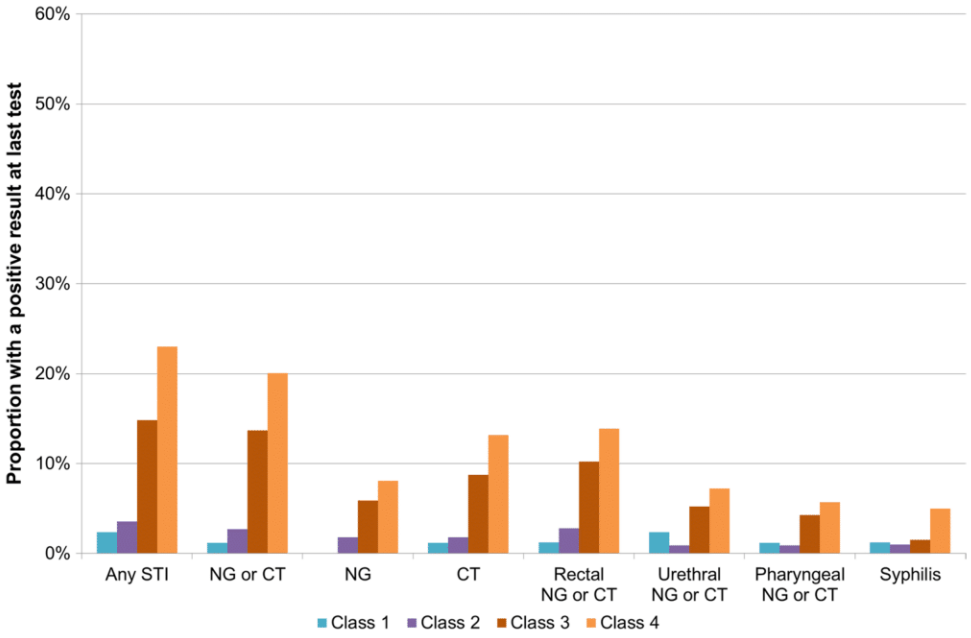

Fig. 2 Proportion of participants in each class with a positive test result at the most recent visit prior to survey completion

increase between Classes 4 and 3 observed for rectal infections (PR = 1.29 [95% CI = 1.07–1.56], Table 6).

Discussion

In this cohort of Australian GBM previously enrolled in a PrEP implementation study and who were still using PrEP 1 year post-study closure, we observed highly heterogeneous attitudes towards STIs and levels of sexual risk behaviours. Using LCA, we described four distinct groups of PrEP users exhibiting characteristic differences in behaviours, attitudes and risk related to STIs. Classes 1 and 2 were comprised mostly of GBM with no or very few casual partners, respectively. The majority (78%) of the cohort were classified into Classes 3 and 4, two groups that were distinguished by disparate attitudes towards STIs but had similarly high patterns of risk and STI diagnosis rates when compared to the others in the cohort. While GBM in Class 4 reported low concern about being diagnosed with an STI, GBM in Class 3 worried about STIs and considered STIs to be a serious health issue.

Approximately half of GBM allocated to Class 3 (high concern, higher risk) and Class 4 (low concern, highest risk) were diagnosed with an STI in the 12 months prior to completion of the follow-up survey. Given this relatively high incidence of STIs, GBM from both classes would benefit from additional STI prevention strategies. However, the receptiveness and motivation of each class to take up different interventions will likely vary considerably. When considering Class 4, there is an apparent degree of conflicting attitudes towards STIs; many (51%) acknowledge that getting an STI could seriously affect their health and that it is important to avoid STIs (64%), however few worried about getting an STI (12%), despite high rates of STI diagnoses detected in the previous 12 months. This may translate to a recognition that, while their current behaviour does put them at risk of the potential harms of STIs, the cost of reducing that harm (e.g. having fewer sexual partners) is greater than the perceived derived benefit (i.e. having fewer STIs). GBM in Class 4 may therefore be most receptive to strategies with minimal imposition on their sexual practices, such as rapid point-of-care testing or home testing, STI prophylaxis [33, 34], or, in the future, STI vaccines [35]. In contrast, GBM in Class 3, who worry about STIs yet still have high rates of STI diagnosis, may be more willing to adopt prevention strategies involving behavioural change if they can see that the direct benefit would be less STIs.

Classes 3 and 4 also reported different levels of drug use. Compared to those in Class 3, those in Class 4 were more likely to have ever injected drugs (15% vs. 7%), and more likely to have engaged in chemsex in the last 6 months (30% vs. 19%). As the sexual behaviours that participants were asked about revolved mostly around condom use, partner number and sexual positioning, we were unable to explore the frequency of more specific sexual practices associated with increased STI risk across classes, including participation in group sex or sex at sex-on-premises venues. While GBM in Class 4 had the highest positivity across each STI outcome, the greatest relative increase in past-12-month positivity compared to Class 3 was observed for rectal infections (29% higher) and syphilis (43% higher), indicating that Class 4 may be more likely to engage in high-risk receptive anal sex (e.g. condomless receptive sex in group sex

Table 6 Prevalence ratios for STI diagnosis in the past 12 months between classes

	Class 2 compared to Class 1		Class 3 compared to Class 1		Class 4 compared to Class 1		Class 3 compared to Class 2		Class 4 compared to Class 2		Class 4 compared to Class 3	
	PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P	PR (95% CI)	P
Any STI (gonorrhoea, syphilis or chlamydia)	1.28 (0.74–2.22)	0.378	2.56 (1.63–4.03)	< 0.001	3.01 (1.92–4.73)	< 0.001	2.00 (1.42–2.82)	< 0.001	2.35 (1.67–3.31)	< 0.001	1.18 (1.03–1.35)	0.019
Gonorrhoea or chlamydia	1.24 (0.71–2.17)	0.440	2.43 (1.54–3.83)	< 0.001	2.86 (1.82–4.50)	< 0.001	1.95 (1.37–2.78)	< 0.001	2.30 (1.62–3.27)	< 0.001	1.18 (1.02–1.36)	0.025
Gonorrhoea	1.15 (0.54–2.43)	0.717	2.29 (1.25–4.18)	0.007	2.37 (1.29–4.34)	0.005	1.99 (1.21–3.27)	0.007	2.06 (1.25–3.40)	0.005	1.04 (0.82–1.31)	0.769
Chlamydia	1.12 (0.59–2.14)	0.733	2.33 (1.39–3.90)	0.001	2.76 (1.65–4.62)	< 0.001	2.08 (1.35–3.19)	0.001	2.47 (1.61–3.78)	< 0.001	1.19 (0.99–1.42)	0.063
Rectal (NG or CT)	0.93 (0.49–1.78)	0.826	1.95 (1.18–3.21)	0.009	2.51 (1.53–4.12)	< 0.001	2.09 (1.32–3.31)	0.002	2.70 (1.71–4.26)	< 0.001	1.29 (1.07–1.56)	0.008
Urethral (NG or CT)	1.24 (0.54–2.87)	0.607	2.00 (1.01–3.99)	0.048	2.16 (1.08–4.32)	0.029	1.61 (0.93–2.79)	0.088	1.74 (1.00–3.02)	0.050	1.08 (0.81–1.44)	0.607
Pharyngeal (NG or CT)	1.38 (0.48–3.96)	0.551	3.25 (1.36–7.77)	0.008	3.87 (1.62–9.26)	0.002	2.36 (1.22–4.54)	0.010	2.81 (1.46–5.41)	0.002	1.19 (0.90–1.57)	0.218
Syphilis	1.22 (0.21–7.10)	0.829	3.33 (0.82–13.61)	0.094	4.79 (1.18–19.46)	0.028	2.74 (0.86–8.76)	0.089	3.95 (1.24–12.51)	0.020	1.44 (0.92–2.24)	0.107

PR prevalence ratio

setting). Taken together, these data suggest that respondents in Class 4 may benefit from comprehensive harm reduction strategies that address both STI risk and risks arising from substance use.

Our analysis also revealed a level of anxiety towards STIs among some PrEP users. In particular, Class 3 was characterised by high levels of concern around STIs, with 73% saying they think about STIs often, in contrast with only 9% in Class 4 participants. Novel prevention strategies that reduce risk of STI acquisition risk, such as doxycycline pre- or post-exposure prophylaxis [33, 34], may be beneficial in reducing and improving both mental and physical wellbeing among some PrEP users at heightened risk of STIs. Research has shown that PrEP has been associated with large reductions in HIV-related anxiety among Australian GBM [36]. However, in the case of doxycycline prophylaxis, the potential benefit of reduced anxiety would need to be balanced against the theoretical potential harms caused by long term antibiotic use. A further distinction between Classes 3 and 4 was the frequency at which they reported discussing STI testing with their partners; 35% of Class 3 said they discussed STI testing most or all of the time, compared to only 15% of Class 4. However, overall more than three-quarters of PrEP users in our analysis reported discussing STI testing with partners at least some of the time. PrEP users who express comfort in discussing STI testing with casual partners may be good candidates for partner-centred prevention strategies, such as partner notification technologies, as well as for approaches relying on community diffusion of health promotion messages.

Biobehavioural data collected annually among GBM in Melbourne show that consistent condom use with casual partners has declined from 41% in 2016 to 22% in 2020 [37]. In our cohort of PrEP users, less than 3% of participants reported consistent condom use with casual partners in the past 6 months. Compared to GBM in Classes 4 and 2, GBM in Class 3 had a higher level of overall condom use with casual partners, with only 29% reporting never using condoms, compared to 49% in Class 4 and 46% in Class 2. Although condom use was higher among GBM in Class 3 than in Class 2, STI positivity was higher in Class 3 compared to Class 2. In contrast, GBM in Class 2 reported fewer casual partners in the past 6 months (median, 4) than those in Class 3 (median, 10). These findings reflect a previous survival analysis among the PrEPX cohort in which greater number of casual partners was independently associated with greater STI risk, whereas decreased condom use was not [9]. It is evident that selective use of condoms with casual partners is common among some GBM, with approximately half of those in Class 3 reporting using condoms some or about half of the time. Whilst acknowledging the potential complexity of health promotion messaging associated with this

finding, it is an issue worth addressing. Without diminishing the message of the importance of condom use overall, it is important to understand how to communicate that there are circumstances when condom use likely provides the greatest benefit and protection against STI risk—such as with a new partner or in a group sex setting.

Our findings that certain subgroups of GBM are at increased risk of STIs are consistent with previous research utilising LCA [16, 18]. However, while previous work has shown associations between certain characteristics and behaviours among groups of GBM and increased STI risk, this is the first LCA to our knowledge which incorporates both behaviours and attitudes towards STIs as class indicators. We believe that in the context of PrEP users, individuals' behaviours are so closely intertwined with their attitudes towards STIs, that neither can truly be said to be causing the other. Rather, behaviours and attitudes are likely driven by a single construct which we aimed to model as latent class membership. This is also the first LCA to be undertaken specifically among GBM who have been using PrEP for a considerable length of time. Attitudes among GBM may change in the context of increasing PrEP use, including through the normalisation of frequent testing and increasing STI incidence. The way in which PrEP users utilise particular STI prevention strategies will likely depend on their attitudes towards STIs. Successful targeting of strategies may need to rely not only on behavioural indicators and previous STI risk, but also on individuals' attitudes and motivation to utilise different strategies. Our findings suggest that tools used to screen patients for STI risk could be guided not only behavioural risk factors, but also by items on patients' attitudes towards STIs. Future research should aim to identify and refine which attitudinal questions are most indicative of STI risk in this population. Engaging in conversation to better understand patients' attitudes around STIs may help clinicians recommend interventions most likely to be adopted by the patient.

Limitations

There are several limitations to our analysis. First, only one quarter of participants in the PrEPX Study responded to the survey 1 year after study completion. Sensitivity analysis of characteristics of those who responded and those who did not revealed that respondents were older and less likely to report injecting drug use and methamphetamine use at enrolment. However, there was no difference in the HIV-related sexual risk criteria between groups. Second, some key behavioural variables which have been shown to be strong indicators of STI risk among GBM using PrEP, such as participation in group sex [9], were not included in the survey. Further analysis of specific sexual practices associated with STI risk among this cohort may be warranted. Third, only 78% of those included in the LCA had available STI testing data from the ACCESS surveillance system. However, missing testing data is likely due to some participants accessing their PrEP, and therefore being tested, outside of the ACCESS clinical network, rather than not being tested for STIs; all participants were still using PrEP at the time of the survey completion and 98% of participants reported being tested for STIs at their most recent PrEP clinic visit prior to survey completion. It is unlikely that attending a different clinic for STI testing is greatly influenced by STI risk. Fourth, we were only able to look at associations between class membership and risk of bacterial STIs, and not viral STIs. As the attitudinal questions included in the survey did not explicitly mention bacterial STIs, we were not able to discern any differences in attitudes towards curable bacterial STIs compared to non-curable STIs, such as human papillomavirus or herpes simplex virus. Concern towards contracting life-long viral STIs may have influenced some participants' responses. Finally, this analysis was restricted to GBM currently using PrEP and may not be generalisable to GBM not using PrEP or GBM in general. However, the issues explored in this work are particularly relevant to STI control in the era of PrEP, given rapid uptake of PrEP among Australian GBM has coincided with declines in condom use and increases in STI incidence.

Conclusions

GBM using PrEP in Australia are a priority population for bacterial STIs, however, our study shows that their beliefs and attitudes towards STIs vary considerably and this will likely influence their receptivity to different STI prevention strategies. We found that PrEP users with the highest risk of STIs reported the highest rates of injecting drug use and chemsex, suggesting that this group of PrEP users would benefit from harm reduction strategies that address both STI risk and risks resulting from drug use. A multifaceted and targeted public health response which considers and monitors how different interventions are received and adopted by PrEP users will be required to curtail the high incidence of STIs among this population.

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Author Contributions MWT lead the data analysis and manuscript preparation. MWT, EJW and MAS conceived the analysis. EJW, KR, JA and DM designed the follow-up survey. JA curated the data. EJW was the principal investigator of the PrEPX study. All authors contributed to data interpretation and have contributed to the intellectual content and preparation of the manuscript.

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Declarations

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Informed Consent Informed consent was obtained from all individuals in the PrEPX study.

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Appendix B3. Chapter 6 in *Sexually Transmitted Diseases*

Citation:

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The Potential Impact of a Gel-Based Point-of-Sex Intervention in Reducing Gonorrhea Incidence Among Gay and Bisexual Men: A Modeling Study

Michael W. Traeger, MSc,† Tom Tidhar, BSc,* Martin Holt, PhD,‡ Chris Williams,§¶ Edwina J. Wright, MBBS, PhD,*||** Mark A. Stoové, PhD,*††† Nick Scott, PhD,*† and Margaret E. Hellard, MBBS, PhD*†||*

Background: Increases in sexually transmitted infections among gay and bisexual men (GBM) over the past decade have coincided with declines in condom use and rapid uptake of HIV preexposure prophylaxis (PrEP). We explored the impact of an antimicrobial gel-based point-of-sex intervention (gel-PSI) with a lower efficacy for reducing gonorrhea transmission risk than condoms on population-level gonorrhea incidence among GBM in Victoria, Australia.

Methods: A deterministic compartmental model of HIV and gonorrhea transmission was used to project annual gonorrhea incidence from 2020 to 2025. Individuals were classified as HIV-negative (PrEP or non-PrEP users) or HIV-positive, and further stratified by gonorrhoea risk (high/low). All possible scenarios where between 0% and 100% of GBM using condoms transitioned to gel-PSI (considered a downgrade in protection) and 0% and 100% of GBM not using condoms transitioned to gel-PSI (considered an upgrade in protection), with gel-PSI efficacy ranging from 20% to 50%, were run.

Results: The baseline scenario of no gel-PSI uptake (status quo) projected 94,367 gonorrhea infections between 2020 and 2025, with an exponentially increasing trend in annual infections. For a gel-PSI efficacy of 30%, a net reduction in cumulative gonorrhea incidence was projected, relative to the status quo, for any ratio of proportion of condom users "downgrading" to proportion of noncondom users "upgrading" to gel-PSI use of less than 2.6. Under the supposition of equal proportions of condom users and noncondom users switching to gel-PSI, a relative reduction was projected for any gel-PSI efficacy greater than 16%.

Conclusions: Our model suggests that the introduction of a gel-PSI could have benefits for controlling gonorrhea transmission among GBM, even in scenarios where the gel-PSI is considerably less efficacious than condoms and when gel-PSI uptake leads to consequent reductions in consistent condom use.

Globally, gay and bisexual men (GBM) are disproportionately affected by sexually transmitted infections (STIs), with recent data showing sharp increases in gonorrhea, chlamydia, and syphilis infections in recent years among GBM in Australia, the United States, and across Europe.[1–3] Although the introduction of highly sensitive nucleic acid amplification tests and increases in testing among GBM[1,4] have likely contributed to rising STI notifications, declining condom use among GBM,[5,6] coinciding with wide-scale implementation of multiple HIV biomedical interventions, including treatment as prevention for HIV[7] and HIV preexposure prophylaxis (PrEP),[8,9] is also considered a key factor driving increased STI transmission risk.

Mathematical modeling has suggested that the high frequency of STI testing associated with PrEP uptake among GBM may help reduce STI incidence in the years after PrEP implementation.[10] However, there is little real-world evidence showing reduced STI incidence as a result of increased STI testing frequency among PrEP users, and findings from a recent modeling study of various testing scenarios on syphilis epidemiology suggest that despite having overall benefits, increased testing due to PrEP implementation alone is unlikely to reverse the background trend of increasing syphilis transmission.[11]

In contrast to efforts to increase testing, interventions used at the time of sex may offer a more affordable and acceptable method of STI prevention for GBM, and be more effective in preventing transmission. Various point-of-sex interventions aimed at reducing STI transmission risk have been suggested, such as antimicrobial lubricants, rectal gels, and creams.[12–14] Microbicidal products to prevent HIV transmission have also been explored; however, there has been limited success in developing a highly efficacious product,[15] and there are limited data on efficacy of microbicidal interventions on STI transmission. In addition, acceptability and willingness to use antimicrobial products vary among GBM, depending on availability, effectiveness, cost, and perceived risk.[12,16,17]

Antimicrobial gel-based products may not reduce the risk of STI transmission as much as condoms, but even a product used during sex with modest efficacy would provide individual-level

From the *Burnet Institute; †School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria; ‡Centre for Social Research in Health, University of New South Wales, Sydney; §PrEP'D for Change; ¶Thorne Harbour Health; ||Department of Infectious Diseases, Alfred Health and Monash University; **Peter Doherty Institute, University of Melbourne; and ††School of Psychology and Public Health, La Trobe University, Melbourne, Victoria, Australia

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Correspondence: Michael W. Traeger, MSc, 85 Commercial Rd, Melbourne, Victoria 3004, Australia. E-mail: michael.traeger@burnet.edu.au.

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benefits for GBM who are currently not using condoms or using them infrequently. However, the population-level impact of a partially effective, point-of-sex intervention on STI transmission will be influenced by a number of factors, including product efficacy and acceptability. Another important consideration is how risk reduction practices used by GBM may alter with the availability of a new product that is less effective at preventing STIs but has less of an impact on sexual pleasure compared with condoms. Importantly, reductions in STI transmission resulting from uptake of such an intervention by some GBM may be counteracted by increases in STI risk among GBM who transition from using condoms to using the less effective product. In other words, GBM who transition from no condom use to using the new intervention will experience an "upgrade" in protection from STI acquisition, whereas GBM who transition from condom use to using the new intervention will experience a "downgrade" in protection. Alongside product effectiveness, the population-level benefits of such a product are dependent on the level of uptake among GBM who do and do not engage in more efficacious STI prevention strategies.

Given concerns around increasing gonorrhea incidence among Australian GBM,[18] including in the context of the rapid uptake of PrEP,[19] we used a mathematical model of HIV and gonorrhea transmission among GBM in the state of Victoria to evaluate the population-level effectiveness of differential uptake of a new antimicrobial gel-based point-of-sex intervention (gel-PSI) in reducing gonorrhea incidence among GBM. We estimated the threshold of uptake among noncondom users and condom users required for an overall reduction in gonorrhea incidence based on varying hypothetical levels of product efficacy.

METHODS

We used a population-level, deterministic, compartmental model of HIV and gonorrhea transmission among GBM in Victoria, Australia (Fig. 1). The model used a series of ordinary differential equations representing compartment transition rates; individual sex acts were not explicitly modeled. Estimates and

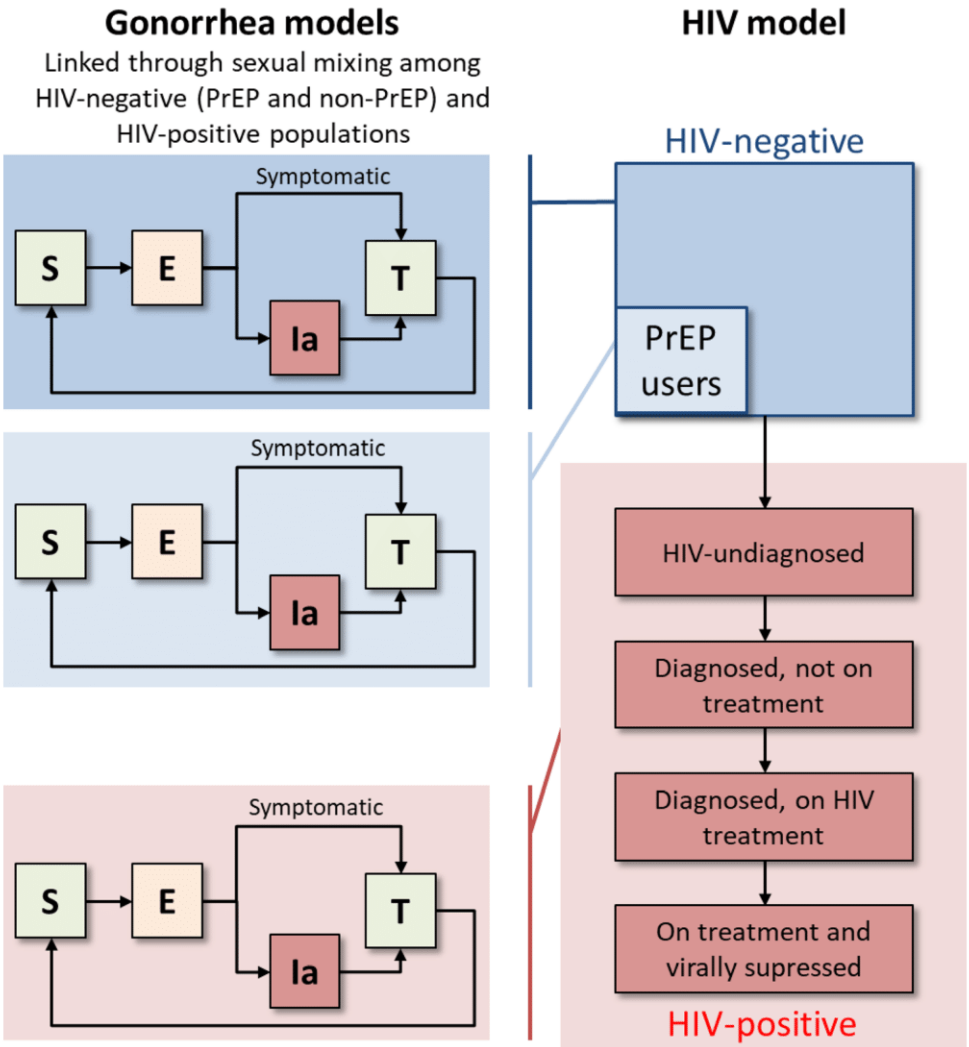

Figure 1. Model schematic. An HIV transmission and care cascade progression model was coupled with a gonorrhea model for 3 subpopulations of GBM: HIV-positive, HIV-negative not using PrEP, and HIV-negative using PrEP. The gonorrhea models are linked through sexual mixing among the 3 subpopulations. Gonorrhea model compartments represent susceptible (S), exposed (E), infected and asymptomatic (Ia), and treatment (T; GBM with symptomatic gonorrhea were model to commence treatment immediately). Each subpopulation was further stratified so that a fraction was at higher risk of gonorrhea (not shown).

sources for model parameters described hereinafter are provided in Table 1. Analysis was conducted using R (version 3.5).

HIV Model Dynamics

The model population was classified into 3 subpopulations; HIV-negative GBM using PrEP, HIV-negative GBM not using PrEP, and HIV-positive GBM. HIV-positive individuals were stratified by current stage in the HIV care cascade (undiagnosed, diagnosed but not on treatment, on HIV treatment and not virally suppressed, or on HIV treatment and virally suppressed) and were able to progress through the cascade. During each time step, HIV-negative individuals seroconverted to HIV-positive, moving to the HIV-positive undiagnosed compartment, at a rate dependent on (1) average condom use in the population, (2) PrEP coverage among HIV-negative individuals, (3) the dynamic prevalence of HIV in the model (weighted to account for a removal of infectiousness among HIV-positive people who were virally suppressed), and (4) a force of infection constant that was used to fit the model to observed HIV notification data over time in Victoria. Calibration parameters, such as the force of infection constant above, are used in population-level models to fit to data without explicitly modeling individual behaviors, which influence transmission risk, such as rate of partner change and sexual positioning, for which data are limited.

Gonorrhea Model Dynamics

A gonorrhea model was included for each HIV subpopulation (Fig. 1). The gonorrhea models classified individuals as being susceptible (S), exposed (E), infected and asymptomatic (Ia), or undergoing treatment (T). Gay and bisexual men with symptomatic gonorrhea were assumed to commence treatment immediately. In the model, susceptible individuals could become infected with gonorrhea at a rate that was dependent on (1) average condom use in the subpopulation, (2) the dynamic gonorrhea prevalence among each of the subpopulations and their level of sexual mixing between subpopulations, and (3) a force of infection constant that was used to fit the model to observed gonorrhea notification data among HIV-negative (PrEP and non-PrEP users combined) and HIV-positive GBM over time in Victoria. Individuals who became infected with gonorrhea moved from susceptible (S) to exposed (E), and after an incubatory period of 5 days, a proportion became symptomatic and were assumed to commence gonorrhea treatment (T), whereas the remaining proportion became infected and asymptomatic (Ia). Individuals in the exposed or asymptomatic gonorrhea infection stages were only treated after a test (testing rates described hereinafter). After gonorrhea treatment, individuals returned to the susceptible compartment after 7 days, the recommended period of abstinence after receiving treatment. To capture heterogeneous levels of risk among the GBM population, each gonorrhea model (i.e., among the subpopulations HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive) included a stratification for gonorrhea infection risk (high risk vs. low risk for gonorrhea infection).

Model Parameters

Annual Victorian GBM population size, PrEP coverage, and HIV prevalence were estimated using Australian notification and surveillance data (Supplementary Methods 1, http://links.lww.com/OLQ/A523). For each subpopulation (HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive), gonorrhea testing rate was modeled as a constant parameter, estimated using surveillance data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-borne Viruses

TABLE 1. Model Parameters

Parameter	Value	Reference/Comment
HIV parameters		
Effectiveness of latex condoms at preventing HIV	91%	Estimated condom effectiveness during anal sex between men in 2 prospective cohort studies [S1]
Effectiveness of latex condoms at preventing gonorrhea	75%	Conservative estimate (Supplementary Methods 4, http://links.lww.com/OLQ/A523)
Effectiveness of PrEP at preventing HIV transmission	99%	US CDC PrEP effectiveness estimate [S2]
Reduction in HIV infectiousness when on treatment	100%	Reduction in HIV transmission from Opposites Attract study [S3]
Gonorrhea parameters		
Duration of exposed stage for symptomatic individuals	5 d	[S4]
Duration of treatment	7 d	Australian STI guidelines recommend abstaining from sex for 7 d after treatment [S5]
Proportion of GBM with gonorrhea who are symptomatic	29%	Calculated from ACCESS study data. Proportion diagnosed with either rectal infection only or including urethral infection, and corresponding probabilities of being symptomatic (Supplementary Methods 4, http://links.lww.com/OLQ/A523)
Increased gonorrhea risk for high-risk GBM	7.5	Estimated from the PrEPX study [S6] (Supplementary Methods 6, http://links.lww.com/OLQ/A523)
Proportion of GBM at high risk of gonorrhea	13%	
Gonorrhea testing frequency		
HIV-negative GBM on PrEP	1/90 d	Australian PrEP guidelines recommend quarterly testing [S7]
HIV-negative GBM not on PrEP	1/224 d	Previous analysis of Victorian GBM in ACCESS data [S8]
HIV-positive GBM	1/133 d	Previous analysis of Victorian GBM in ACCESS data [S8]
Sexual risk parameters		
Proportion of sex acts that are HIV serodiscordant (HIV-negative non-PrEP users)	10%	Estimated from large cross-sectional survey of GBM [S9]
Proportion of sex acts that are HIV serodiscordant (HIV-negative PrEP users)	17%	
Proportion of sex acts that are HIV serodiscordant (HIV-positive GBM)	34%	
Relative condom use of GBM on PrEP and HIV-positive GBM compared with HIV-negative GBM not on PrEP	0.3	Estimated from Melbourne Gay Community Period Survey 2019 [S10]

and Sexually Transmitted Infections (ACCESS) surveillance project (Supplementary Methods 2, http://links.lww.com/OLQ/A523). Condom use was included as a time-varying parameter for each subpopulation, reflecting average condom use in that population, and was estimated using Victorian biobehavioral surveillance data (Supplementary Methods 3, http://links.lww.com/OLQ/A523). Condom effectiveness, gonorrhea symptomatic rate, and sexual mixing were estimated from the literature (Supplementary Methods 4, http://links.lww.com/OLQ/A523) and the proportion of individuals across each subpopulation classified as "high risk" for gonorrhea and the relative increase in gonorrhea acquisition risk were calculated from previously reported STI data from GBM enrolled in a Victorian PrEP study (Supplementary Methods 5, http://links.lww.com/OLQ/A523).

Model Calibration

The force of infection constant for HIV and the diagnosis rate for HIV in the model were calibrated to best-fit time-series data for the estimated number of HIV-positive GBM in Victoria and Victorian HIV notifications attributed to male-to-male sex. Among people diagnosed with HIV, the proportion who were on treatment and the proportion who were virally suppressed in the model were fitted to time series data from Victoria (Supplementary Table 2, http://links.lww.com/OLQ/A523). For all forward projections, the HIV care cascade was modeled to continue to follow Australian trends toward achieving and maintaining 95% of people living with HIV diagnosed, 95% of people diagnosed started on treatment, and 95% of people on treatment virally suppressed by 2030 (Supplementary Fig. 1, http://links.lww.com/OLQ/A523).

Once the HIV model was calibrated, the force of infection constants for gonorrhea among HIV-negative and HIV-positive GBM was calibrated to best-fit time-series data for gonorrhea notifications (Supplementary Table 4, http://links.lww.com/OLQ/A523). Both the HIV and gonorrhea models were calibrated by minimizing the sum of squares between the model and data using the Nelder-Mead method. A sensitivity analysis was conducted in which the gonorrhea force of infection was held constant from 2018 onward, rather than dynamic and dependent on gonorrhea prevalence, to test the impact of gel-PSI if background exponential growth trends in gonorrhea incidence became more linear in the projected years.

Introduction of a Gel-PSI and Model Outcomes

Uptake Threshold Ratios for Net Benefit

The main model outcome was cumulative gonorrhea incidence between 2020 and 2025 (inclusive). Each subpopulation (HIV-positive PrEP, HIV-negative PrEP, and HIV-negative non-PrEP) consisted of GBM whose primary method of gonorrhea prevention was no STI prevention, using condoms, or using the gel-PSI. As the coverage of different prevention methods changed among each subpopulation, this was modeled to scale the force of infection according to an effectiveness-weighted prevention factor (i.e., the sum of prevention methods of coverage multiplied by their effectiveness).

First, differential levels of gel-PSI uptake by current condom use were explored, with no differential uptake by HIV or PrEP status. Scenarios were run where between 0% and 100% of GBM currently using no prevention (across HIV-positive PrEP, HIV-negative PrEP, and HIV-negative non-PrEP) upgraded to gel-PSI and 0% and 100% of GBM using condoms downgraded to gel-PSI. These changes were implemented to be phased in over a 2-year period (2020–2022) and held constant out to 2025. The threshold ratio of percentage "downgrading" (from condoms to gel-PSI) to "upgrading" (from no prevention to gel-PSI) for a net reduction in cumulative gonorrhea incidence from 2020 to 2025 was calculated. This was repeated for theoretical levels of gel-PSI effectiveness for preventing gonorrhea of 20%, 30%, 40%, or 50%. In all of these scenarios, the effectiveness of the gel-PSI was assumed to be lower than the effectiveness of condoms in reducing gonorrhea transmission risk.

Differential Uptake Among Subpopulations

Several specific scenarios of gel-PSI uptake were then explored with differential uptake across the 3 subpopulations (HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive) and across those already using or not using condoms before gel-PSI introduction. In these scenarios, we used a gel-PSI efficacy of 30% for reducing gonorrhea transmission-risk.

- Scenario a: use of the gel-PSI increased to a threshold of 50% of each subpopulation (HIV-positive, HIV-negative not on PrEP, HIV-negative on PrEP), with only those not using condoms upgrading to gel-PSI and condom users remaining as condom users
- Scenario b: 50% of condom users downgrade to gel-PSI and 50% of noncondom users upgrade to gel-PSI
- Scenario c: all condoms users across each subpopulation downgrade to gel-PSI
- Scenario d: all PrEP users (condom and noncondom users) switch to gel-PSI

Given that the uptake of the gel-PSI among individuals at risk of HIV (HIV-negative not on PrEP) would likely depend on the gel-PSI's effectiveness at also reducing HIV, we then explored scenarios with differential levels of uptake between those at risk of HIV (HIV-negative not on PrEP) and those not at risk of HIV (HIV-negative on PrEP and HIV-positive):

- Scenario e: 50% of PrEP users and HIV-positive GBM (both condom users and noncondom users) switch to gel-PSI, whereas non-PrEP users have no gel-PSI uptake.
- Scenario f: 50% of GBM not on PrEP (condom users and noncondom users) switch to gel-PSI, whereas PrEP users and HIV-positive GBM have no gel-PSI uptake.

We report the net absolute difference and relative difference in cumulative gonorrhea infections from 2020 to 2025 (inclusive) between each scenario and the baseline scenario of no gel-PSI uptake (status quo).

Sensitivity Analyses

Sensitivity analyses were run to examine the influence of key assumptions in model parameters. Using scenario b (50% upgrade and 50% downgrade in STI prevention among noncondom users and condom users, respectively, and a gel-PSI efficacy of 30%), we explored the effect of varying the following parameters on cumulative gonorrhea incidence from 2020 to 2025 and the relative reduction between scenario b and no gel-PSI uptake: the effectiveness of condoms at reducing gonorrhea transmission risk from 75% to 50% and 100%; sexual mixing by changing the proportion of serodiscordant sex acts to 0% (complete serosorting), 50% of sex acts serodiscordant and mixing at random (no serosorting); increasing PrEP uptake post-2020 to reach 50% and 75% of HIV-negative GBM by 2025; proportion of gonorrhea

cases (any anatomical site), which were symptomatic from 45% to 25% and 75%; increased risk factor for the high risk for the gonorrhea group from 7.5 to 2, 10, and 20; condom use among HIV-negative GBM from the remaining stable at 29% to 2025 to reducing to 15% and 5% by 2025 (with condom use among PrEP users and HIV-positive GBM 0.3 times that of non-PrEP users); and increased gonorrhea testing rates among non-PrEP users by reducing mean number of days between tests by 25% and 50% by 2025.

RESULTS

Projected Gonorrhea Notifications to 2025

Calibration of the gonorrhea model to notification data was fairly accurate among both HIV-negative and HIV-positive populations (Fig. 2; see Supplementary Fig. 2, http://links.lww.com/OLQ/A523 for calibration of the HIV model to HIV notification data). In the baseline scenario of no gel-PSI uptake (status quo), projected annual gonorrhea incidence increased exponentially, reaching approximately 23,848 infections among Victorian GBM in the year 2025 (Fig. 3) equating to a cumulative incidence of 94,367 gonorrhea infections from 2020 to 2025. Supplementary Figure 3, http://links.lww.com/OLQ/A523 shows projected annual incidence attributable to each subpopulation (HIV-positive PrEP, HIV negative on PrEP, and HIV negative not on PrEP).

Prevention Upgrade and Downgrade Thresholds

After the introduction of a gel-PSI with an efficacy of 30%, compared with the baseline scenario of no gel uptake among the population, a relative reduction in cumulative gonorrhea incidence from 2020 to 2025 was observed for any ratio of proportion of condom users downgrading to proportion of noncondom users upgrading to gel-PSI use of less than 2.6 (Fig. 4). For example, if 50% of condom users downgraded to gel-PSI, provided that at least 20% of noncondom users upgraded, a relative reduction in gonorrhea incidence was observed for a gel efficacy of 30%. If 50% of condom users downgraded to gel-PSI under a gel efficacy of 50%, a net benefit was observed provided at least 7% on noncondom users upgraded, with the threshold ratio of proportion of condom users downgrading to proportion of noncondom users upgrading to gel-PSI use equal to 7.4 (Fig. 4). If the proportion of condom users downgrading to gel-PSI was equal to the proportion of noncondom users upgrading to gel-PSI, a net reduction in gonorrhea notifications was projected for a gel-PSI with efficacy of 16% or higher.

Intervention Uptake Scenarios

Change in cumulative gonorrhea incidence across each scenario relative to the baseline scenario of no gel-PSI uptake is shown in Table 2. All but one scenario (scenario c, only condom users downgrading to gel-PSI) projected a relative reduction in cumulative gonorrhea incidence from 2020 to 2025 (Fig. 4). All scenarios project an increasing trend in annual gonorrhea incidence among GBM to 2025 and beyond.

Sensitivity Analyses

Having a constant force of infection from 2018 onward led to a moderate reduction in both the cumulative gonorrhea incidence and relative reductions after gel-PSI uptake scenarios (Supplementary Fig. 5, http://links.lww.com/OLQ/A523); however, benefits were still observed across most scenarios (Supplementary Table 5, http://links.lww.com/OLQ/A523). Altering the specified model parameters moderately affected the cumulative gonorrhea incidence projected to 2025 (Supplementary Fig. 6, http://links.lww.com/OLQ/A523); however, altering these parameters only had small effects on the relative impact of the gel-PSI intervention (under scenario b; 50% uptake among condom users and 50% uptake among noncondom users, assuming a gel-PSI efficacy of 30%; Supplementary Fig. 7, hhttp://links.lww.com/OLQ/A523). All sensitivity scenarios returned a relative reduction in cumulative gonorrhea incidence from 2020 to 2025 of between 19%

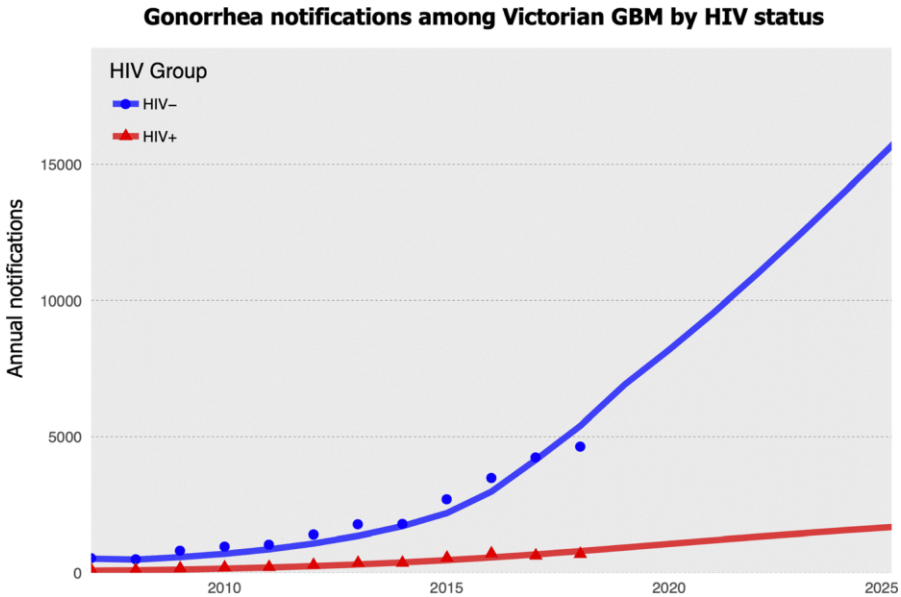

Figure 2. Annual gonorrhea notifications among GBM in Victoria (dots) versus calibrated model projections (lines) for HIV-negative (blue) and HIV-positive (red) GBM.

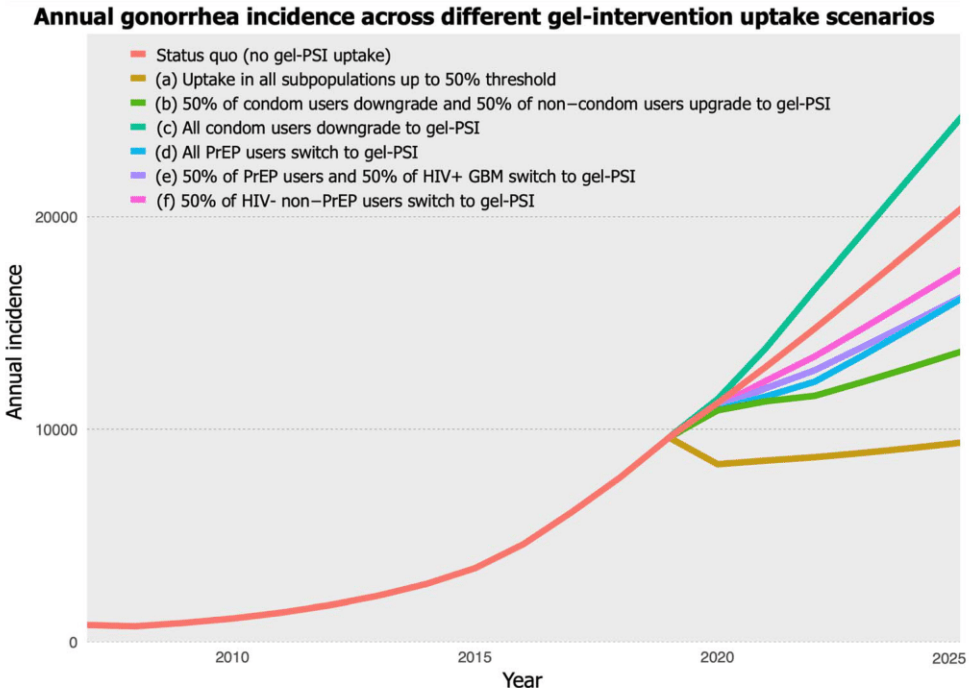

Figure 3. Projected annual gonorrhea incidence among Victorian GBM from 2007 to 2025 for different model scenarios of uptake of a gel-PSI according to HIV status, PrEP use, and condom use.

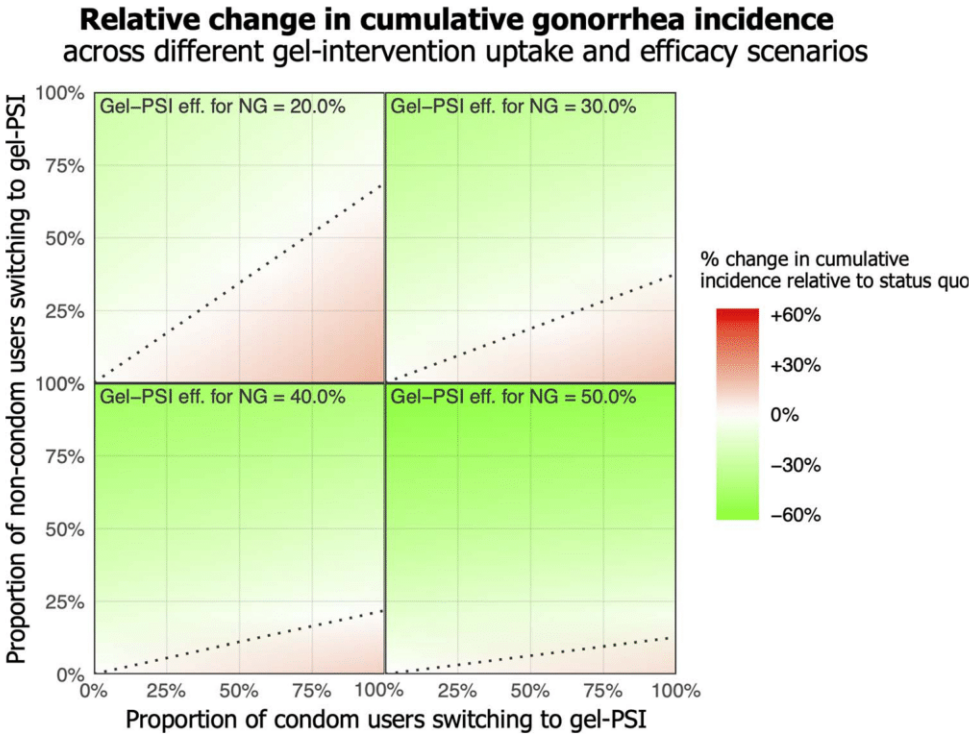

Figure 4. Population-level impact of gel-based intervention according to gel efficacy, intervention uptake among noncondom users, and intervention uptake among condom users. Compared with the status-quo scenario of no gel-PSI, heat maps show the difference in cumulative gonorrhea incidence from 2020 to 2025 among GBM in Victoria according to the proportion of condom users who "downgrade" to gel prevention (*x* axes), the proportion of noncondom users who "upgrade" to gel prevention (*y* axes), and the effectiveness of the intervention for reducing gonorrhea transmission (panels for 20%, 30%, 40%, or 50% efficacy). Green and red shadings represent positive and negative population-level benefits, respectively, with the dotted line representing zero net effect on cumulative gonorrhea incidence.

TABLE 2. Cumulative Gonorrhea Incidence Among Victorian GBM From 2020 to 2025 Across Different Model Scenarios of Uptake of a Gel-PSI According to HIV Status, PrEP Use, and Condom Use

	Scenario	Cumulative Incidence 2020–2025	Difference in Cumulative Incidence to Status Quo	Relative Reduction in Cumulative Incidence, %
	Status quo (no gel-PSI uptake)	94,367		
a	Uptake in all subpopulations up to 50% threshold*	52,988	−41,379	−44
b	50% of condom users downgrade and 50% of noncondom users upgrade	72,559	−21,808	−23
c	All condom users downgrade to gel-PSI	107,720	13,353	14
d	All PrEP users switch to gel-PSI	79,081	−15,286	−16
e	50% of PrEP users and HIV-positive GBM switch to gel-PSI	80,860	−13,507	−14
f	50% of non-PrEP users switch to gel-PSI	85,203	−9164	−10

*Fifty percent of each population upgrade to using the gel-PSI, assuming no change to those already using condoms.

and 28% compared with no gel-PSI uptake (Supplementary Table 6, http://links.lww.com/OLQ/A523).

DISCUSSION

Our model demonstrated that the introduction of a hypothetical gel-PSI, which is less efficacious than latex condoms in reducing gonorrhea acquisition risk per sex act, led to a population-level decrease in gonorrhea incidence among GBM relative to the status quo in most uptake scenarios. Intuitively, greater reductions in gonorrhea incidence were projected with greater uptake of the intervention among those not already using condoms.

The rate of uptake of such a point-of-sex intervention among GBM already using and not using condoms will depend on a range of factors including efficacy, product availability, acceptability, cost, safety, and effect on sexual pleasure. The proportion of HIV-negative GBM not using PrEP who would transition from using condoms to using the gel-PSI would also likely depend on the product's efficacy in reducing HIV transmission risk and gonorrhea risk. However, among HIV-negative GBM on PrEP and HIV-positive GBM, reduction in HIV transmission risk would not have a substantial impact on the likelihood of uptake, given the negligible risk of HIV acquisition or transmission in these groups.

A key factor in determining the impact of the gel-based intervention is estimating the negative effects of reduced condom use among GBM who switch to the lower-efficacy gel-based intervention. In our model, we explored this trade-off in protection and found that, in most scenarios, it was outweighed by the benefits of noncondom users upgrading to gel-based prevention. In scenarios where all condom users downgraded to using the less-efficacious gel-based intervention, even with an intervention that reduces gonorrhea transmission risk per sex act by only 50%, net benefits were observed provided 12% or more of noncondom users started using the gel-PSI.

The likelihood of overall benefits is further enhanced by the different risk profiles of condom users who may downgrade to gel-based prevention compared with noncondom users who may upgrade to gel-based prevention. Given the risk-based eligibility criteria for PrEP in Australia[20] and the estimated high level of PrEP coverage among those eligible for PrEP,[21,22] it is reasonable to suggest that HIV-negative GBM not using PrEP are a population at reduced risk of gonorrhea infection. Therefore, reductions in condom use among this population will likely have a modest effect on gonorrhea transmission when compared with the beneficial effects of uptake of the gel intervention among PrEP users. It is also reasonable to suggest that an intervention with minimal effect on sexual pleasure would have a high uptake among those who do not use condoms, as reduced sexual pleasure is a well-established barrier to condom use among GBM.[23] In considering these factors, our model suggests that in the Australian context, a new intervention with minimal impact on sexual pleasure would likely lead to a net reduction in gonorrhea incidence among GBM.

Although we did not explicitly model sexual network dynamics in our study, it is likely that the population-level impact of a new point-of-sex intervention would be maximized through high uptake among sexual networks of high STI transmission. Recent data from Victoria show that STIs among PrEP users are highly concentrated among GBM experiencing repeat infections, and that increased partner numbers and participation in group sex are associated with increased STI risk in the context of PrEP, suggesting that networks of high STI transmission exist within populations of PrEP users.[19] Interventions targeted toward a relatively small proportion of GBM at increased risk of STIs could have a substantial impact on interrupting STI transmission.

Despite previous research showing the high acceptability of hypothetical antimicrobial products among GBM,[17,24] early research showing the potential for such products in reducing STI acquisition risk,[25] and our findings that antimicrobial products with low efficacies could still be beneficial at the population level, there remain no such products with regulatory approval or commercial availability in any country. A barrier to the promotion and uptake of such products is the potential for antimicrobial resistance, a growing concern for gonorrhea. More recent qualitative research reports that, although some GBM show interest in antimicrobial interventions, including the use of antibiotics for STI prophylaxis, many have concerns around the potential for antimicrobial resistance and adverse health effects and show hesitance toward the widespread use of antibiotics for such purposes.[26] Although such attitudes may hinder community-level uptake of a gel-based antimicrobial intervention, our projections suggest that even relatively low levels of uptake may have population-level benefits. To offset the potential threat posed by increased antibiotic resistance after uptake, it would be important to couple the antimicrobial-based intervention with regular screening and comprehensive resistance testing. In addition, further research would be required to asses any adverse effects of the regular use of microbicides on the rectal microbiome.

Despite the introduction of the gel-PSI leading to a net reduction in gonorrhea incidence in most scenarios, almost all scenarios projected an increasing trend in gonorrhea incidence to the year 2025 and beyond. These findings highlight that even with a fairly efficacious product and reasonable uptake among the GBM population, a point-of-sex intervention that reduces gonorrhea acquisition risk will likely not be enough to curtail the rise in incidence of gonorrhea. A combination of preventive measures,

including high rates of asymptomatic screening and a gonorrhea vaccine, will likely be required to reverse the trend of increasing gonorrhea transmission. Although we have explored a hypothetical gel-based product, many interventions could be used to partially reduce the risk of gonorrhea transmission. The implications of our findings could be applicable to other novel prevention strategies, such as using mouthwash before or after oral sex to reduce risk of pharyngeal gonorrhea,[27] microbicidal rectal enemas used before or after receptive sex, or antibiotic preexposure or postexposure prophylaxis for the prevention of STIs.[28,29] Furthermore, an antimicrobial intervention would likely have concurrent benefits for other infections not explored in this model, such as chlamydia and syphilis.

There are several limitations to our analysis. First, we did not model anatomical site-specific gonorrhea transmission. Recent evidence suggests that oral transmission of gonorrhea may account for a large proportion of new infections,[30] and this would not have been captured in our model. Second, although we were able to add parameters for sexual mixing between populations, these were based on behavioral surveys conducted among a select sample of GBM, and data were aggregated rather than event level. The lack of setting-specific, individual-level sexual partnership data precluded accurate estimates of sexual mixing patterns between subpopulations of GBM, including mixing based on HIV status, PrEP status, and STI risk. Furthermore, it is possible that after the introduction of such a product, sexual networks may change as individuals' use of the product may influence partner selection. However, altering our sexual mixing parameters in sensitivity analysis had little effect on model projections. Third, we were not able to incorporate more complex network dynamics, such as heterogeneity in partner turnover across groups of GBM, differentiation of casual and regular partnerships, or overlap of concurrent partnerships, all of which would have important implications for gonorrhea transmission. Fourth, although our model projects an exponentially increasing annual incidence of gonorrhea among the population, it is important to note that this is in the scenario of no other interventions being introduced or additional behavior changes in response to increasing transmissions. In reality, it is likely that some other limiting factor or factors would curtail the exponential growth in gonorrhea incidence. Finally, there is also uncertainty associated with recency and representativeness of data and parameter estimates; however, sensitivity analyses indicated that these were unlikely to alter our main conclusions.

Our study shows that interventions used at the point-of-sex that may only have a modest effect in reducing individual STI acquisition risk, such as gel-based antimicrobial lubricant, are likely to provide population-level benefits among GBM. Commercial development and regulatory approval of these products should be expedited. Despite potential benefits, such interventions are alone unlikely to reverse the increasing trend of increasing STIs, and additional interventions will be required.

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Appendix B4. Chapter 8 in *Sexual Health*

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SEXUAL HEALTH

Why risk matters for STI control: who are those at greatest risk and how are they identified?

Michael Traeger[A,B,*] and Mark Stoové[A,B]

For full list of author affiliations and declarations see end of paper

***Correspondence to:**
Michael Traeger
Burnet Institute, 85 Commercial Road, Melbourne, Vic. 3004, Australia
Email: michael.traeger@burnet.edu.au

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ABSTRACT

Identifying groups most at risk of sexually transmissible infections (STIs) is important for prioritising screening, targeting prevention strategies and alleviating the burden of STIs. However, identifying those at risk of STIs is complicated by stigma associated with STIs, undisclosed risk behaviour, and the fact that STI epidemics are diversifying beyond traditional risk groups typically characterised by demographics and sexual behaviours alone. In this review, we describe the epidemiology of STIs among traditional and emerging risk groups, particularly in the context of uptake of HIV pre-exposure prophylaxis (PrEP), increasing STI transmission among heterosexual people, and the concentration of STI burden among specific subgroups not readily identifiable by health services. Risk diversification poses significant challenges, not only for risk-based testing, but also for the costs and resources required to reach a broader range of constituents with preventive and health promotion interventions. As drivers of STI risk are not purely behavioural, but relate to relative STI prevalence within sexual networks and access to sexual health care and testing, localised surveillance and research is important in ensuring risk is appropriately understood and addressed within local contexts. Here, we review the evidence on the benefits and harms of risk-guided versus population-based screening for STIs among key populations, discuss the importance of risk-guided interventions in the control of STIs, and explore contemporary approaches to risk determination.

Keywords: chlamydia, gonorrhoea, risk assessment, risk populations, screening, sexual health, STIs, syphilis.

Introduction

There are an estimated 374 million new infections of curable sexually transmissible infections (STIs), such as chlamydia, gonorrhoea, syphilis and trichomoniasis, annually.[1] If left untreated, these infections can lead to serious sequelae, including pelvic inflammatory disease (PID), infertility, increased risk of HIV acquisition and, in pregnancy, neonatal death. With the majority of acute bacterial STIs being asymptomatic, identifying groups most at risk of infection is important for prioritising screening, targeting prevention strategies and alleviating the burden of STIs. Not adequately identifying people at high risk of STIs can limit the effectiveness of preventive interventions and lead to unnecessary testing and health-systems costs. Identifying those at risk of STIs risk is also complicated by the stigma associated with STIs and associated behaviours that limit individuals' disclosure of information about risk practices. Risk-based STI testing guidelines have traditionally centred on grouping people according to demographics and behaviours that have been identified in research and clinical practice as being associated with greater likelihood of STI diagnosis. However, the periodic emergence of STI epidemics among non-traditional risk populations, and the clustering of STIs in behaviourally specific subgroups within traditional risk populations, complicates the delivery of preventive interventions and care.

In this review, we describe the epidemiology of STIs among traditional and emerging risk groups, and explore contemporary approaches to risk determination. We review the evidence on the benefits and harms of risk-guided versus population-based screening for

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STIs among key populations, describe novel methods to identify risk, and discuss the importance of risk-guided interventions in the control of STIs.

Traditional and emerging risk populations

The burden of STIs has historically been concentrated among what are typically referred to as 'key populations'. The World Health Organization's (WHO) global health sector strategy on STIs suggests that each country needs to 'define the specific populations that are most affected by STI epidemics' and that their response should be 'based on epidemiological and social context'.[1] These key populations are broadly categorised based on demographics such as gender and age, and specific sexual behaviours, such as number and gender of sexual partners. Specific populations that are highlighted in WHO guidance include adolescents and young people, men who have sex with men (MSM), transgender people, sex workers, and people who use drugs.

Adolescents

Although young people and adolescents have been long recognised as a priority population for STIs,[2] targeted approaches are challenged by the fact they represent a substantial percentage of the general population and a behaviourally heterogeneous group. An analysis of data from the Global Burden of Diseases study found that adolescents have a higher STI burden than other age groups, and although overall the age-standardised incidence rate of STIs is trending down globally, the actual number of incident infections is increasing, likely due to the growth in the sexually active population and an increasing number of infections in adolescents.[3] Although there are biological factors which increase risk (e.g. young females can be more susceptible to chlamydia and HPV due to lower production of cervical mucous and increased cervical ectopy[4]), key drivers of risk among young people and adolescents include simultaneously being more likely to engage in sexual risk behaviour (e.g. concurrent partners and condomless sex)[2] and less likely to access sexual health services.[5] Low rates of seeking sexual health care among adolescents are likely, in part, to be associated with concerns about confidentiality and discomfort in discussing sexual health concerns, as well as lack of knowledge about available services.[6] Typically lower rates of general health-seeking behaviours among males drive lower rates of STI screening in general practice,[7] with testing among heterosexual males more likely to be driven by symptomatic presentation or partner notification.[8]

Trends in STI diagnoses among young people are dynamic and fluctuate across many settings. A recent analysis of data from the US found that among the youngest group, those aged 12–17 years, chlamydia and gonorrhoea positivity decreased, whereas it increased for the other age groups.[9] Insights garnered from behavioural epidemiology data can be used to understand such changes and also guide priorities for risk-based screening and other interventions. In this study, the authors suggest decreasing positivity among those aged 12–17 years may be associated with a declining proportion of high school students who report ever having sex, having fallen from 47.4% in 2011 to 39.5% in 2017.[10] In contrast, repeated behavioural surveillance of high school students in Australia found the proportion of students reporting ever having penetrative sex increased from 34.7% in 2002 to 46.6% in 2018.[11] As routine presentation to primary care remains the main access point to the healthcare system for many young people, opportunistic STI screening relies on clinicians being comfortable asking young people about sex and sexual risk, and creating 'safe' clinical environments where young people feel comfortable discussing and disclosing information about sexual practices.

Heterosexuals

Although MSM in high-income countries carry a significant burden of STIs, there is evidence that prevalence of STIs is increasing among heterosexual populations. For example, although gonorrhoea has been historically concentrated among MSM in Australia,[12] there has been a 475% increase in gonorrhoea notifications among females in the state of Victoria, Australia, from 2010 to 2019.[13,14] Similarly, whereas syphilis diagnoses in Australia remains concentrated among MSM residing in inner urban locations, syphilis is increasing in heterosexual men and women in Australia, especially those residing outside of inner-city suburbs.[15] Although the reasons for STI increases among heterosexuals in outer-suburbs are not fully understood, they may be reflective of less access of sexual health services.[14] Australian HIV surveillance data shows that, for HIV, women are often diagnosed late and report no prior history of HIV testing.[16] Genomic analyses also suggest that transmission of gonorrhoea into heterosexual populations may be facilitated through the bridging of sexual networks via populations of men who have sex with men and women.[17]

Further, although the burden of STIs among young heterosexuals has been well described, more evidence is coming to light of emergent STI epidemics among older heterosexual populations. In the US, the Centers for Disease Control and Prevention (CDC) reports a doubling of STIs among those aged >65 over the last 10 years.[18] Reasons for increasing STI rates among older populations may relate to lower levels of sexual health knowledge[19] and inaccurate risk perception[20] among older generations.

Men who have sex with men

Although STI epidemics may be diversifying beyond traditional risk groups, STI burden remains clustered within networks of people who may share specific risk practices

with high rates of assortative partner mixing. MSM are at increased risk of STIs due to a combination of biological and behavioural factors (e.g. more partners, more concurrent partners, type of partners) and the relative prevalence of STIs within sexual networks that contributes transmission risk. Although MSM are recognised as a priority group for STIs globally, the population of MSM comprises a diverse group, with different behaviours, identities and healthcare needs, and consequently risk varies across specific subgroups. For example, MSM living with HIV have historically had higher rates of STIs such as syphilis[21] and sexually acquired hepatitis C,[22] likely associated with smaller sexual networks with high rates of partner mixing, which sustain high prevalence and onward transmission. Given the often differing prevalence of STIs between HIV-negative MSM and MSM living with HIV, and specific sexual network dynamics, behavioural and demographic predictors of STI risk often vary between the two groups.[23] Further, rates of specific STIs within risk populations often vary based on age. For example, among MSM in Australia, gonorrhoea is more common among those aged 20–29 years compared to syphilis, which is most common among those aged 30–39 years.[24]

The concentration of STI risk among subgroups of MSM is also diversifying. Advances in biomedical interventions for HIV over the past decade, including Treatment as Prevention (TasP) and pre-exposure prophylaxis (PrEP), have led to changes in behaviour and STI epidemiology among MSM. Although declines in condom use at the population[25,26] and individual level[27–29] associated with the roll-out of PrEP in high-income countries have occurred in parallel to increases in STI incidence,[30,31] disentangling and quantifying the direct effect of PrEP rollout on STI incidence is difficult.[32] Some countries that have seen significant uptake of PrEP were observing increases in STIs and declines in condom use among MSM prior to this scale-up.[33] Even prior to epidemiological evidence emerging, assumptions regarding declines in condom use in the context of PrEP has led to specific STI testing guidelines for PrEP delivery.[34] STI testing guidelines for PrEP also acknowledge the risk-based criteria for PrEP prescribing[35–37] and high rates of STI diagnosis prior to PrEP initiation.[30,38] Surveillance data from Australia, where PrEP has been available since early 2016 through large demonstration projects[39,40] and more widely available since April 2018 when PrEP was approved as a government subsidised medicine, have shown that, although rates of chlamydia and gonorrhoea have stabilised among MSM using PrEP, syphilis continues to increase.[41] Continuing increases in syphilis among PrEP users is likely reflective of greater comfort in,[42] and increased rates of,[43] serodiscordant sex in the era of HIV TasP and PrEP, and the greater differential in syphilis prevalence between MSM living with HIV and HIV-negative MSM compared to chlamydia and gonorrhoea. Further still, within risk groups such as PrEP users, the burden of STIs is highly skewed towards those experiencing repeat or concurrent infections. Analysis of PrEP users enrolled in an early demonstration project in Australia found that 50% of PrEP users were not diagnosed with an STI during follow up, and that one-quarter of PrEP users accounted for three-quarters of STIs.[30] These trends have continued to be observed into the years following widespread PrEP implementation in Australia[41] and in other settings such as the UK.[44]

Travellers and migration

With early detection and treatment of STIs to prevent onwards transmission a key STI prevention strategy, there is an increasing focus on the impact of higher risk behaviours and settings associated with international travel and migration on local STI transmission. International travellers returning from high-prevalence settings are at increased risk of STIs,[45] and if not identified upon arrival, risk introducing new strains of STIs and seeding new clusters of transmission. Pre-emptive sexual risk screening during clinical visits prior to travel, for example for vaccines, could provide an opportunity to offer STI interventions, such as STI immunisation, PrEP or self-initiated antibiotic treatment of bacterial STIs, while also prompting travellers to be screened for STIs when they return.[46]

Migrants arriving in high-income countries often face additional barriers to accessing sexual health care driven by cultural aspects of stigma, knowledge gaps in health literacy, and ineligibility for subsidised care.[47] For example, in Australia, newly arrived Asian-born MSM have been identified as an emerging priority group for HIV,[48] with qualitative work highlighting that lack of access to subsidised PrEP introduces a cost barrier for many newly-arrived MSM.[49] Similar structural barriers exist for access to routine HIV and other STI testing for this group, which potentially contribute to higher observed incidence of HIV among Asian-born MSM and high rates of testing positive for HIV at first presentation for testing.[50] The impact of inequitable access to health care on STI risk may be compounded by changes in sexual risk-taking behaviour following migration, especially among MSM emigrating from countries with typically repressive social norms to countries with more progressive views and greater access to gay venues and community.[51] Similarly, migrant sex workers are often at greater risk of STIs than non-migrant sex workers, although the interaction between migrant status and country income level has been shown to vary depending on local epidemiology and legal contexts.[52] STI risk has been shown to be higher among migrant sex workers who do not have contact with outreach workers,[53] further highlighting the impact of unequal access to health care and harm-reduction services on STI risk among migrant populations. Lastly, movement across communities within countries may also be contributing to STI transmission. Recent modelling work suggests that high population

mobility likely contributes to high levels of STI prevalence among remote indigenous communities in Australia.[54]

Technology and risk environments

Across a diverse range of traditional and non-traditional risk groups, specific behaviours may be associated with particular risk environments or the use of digital technologies to meet partners that pose challenges for risk-based screening in clinics and for targeted interventions and health promotion. For example, among MSM, meeting partners at sex-on-premises venues may be associated with increased risk, as STI prevalence is high among MSM attending these venues.[55] Meeting partners online or through 'hookup' apps has also been shown to be associated with greater STI risk among MSM.[56] For heterosexual people, although a recent review found no evidence of an association between online-partner seeking and lower condom use or STI status,[57] among young heterosexual people, use of geo-social dating apps has been linked to increased rates of casual sex, having multiple partners and having sex without discussion about STI status.[58] Other subcultural behaviours associated with increased STI risk, such as 'swinging',[59] may not be readily identified at STI clinics. Practices such as those mentioned above typically cluster within specific geographic and social or sexual networks, and therefore relative risk can be temporally and significantly elevated in the context of undiagnosed infections entering specific networks, resulting in outbreaks of STI infections.

With more evidence of diversifying STI risk, there is a need to go beyond broad, risk-group categorisations based on age, sex and sexuality. Risk diversification poses significant challenges, not only in terms of risk-based diagnostic testing, but also in relation to the costs and resources associated with reaching a broader range of constituents with preventive and health promotion interventions. Here, continued STI surveillance and research, including qualitative and ethnographic research to understand contextual factors that drive risk, is important and emerging data need to be monitored closely to guide and inform policy and practice. Early detection of risk diversification is crucial, given STI control becomes increasingly challenging as prevalence increases in emergent risk populations. Strategies must continue to promote high intervention coverage among known risk groups, but also consider targeted interventions that focus on individuals at greatest risk within these groups.

Rethinking risk – more than just behaviours

As described above, defining traditional risk groups on the basis of broad demographic and sexual behaviour may be inadequate for efficient and effective STI prevention and clinical interventions. To guide targeted interventions towards those at greatest risk, strategies that include non-behavioural considerations may be beneficial. For example, although condom use may be strongly associated with HIV risk, there is mixed evidence of the association between condom use and STI risk, relative to other factors; evidence suggests that among MSM using PrEP, condom use is less predictive of STI risk than sexual networks and the practices that contribute to defining these networks.[30] The estimated per-partner effectiveness of condoms for bacterial STIs[60] is also much lower than for HIV,[61,62] and high levels of extra-genital transmission of STIs among MSM have been reported.[63] Practitioners should therefore consider, dependent upon local epidemiology and context, a broader suite of factors when screening for risk, beyond traditional notions of broad demographic risk or condom-based definitions of 'safe sex'.

Neighbourhoods and access to health care

Key drivers of STI risk are not purely behavioural, but relate to STI prevalence within respective communities and sexual networks, as well as individuals' access to sexual health care and testing. Less access to testing and health care means that STIs remain undiagnosed for a long period of time, and individuals have more chance of passing infections on to their sexual partners. This is evident among populations of black MSM in high-income countries such as the US, the UK and Canada, who are at increased risk of HIV compared to white MSM, despite there being no evidence that black MSM have more partners or engage in more serodiscordant condomless sex than other MSM.[64] A wealth of data highlights that black MSM in the US are often faced with poor access to culturally competent health services, including HIV and STI testing, and experience stigma and discrimination that impede access to services.[65] Similarly, Aboriginal communities living in remote regions of Australia experience disproportionately high rates of STIs, with chlamydia and gonorrhoea prevalence among young people in these communities among the highest in the world.[66,67] With others demonstrating similar numbers of sexual partners and a similar average age at sexual debut among young Aboriginal Australians compared to non-Indigenous young people,[68] discrepancies in STI incidence are likely driven by structural barriers (e.g. access to testing affecting rates of undiagnosed infections). Despite clinical guidelines and specialist support for primary healthcare clinicians visiting these remote communities, rates of re-testing and clinical follow up within recommended timeframes in Aboriginal communities are suboptimal.[69] Remote Aboriginal communities are faced with significant clinician-level barriers to STI testing, such as high levels of clinician turnover, a lack of familiarity with STI protocols, and prioirtisation of other urgent health concerns by clinicians.[70] The impact of access to health care on HIV outcomes is also reflected in Australian migrant communities, especially those from South-East Asia and Sub-Saharan Africa and those from countries that

are ineligible for reciprocal healthcare agreements, where larger gaps in the HIV care cascade are observed compared with non-migrants.[71] Lower rates of repeat HIV testing are also observed among HIV-negative migrants.[50] Addressing disproportionate rates of STIs among both Aboriginal and migrant communities will require systemic change and removal of structural barriers to accessing health care.

Further highlighting the important role of environmental and socio-structural factors in contributing to STI risk, differences in laws and practices that maintain racialised inequities (e.g. inequitable urban housing policies) at the neighbourhood level have been shown to be greater predictors of HIV risk than sexual risk behaviours.[72] In the US, higher rates of gonorrhoea have been linked to neighbourhood-level determinants of health, including higher rates of single mothers and lower socio-economic status.[73] Analysis of syphilis distribution in Canada suggests that spatial clustering of syphilis diagnoses is not fully explained by distribution of MSM populations or different rates of testing across areas, suggesting that additional neighbourhood-levels factors are likely driving transmission.[74] These data highlight the importance of localised surveillance and research to ensure risk is appropriately understood and addressed within local contexts.

Changes in risk

It is also important to consider that risk changes over time, and that if an individual does not meet certain risk criteria for screening or a prevention intervention, they may in the future. For example, early PrEP guidelines in Australia recommended prescribing PrEP even in the absence of recent risk, if individuals anticipated risky behaviour in the near future.[34] Similar considerations for STI interventions should be considered. Latent transition analysis among both heterosexuals[75] and gay and bisexual men[76] show that individuals' allocation into specific risk groups remains relatively stable. However, changes in risk are often observed when people move out of monogamous relationships. This is reflected in risk-based STI guidelines for young heterosexuals,[77] and latent transition analysis of MSM regularly attending for STI testing.[76] Further, these data reflect states of risk prior to the introduction of PrEP. Given the evidence of changes in STI risk follow PrEP initiation,[27] and that people transition in and out of PrEP use based on personal risk perception over time,[78] regular assessment of current risk among people presenting to health services with any history of PrEP use is warranted. Further, the coronavirus disease 2019 (COVID-19) pandemic and associated public health orders have led to significant changes in sexual behaviour[79] and breaks in PrEP use[80,81] among MSM, decreases in casual sex among heterosexuals,[82] and significant declines in the frequency of STI testing.[83] Drops in testing in the presence of ongoing sexual risk have the potential to increase pools of undiagnosed infection.

Screening for STIs

Although testing is crucial for the control of STIs, guidelines on who to test, and how often, vary. Many guidelines highlight specific populations that should be considered for STI screening, or recommend clinicians take a sexual history to determine if individuals should be screened. Among populations where STIs are highly asymptomatic (e.g. extra-genital infections among MSM), informed decisions around how to screen in the absence of symptoms rely on understanding epidemiological contexts (historical and emerging). Although broad-based guidelines, which recommend testing of entire populations (e.g. regular testing of all sexually active MSM or STI testing at each PrEP prescribing visit), may lead to greater testing coverage and frequency, they present challenges for managing clinic capacity and may impact the cost and cost-effectiveness of sexual health services. Such strategies consume a lot of resources and are not often feasible in resource-constrained settings or where testing is not fully subsidised. Further, broad-based recommendations obfuscate the need for nuanced risk screening and targeted higher frequency testing for those at particularly high risk or those who are diagnosed with STIs recurrently.

Opportunistic testing during routine visits

Opportunistic testing, when a test if offered in-clinic during a routine patient visit, often occurs after clinicians take a sexual history, following an electronic prompt, or if the patient is identified as belonging to a specific high-risk group for which STI testing is recommended. For example, in the US, the CDC and US Preventive Services Task Force recommend annual chlamydia and gonorrhoea screening for all sexually active females aged <25 years, and annual screening for women aged >25 years with a risk factor (more than one sex partner, a sex partner with concurrent partners, a new partner).[84] Although such recommendations allow clinicians to assess risk on an individual basis, significant challenges associated with risk screening exist. Clinician barriers include discomfort around engaging in sexual health discussion or asking sensitive questions, feeling inadequately trained, and difficulty incorporating a sexual screen into a regular visit due to time constraints.[85] Barriers may also be magnified among doctors who serve ethnically diverse populations.[86] Patient sexual history may also be hindered due to patient concerns around confidentiality and stigma, lack of perceived risk and lack of sexual health awareness.[87] Some of these barriers can be overcome by implementing computer-assisted self-interviewing in clinic waiting rooms, where patients

complete an electronic survey that asks about their sexual history and specific risk factors.[88]

Universal screening of key populations

In contrast to its screening recommendations for women (women aged <25 years screened annually, those aged >25 years only screened if a risk factor is present), the US CDC recommends annual screening for all sexually active MSM, and more frequent screening (3–6 months) for MSM at increased risk (defined has having multiple partners or persistent risk behaviours).[89] In Australia, guidelines were updated in 2019 by removing specific risk-based recommendations for screening frequency among MSM and recommending uniform 3-monthly testing for bacterial STIs for all sexually active MSM, regardless of the number of partners, STI history or presence of specific risk behaviours.[90] Although increasing rates of STIs among MSM may warrant high-frequency screening, in the context of highly skewed STI incidence among certain subgroups of MSM[41] and resource and time constrains in general practice, not distinguishing between high- and low-risk MSM may lead to ineffective or less cost-effective STI screening practices.

It is not clear whether the implementation of ambitious guidelines, which recommend high-frequency screening for all MSM regardless of risk-factors, such as those in Australia, will lead to greater increases in testing frequency among those already being tested, or in testing coverage across the whole population, with little evidence to suggest this strategy would have an impact on STI prevalence. Although sexual health clinics may be able to achieve such testing rates, in jurisdictions where STI testing is mainly conducted in general practice, the burden of trying to screen all MSM four times a year might mean adequate screening is not achieved among those who it would benefit the most, and universal screening at high frequency is likely not feasible in settings where testing is not covered by universal healthcare arrangements.

Effect of screening on STI prevalence

Evidence for the effectiveness of broad-based population-level screening on test uptake and STI prevalence is mixed, and the benefits and harms of broad-based population testing versus more specific risk-guided testing protocols vary between population. Risk-based opportunistic screening in the US, based on taking a sexual history, has largely not been successful in achieving high rates of chlamydia screening among high-risk young women,[91] largely due to low rates of practitioners in general practice undertaking a sexual history. A 2006 survey found that only 55% of primary care physicians asked about sexual histories as part of regular examinations.[92] Data from Australia reports that 46% of general practice clinicians would not take a sexual history of MSM presenting for a routine check up.[85]

Even if clinician- and patient-level barriers are overcome, there is little evidence to suggest that high coverage of opportunistic screening among heterosexuals has an impact on STI prevalence. A large cluster randomised controlled trial of opportunistic chlamydia testing in rural GP services in Australia, which implemented a protocol involving clinician education, computer alert prompting and reimbursements, found that even with increased testing of eligible patients, the intervention was not associated with a decline in chlamydia prevalence.[93] However, it was associated with a decline in PID presentations at nearby hospitals. Additional data from the US shows that although screening among heterosexuals may not reduce chlamydia prevalence, it is a potentially effective approach to reduce PID.[94] Another large cluster-randomised controlled trial, which assessed a multi-pronged intervention of continuous quality improvement (review of clinical data, education, implementation of systems-level changes aimed at improving STI practice) in general practice clinics serving remote indigenous populations in Australia, again found increases in testing, but no changes in population-level prevalence of STIs.[95]

Strategies to increase STI testing capacity

Consideration of adapted service models and strategies to enhance STI testing efficiency in established services may be required to maintain capacity for broad risk-based STI screening practices, while also increasing testing coverage and frequency among those at particularly high risk. Although technology-based systems to reduce the burden of high frequency testing on patients have been implemented at the clinic and laboratory level (e.g. results delivered by SMS[96]), frequent testing can be challenging because of restricted clinic operating times. These types of health systems barriers make increasing patient-driven demand for STI testing difficult. For example, evaluation of a large Australian health promotion campaign targeting MSM for HIV and STI testing found that despite substantial investment in health promotion and a high proportion of MSM recalling campaign messages, only a modest increase in chlamydia and gonorrhoea testing was achieved, and the campaign had minimal impact on HIV or syphilis testing.[97] Social marketing initiatives aimed at creating demand for testing must also be accompanied by structural changes that make STI testing more convenient.

In order to achieve high rates of testing, adaptive and convenient service models that reduce the burden on patients will be required. A recent scoping review of HIV and STI testing preferences among MSM in high-income countries identified the convenience and privacy of self-testing, and the need to provide a variety of testing options, as key themes of testing preferences.[98] A 2016 review of interventions aimed at increasing STI screening found that

the most effective interventions included incorporating collection of STI specimens as standard procedure regardless of the reason for the visit, and the use of electronic health records as a reminder to offer screening.[99] Models that streamline clinic visits, including patients self-collecting specimens, computer-assisted questionnaires, test-and-go services, and rapid testing with same-day results, have been shown to increase screening while also reducing costs and time between testing and treatment.[100] The incorporation of all these elements into a single, free, express testing service, Dean Street Express in London, was shown to reduce mean time between test and notification to 0.27 days, compared to the standard clinic's 8.95 days, which was projected to have prevented 196 chlamydia and/or gonorrhoea infections over 1 year after implementation.[101] Nurse-led test-and-go services, which remove the need for doctor consultation and reduce testing times, have also been shown to capture clients with different demographics, yet still detect a similar rate of STI positivity, compared to standard doctor-led testing.[102]

Opt-out testing

Another strategy, opt-out testing, involves testing all patients in a specific risk group, regardless of the presence of sexual risk factors, with the aim of increasing screening rates. Population-based opt-out screening methods remove the burden of clinicians to initiate sexual history taking, and decide if a test is appropriate or needed. However, opt-out testing does place the burden on clinicians to ensure appropriate disclosure of the test to patients in pre-test discussions to ensure they are aware of the implications of a positive result and have the opportunity to opt out. Surveillance data from Australia showed opt-out testing increased rates of syphilis testing among MSM living with HIV.[103] Modelling work suggests that an opt-out testing strategy for all women aged 15–24 years in the US would likely reduce chlamydia prevalence, and be more cost-effective compared to a risk-based screening strategy; however, this was dependent on individuals' insurance coverage.[104] In limited-resource settings or where universal health care is not available, overall effectiveness and cost-effectiveness of such strategies would be significantly reduced.

Targeted testing of those at greatest risk

A modelling study of syphilis among Canadian MSM found that increasing screening frequency among those already engaged in testing had a greater reduction on syphilis incidence than increasing screening coverage (i.e. the proportion of the population tested).[105] Another modelling study of MSM in the US found that both increasing the rate of screening from current levels to biannual among all sexually active MSM currently being tested, and increasing the coverage of biannual screening to 30% of all 'high-risk' MSM, each reduced chlamydia and gonorrhoea incidence by approximately a 75% reduction over 10 years. The authors suggest that more frequent screening for all MSM, and scaling up targeted screening for men with multiple recent partners, were the most effective strategies.[106] US guidelines recommend syphilis screening in MSM, people with HIV and pregnant women, but do not provide routine screening recommendations for HIV-negative heterosexual populations. Modelling work suggests that achieving such a strategy may have an impact on transmission in states with more MSM-focused outbreaks, but would have little or no impact on transmission in states where syphilis is more evenly distributed between MSM and heterosexual populations.[107]

Guiding public health strategies to increase active case-finding using epidemiological trends can quickly and efficiently respond to new STI outbreaks. For example, many countries utilise existing networks of general practice clinicians to issue alerts around increasing rates of STIs in certain geographical areas or subpopulations. In the UK, outbreaks are detected by local surveillance undertaken by clinicians or health protection teams via the detection of higher than expected numbers of diagnoses.[108] These are sometimes supplemented by more systematic approaches that utilise automated spatiotemporal detection tools to routinely analyse notification data.[109] Following an investigation to declare and determine the spread of an outbreak, initial stages of outbreak response usually involve alerting clinicians and appropriate organisations through established communication systems. Similar alerts in Australia are commonly issued through the general practitioner network.[110] Sustained outbreak control can then include strategies such as active case-finding, qualitative data collection to understand drivers of the outbreak, outreach programs targeting specific venues or populations, and widespread promotion through social and traditional media.[108] These strategies can also facilitate targeted communication to non-primary care clinicians who may not be routinely involved in STI care. For example, recent increases in congenital syphilis, likely related to low rates of syphilis screening and issues with continuity of care and treatment during pregnancy among patients tested in antenatal hospital clinics in Australia,[111] led to specific guidance targeted at increasing syphilis testing during pregnancy. The success of such strategies relies on surveillance infrastructure to identify and characterise new STI outbreaks in a reliable and timely manner, and appropriate levels of funding and technical support to resource a timely response.

Over-screening

In addition to the burden of frequent STI testing incurred by the patient, there are potential harms associated with over-screening for STIs, including anxiety, psychological harm

associated with false positives or negatives, or possible change in risk behaviour. However, the US CDC reports there is currently limited data on psychological or other harms associated with screening for chlamydia and gonorrhoea among women and heterosexual men.[112] Among MSM, there is growing evidence that high antibiotic consumption among PrEP users may be driving antibiotic resistance. Given high rates of bacterial STIs among PrEP users, and high frequency screening and treatment, PrEP users have high levels of macrolide consumption, as well as for cephalosporins, fluoroquinolones and tetracyclines.[113] In some European countries, consumption of macrolides is 52-fold higher among PrEP users compared to community-level consumption.[113] Cohorts of PrEP users around the world are commonly characterised by having high rates of partner change,[27] translating to high and stable prevalence of chlamydia and gonorrhoea. Long-term surveillance data in Australia suggest that sustained high-frequency testing of PrEP users (3-monthly) for >4 years has not curbed rates of chlamydia or gonorrhoea in this group.[41] In contrast, such high-frequency screening is costly and may be driving antimicrobial resistance.[114] Modelling work suggests that even low levels of screening for the largely asymptomatic STI *Mycoplasma genitalium* among MSM is leading to increased antibiotic resistance through increased, arguably unnecessary treatment.[115] In its resistance threats 2019 report, the US CDC has listed drug-resistant gonorrhoea on its Urgent Threats list, and *Mycoplasma genitalium* on its watch list.[116] Surveillance of antimicrobial resistance is crucial in the context of high-frequency screening and transmission. In light of the threat of antimicrobial resistance, there is a growing case for reconsidering the evidence base for high-frequency screening of STIs, which are mostly asymptomatic, among populations with high and stable prevalences.[117]

Identifying risk

With the aforementioned barriers to clinician-led discussions on sexual history during routine care, and the need for increased client-driven demand for testing, methods to appropriately and efficiently identify risk, both from the clinician perspective and including individuals' self-perception of risk, are crucial.

Service-identified risk

For clinical services aiming to identify risk, strategies can go beyond broad testing protocols based on risk group and the use of clinical data and automated screening tools. For example, previous infection can be used as an indicator of risk. History of an STI has consistently been shown to be one of the strongest indicators of future risk among both MSM[118] and adolescent heterosexuals.[119] The strong predictive value of a previous diagnosis is reflective of high rates of reinfection, such as that of syphilis reinfection widely observed among MSM,[120] especially those living with HIV.[118] It is unsurprising then that modelling work suggests that increasing screening frequency among MSM with a prior syphilis diagnosis is equally effective in reducing syphilis prevalence as testing focused on those reporting high partner numbers, and far more effective than distributing testing equally among all MSM.[121] Targeting individuals with a prior diagnosis of syphilis can be done through clinician-led history taking, patient management system alerts or through demand-creation approaches such as community-driven awareness-raising of reinfection risk.

Novel methods for identifying those at risk, including machine learning and prediction modelling using electronic medical records, have also been explored, with varying levels of efficacy. For example, the use of computer-assisted sexual history taking allows data on behavioural risk factors to be analysed using risk prediction models and machine learning. Machine learning has been successfully used to identify those who are eligible for PrEP based on medical records;[122] however, the use of machine algorithms of structured health record data have been shown to poorly differentiate patients with and without repeat STI diagnosis, indicating that they may be less useful for predicting STI risk.[123] Prediction models of routinely collected healthcare data have been used in emergency room settings where laboratory variables are collected and can be used for risk prediction.[124] Despite growing work on machine learning, such techniques require technical capacity, education and training, and access to 'big data' through which to generate predictive algorithms. Also, as prediction methods rely on patient history, they would likely provide less benefit in determining STI risk for patients attending clinics sporadically or for the first time.

Risk self-identification

Along with clinical services being able to adequately identify STI risk, patient-driven demand for STI testing relies heavily on individuals recognising their own risk, and seeking STI testing. An analysis of adults in the UK found that both men and women underestimate their self-risk of STIs, and that many who did perceive themselves as at-risk had not recently accessed STI care.[125] Health promotion, therefore, should not only focus on improving self-identification of risk, but also encourage people to act on their perceived self-risk by accessing care. Perception of the seriousness of STIs has been shown to vary considerably among specific subgroups of MSM at high risk of STIs,[126] and may influence an individual's decision to present for testing following possible exposure to an STI or following windows of risk, if they perceive the health risk of an STI going undiagnosed to be low. Along with perceptions of risk, STI knowledge has also been linked to recent STI testing,[127]

highlighting the importance of health promotion campaigns for increasing STI awareness and access to information on STIs. Peer-led models of care have been shown to provide opportunities for MSM to enhance their risk-reduction knowledge around STIs, with greater benefits among young and less gay community-attached MSM.[128]

Finally, technology is also playing a role in the self-identification of STI risk. As described earlier, MSM who use geo-social networking apps are at increased risk of STIs. This highlights a potential opportunity for community and health organisations to deliver reliable, trusted and easily accessible sexual health information at scale to those at greatest risk via social networking apps. Further, specific mobile phone applications have been designed to screen for STI risk, as well as to help users identify STI symptoms. Although mobile phone apps for the care and prevention of STIs are of high interest to the general public,[129] a 2016 review of available STI-related apps found that many contained incorrect and potentially harmful information.[130] Recent data also suggest that although digital methods of sexual healthcare delivery (i.e. through video consultation) may be acceptable, many still prefer human interaction over automated chat-bots when accessing sexual health information.[131] Further, disparities in utility and uptake of digital health information and interventions exist, with older people[132] and those from racial and ethnic minorities less likely to engage in technology-based interventions.[133]

Conclusion: adopting an adaptive risk-guided approach to STI control

Alongside historically high-risk groups, new risk groups for STIs continue to emerge and diversify. Although the evidence for the effect of population-based screening compared to higher frequency, targeted screening strategies on STI prevalence varies within and across MSM and heterosexual populations and for specific STIs, strategies that reduce clinician- and patient-level barriers, and are adaptive to local epidemiological contexts, have the greatest potential for achieving optimal screening rates and controlling new outbreaks. Such strategies need to remove the burden on clinicians and the assumption of risk, and improve patient convenience in order to increase testing coverage, while still including sufficient nuances to identify those at greatest risk for targeted testing and prevention.

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Data availability. Data sharing is not applicable as no new data were generated or analysed during this study.

Conflicts of interest. MWT has received speaker's honoraria and investigator-initiated research grants from Gilead Sciences. MAS has received investigator-initiated research grants from Gilead Sciences and AbbVie, and consulting fees from Gilead Sciences.

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Author affiliations
[A]Burnet Institute, Melbourne, Vic., Australia.
[B]School of Public Health and Preventive Medicine, Monash University, Melbourne, Vic., Australia.

Appendix C Relevant peer-reviewed papers published during candidature

Appendix C1. Association of HIV PrEP with incidence of STIs among individuals at high-risk of HIV infection

Citation:

Traeger MW, Cornelisse VJ, Asselin J, Price B, Roth NJ, Willcox J, Tee BK, Fairly CK, Chang CC, Armishaw J, Vujovic O, Penn M, Cundill P, Forgan-Smith G, Gall J, Pickett C, Lal L, Mak A, Spelman TD, Nguyen L, Murphy DA, Ryan KE, El-Hayek C, West M, Ruth S, Batrouney C, Lockwood JT, Hoy JF, Hellard ME, Stoové MA, Wright EJ. Association of HIV Pre-exposure Prophylaxis with Incidence of Sexually Transmitted Infections among Individuals at High Risk of HIV Infection. *Journal of the American Medical Association.* 2019;321(14):1380-1390. doi: 10.1001/jama.2019.2947

JAMA | Original Investigation

Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection

Michael W. Traeger, MSc; Vincent J. Cornelisse, MBBS, PhD; Jason Asselin, BSc; Brian Price, MBA; Norman J. Roth, MBBS; Jeff Willcox, MBBS; Ban Kiem Tee, MBBS; Christopher K. Fairley, MBBS, PhD; Christina C. Chang, MBBS, PhD; Jude Armishaw, BNurs; Olga Vujovic, MBBS; Matthew Penn, MBBS; Pauline Cundill, BM; George Forgan-Smith, MBBS; John Gall, MBBS, PhD; Claire Pickett, MBBS; Luxi Lal, BPharm; Anne Mak, BPharm; Tim D. Spelman, MBBS, MSc; Long Nguyen, MCom; Dean A. Murphy, PhD; Kathleen E. Ryan, PhD; Carol El-Hayek, MEpi; Michael West, BA; Simon Ruth, MSSc; Colin Batrouney, BA; John T. Lockwood, BN; Jennifer F. Hoy, MBBS; Margaret E. Hellard, MBBS, PhD; Mark A. Stoové, PhD; Edwina J. Wright, MBBS, PhD; for the PrEPX Study Team

IMPORTANCE Emerging evidence suggests that risk of bacterial sexually transmitted infections (STIs) increases among gay and bisexual men following initiation of HIV preexposure prophylaxis (PrEP).

OBJECTIVE To describe STI incidence and behavioral risk factors among a cohort of predominantly gay and bisexual men who use PrEP, and to explore changes in STI incidence following PrEP commencement.

DESIGN, SETTING, AND PARTICIPANTS The Pre-exposure Prophylaxis Expanded (PrEPX) Study, a multisite, open-label intervention study, was nested within the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) clinic network. A total of 4275 participants were enrolled (July 26, 2016–April 1, 2018) in Victoria, Australia. Of these, 2981 enrolled at 5 ACCESS clinics (3 primary care, 1 sexual health, and 1 community-based HIV rapid testing service), had at least 1 follow-up visit, and were monitored until April 30, 2018.

EXPOSURES Upon enrollment, participants received daily oral tenofovir disoproxil fumurate and emtricitabine for HIV PrEP, quarterly HIV and STI testing, and clinical monitoring.

MAIN OUTCOMES AND MEASURES The primary outcome was incidence of chlamydia, gonorrhea, or syphilis. Incidence rates and hazard ratios describing behavioral risk factors of STI diagnosis were calculated. Incidence rate ratios (IRRs), adjusted for change in testing frequency, described changes in STI incidence from 1-year preenrollment to study follow-up among participants with preenrollment testing data (n = 1378).

RESULTS Among the 2981 individuals (median age, 34 years [interquartile range, 28-42]), 98.5% identified as gay or bisexual males, 29% used PrEP prior to enrollment, 89 (3%) withdrew and were censored at date of withdrawal, leaving 2892 (97.0%) enrolled at final follow-up. During a mean follow-up of 1.1 years (3185.0 person-years), 2928 STIs were diagnosed among 1427 (48%) participants (1434 chlamydia, 1242 gonorrhea, 252 syphilis). STI incidence was 91.9 per 100 person-years, with 736 participants (25%) accounting for 2237 (76%) of all STIs. Among 2058 participants with complete data for multivariable analysis, younger age, greater partner number, and group sex were associated with greater STI risk, but condom use was not. Among 1378 participants with preenrollment testing data, STI incidence increased from 69.5 per 100 person-years prior to enrollment to 98.4 per 100 person-years during follow-up (IRR, 1.41 [95% CI, 1.29-1.56]). After adjusting for testing frequency, the increase in incidence from 1 year preenrollment to follow-up was significant for any STI (adjusted IRR, 1.12 [95% CI, 1.02-1.23]) and for chlamydia (adjusted IRR, 1.17 [95% CI, 1.04-1.33]).

CONCLUSIONS AND RELEVANCE Among gay and bisexual men using PrEP, STIs were highly concentrated among a subset, and receipt of PrEP after study enrollment was associated with an increased incidence of STIs compared with preenrollment. These findings highlight the importance of frequent STI testing among gay and bisexual men using PrEP.

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Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1406

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The PrEPX Study Team members appear at the end of the article.

Corresponding Author: Michael W. Traeger, MSc, Burnet Institute, 85 Commercial Rd, Melbourne, Victoria 3004, Australia (michael.traeger@burnet.edu.au).

HIV preexposure prophylaxis (PrEP) is highly effective in reducing HIV acquisition risk among gay and bisexual men who have high medication adherence.[1-3] Following the regulatory approval of tenofovir/emtricitabine for daily use as PrEP in Australia in 2016,[4] and prior to PrEP becoming subsidized through Australia's Pharmaceutical Benefits Scheme in April 2018, large implementation studies in several Australian jurisdictions, most notably in Melbourne and Sydney, experienced high rates of enrollment and provided more than 15 000 gay and bisexual men with access to PrEP.[5,6] Despite the high efficacy of PrEP and emerging evidence of population-level decreases in incidence of newly acquired HIV following PrEP implementation,[6,7] concerns remain that widespread PrEP uptake may result in behavioral change that leads to increases in bacterial sexually transmitted infections (STIs).[8]

Although early clinical trials reported no evidence of decreased condom use among PrEP users,[1,3] a recent systematic review of 17 open-label PrEP studies found an increase in condomless anal sex and bacterial STIs, especially rectal infections, among gay and bisexual men following PrEP use.[9] However, many studies have lacked comprehensive data for STI incidence prior to use of PrEP,[9] and only a few[10,11] have accounted for changes in population STI rates or for the confounding effect of increased STI testing, as recommended for PrEP users, on STI rates. As PrEP uptake among eligible populations increases, monitoring population changes in STI epidemiology and identifying individuals most at risk will become increasingly important for informing effective and focused STI prevention.

The Pre-exposure Prophylaxis Expanded (PrEPX) study was a multisite, open-label, population intervention study in Victoria, Australia. The primary study objective was to measure changes in population-level HIV incidence in Victoria following study rollout. This article reports findings addressing a key secondary study objective to assess the association of PrEP with STI risk by describing STI incidence among participants and exploring changes in STI risk following study enrollment.

Key Points

Question Is the use of HIV preexposure prophylaxis (PrEP) associated with increased risk of sexually transmitted infections (STIs) among individuals at high risk of HIV infection?

Findings In this longitudinal study of 2981 mostly gay and bisexual men who received daily HIV preexposure prophylaxis, STI incidence was 91.9 per 100 person-years, with 736 participants (25%) accounting for 2237 (76%) of all STIs. Among 1378 participants with preenrollment STI testing data available, receipt of PrEP after study enrollment was associated with an increased incidence of STIs compared with preenrollment (adjusted incidence rate ratio, 1.12).

Meaning Findings suggest the importance of frequent testing for STIs among gay and bisexual men using PrEP.

Methods

Study Design and Data Collection

Ethics approval for the study and the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-Borne Viruses and Sexually Transmitted Infections (ACCESS) project were provided by the Alfred Hospital Human Research Ethics Committee (projects 100/16 and 248/17). All participants provided written consent. The study was undertaken during 2017 in the states of South Australia and Tasmania following funding from respective state governments, however the following analysis pertains only to the Victorian study, which was rolled out first, as per the study protocol. Study enrollment commenced on July 26, 2016, and 4275 people at risk of HIV were enrolled until April 1, 2018. Study methods have been published elsewhere,[12] and the study protocol is available online (Supplement 1). Individuals who met 1 or more prespecified eligibility criteria, based on self-reported HIV risk in the previous 3 months (eMethods in Supplement 2), and were predicted to have ongoing HIV risk in the next 3 months, were eligible to enroll. Participants who did not report the prespecified behavioral criteria were potentially eligible to enroll at the clinician's discretion. During screening for eligibility, clinicians asked potential study participants about their gender identity, their sex/gender assigned at birth, and their perceived sexuality, and responses were self-reported to clinicians. Potential participants were asked whether they identified as Aboriginal or Torres Strait Islander (ATSI) as the health status of indigenous Australians is a priority in Australia's National Strategies for HIV, STIs, and blood-borne viruses.[13] Individuals could decline to answer the question about their ATSI status. Participants were also asked if they were currently using PrEP prior to enrolling into the study. At enrollment and quarterly study visits, participants received PrEP prescriptions, completed a self-reported electronic sexual behavioral survey regarding sexual partners and condom use, and underwent HIV and STI testing. Enrollment and behavioral survey data were collected and managed using REDCap electronic data capture tools hosted at the Burnet Institute.[14] Comprehensive STI screening was undertaken in accordance with the Australian Sexually Transmitted Infection and HIV Testing guidelines,[15] including nucleic acid amplification tests for pharyngeal, anorectal, and urethral chlamydia and gonorrhea; syphilis serology; and fourth-generation HIV testing. STI testing and self-reported behavioral data from visits at baseline and during study follow-up were extracted from participating study sites via the ACCESS project.[16] ACCESS is a national STI and blood-borne virus sentinel surveillance system that routinely extracts deidentified patient data from clinical management systems at selected sexual health and general practice clinics. A number of study sites also participate in the ACCESS project, allowing for monitoring of STI outcomes among study participants. STI pathology results and patient demographic and behavioral data were extracted using specialized data extraction software, and patient records were linked across services using a matching algorithm.

Sample

Data were included from participants who were enrolled at any of the 5 study sites that participated in ACCESS: 3 high-caseload primary care settings, 1 sexual health clinic, and

1 community-based HIV rapid point-of-care testing service. All study participants who enrolled at one of the ACCESS clinics and underwent STI testing at their enrollment visit and at least 1 follow-up visit postenrollment were included in the analysis. To assess potential for selection bias, characteristics of participants included in the analysis were compared with those of participants not enrolled at ACCESS clinics and subsequently excluded from the analysis.

Outcomes

The primary outcome was the incidence of STIs, defined as a diagnosis of chlamydia, gonorrhea, or newly identified (primary, secondary, or early latent [<2 years]) syphilis. Positive results of the same infection at multiple anatomical sites from tests obtained on the same day (eg, pharyngeal gonorrhea and rectal gonorrhea) were considered a single infection, while concurrent diagnoses of different infections at the same or different anatomical sites were considered separate infections. Tests for chlamydia and gonorrhea within 30 days of a previous positive result at the same anatomical site were considered tests of cure and excluded from the analysis.[17] Exploratory outcomes were behavioral risk factors associated with STI diagnosis, as well as changes in STI incidence from 1 year prior to enrollment to study follow-up. Changes in STI incidence were explored only among participants with preenrollment testing data. To determine the independent association of commencing PrEP on STI incidence, a post hoc disaggregation of results by whether participants reported no previous PrEP use (PrEP-naive) or were using PrEP at enrollment (PrEP-experienced) was performed.

Statistical Analyses

Cox proportional hazards regression was used to explore associations between behavioral and demographic characteristics and STI diagnosis by calculating hazard ratios with 95% CIs. The conditional risk set model proposed by Prentice, Williams, and Peterson was used to allow for multiple failures (STIs) per participant.[18] In this Cox model, follow-up time commenced at enrollment visit and baseline STI test results were excluded. Participants were right-censored at time of last follow-up prior to April 30, 2018. Covariates found to be independently associated with STI diagnosis in bivariable analysis ($P < .10$) were included in a multivariable Cox model. Only participants with complete data for all included covariates were included in the multivariable Cox model. The multivariable model was assessed for multicollinearity by computing the tolerance for model covariates, with none showing evidence for multicollinearity (cutoff tolerance for evidence of multicollinearity <0.1).[19] The proportional hazards assumption of the multivariable Cox model was tested using Schoenfeld residuals,[20] with individual covariate and global tests showing no evidence for rejection of the null hypothesis of proportional hazards at the P value of less than .05 significance level.

Time-fixed covariates in the multivariable Cox model included participant age; ATSI status; region of birth (Australia vs outside of Australia); previous use of PrEP; previous use of postexposure prophylaxis; having ever exchanged sex for money; and self-reporting diagnosis of rectal chlamydia, rectal gonorrhea, or syphilis in the 3 months prior to enrollment. Time-varying covariates included reporting of having a regular partner, number of casual oral sex partners (1-5, 6-10, 11-20, 21-50, >50), number of casual anal sex partners (1-5, 6-10, 11-20, 21-50, >50), participation in group sex (none, once or a few times, ≥monthly, ≥weekly), condom use with casual partners (always, usually [>50%], sometimes [≤50%], never), condom use with regular partners (always, usually [>50%], sometimes [≤50%], never), recreational drug use during sex, injection drug use, and self-reported PrEP adherence (daily, 4-6 days per week, 1-3 days per week, intermittent). Recall period for time-varying covariates was past 6 months, and responses were updated at each scheduled study visit.

To explore changes in STI risk following study enrollment, STI incidence was compared before and after enrollment among participants with at least 1 STI test in the ACCESS system longer than 6 months prior to enrollment (≥6 months of preenrollment person-time). Incidence rate ratios (IRRs) with 95% CIs comparing incidence 1 year before enrollment with incidence during study follow-up were calculated for each infection and anatomical site. In this before-and-after analysis, participants were considered at risk and contributed person-time from their earliest negative test for the respective infection and anatomical site in the ACCESS system, or from exactly 1 year prior to enrollment (whichever came later), and STIs diagnosed at the study enrollment visit were counted in the before-enrollment period. The overall change in testing rate across periods was also calculated by visit (number of visits when a test was performed divided by total person-time) and accounting for multiple infections tested for during the same visit (number of tests divided by total person-time).

Negative binomial regression (chosen over a Poisson model to account for overdispersion within the data; likelihood ratio test of $\alpha = 0$, $\chi^2<0.001$) was used to calculate adjusted incidence rate ratios (AIRRs) by including period (1 year preenrollment vs during study follow-up) in the model as an independent covariate. To control for the differential frequency in STI testing between before-enrollment and after-enrollment periods, the individual rate of testing (number of tests divided by person time of follow-up) in each period per participant was included in the model as a continuous variable. For the "any STI" model output, a test performed for each infection (chlamydia, gonorrhea, or syphilis) contributed to the sum of tests used to calculate the testing rate variable. Outcome of the model was number of STI diagnoses per participant in each period with log of individual follow-up time per period as an offset. Robust standard error calculations clustered by participant were used to account for within-participant dependency of number of STI diagnoses between periods. Despite a high proportion of participants experiencing no STIs, a standard negative binomial regression model was chosen over a zero-inflated negative binomial regression model because all participants were considered at risk of STI diagnosis, given the risk-based eligibility criteria for enrollment in the study and the fact that all participants in this analysis had at least 1 test in each period.

Because of the potential for type I error due to multiple comparisons, findings for secondary analyses should be interpreted as exploratory. P values were 2-sided with $\alpha = .05$ and $P < .05$

considered statistically significant. All statistical analyses were conducted using Stata version 14.2 for Windows (StataCorp).

Results

Participant Characteristics

Of the 4275 participants enrolled in the study in Victoria, 2981 were enrolled at ACCESS sites, had at least 1 postenrollment visit, and were included in the analysis (participant characteristics are shown in **Table 1**). Compared with participants not included in the analysis, included participants were more likely to have used methamphetamines in the 3 months prior to enrollment (13.8% vs 7.8%; $P < .001$), however were not significantly different across other self-reported sexual risk behaviors at enrollment (see eTable 2 in Supplement 2 for comparison of included vs excluded participants). Included participants were aged 16 to 72 years at enrollment (median, 34 [interquartile range {IQR}, 28-42]) and 98.5% (n=2936) identified as gay or bisexual men (see eTable 1 in Supplement 2 for breakdown of self-reported gender and sexuality). Previous use of antiretrovirals for reducing HIV-acquisition risk was common; 28.5% of participants (n=849) reported PrEP use before enrollment and 40.7% (n=1212) reported ever taking postexposure prophylaxis. The most common risk-based study eligibility criteria reported (in the previous 3 months) were condomless receptive anal intercourse with a partner with HIV or of unknown HIV status (48.1%; n=1435) or having more than 1 episode of condomless insertive anal intercourse with a partner of unknown HIV status or a partner with HIV not on antiretroviral treatment (35.1%; n=1046). Four-hundred and eighty-four (16.2%) participants self-reported a diagnosis of rectal chlamydia, rectal gonorrhea, or syphilis in the 3 months prior to enrollment, and 407 (13.7%) were diagnosed with an STI at their enrollment visit.

Primary Outcome

Of the 2981 participants included in the analysis, 89 (3%) formally withdrew from the study and were censored at date of withdrawal, leaving 2892 (97.0%) participants still enrolled at the time of final follow-up. Participants were monitored for a total of 3185.0 person-years after enrollment (median follow-up, 1.19 years [IQR, 0.71-1.48). During this time, a total of 2928 STI diagnoses were made among 1427 (48%) participants. The number of STIs diagnosed during follow-up per participant ranged from 0 to 12 (median, 0). The **Figure** shows the proportion of participants diagnosed with 0, 1, or multiple STIs during follow-up and the corresponding proportion of all STIs diagnosed (eTable 3 in Supplement 2 reports the number of STIs diagnosed per person). Multiple infections were observed in 736 (25%) participants, with infections among these participants accounting for 76% of all infections during follow-up. Seven hundred and eighty-eight concurrent infections (different STIs diagnosed during the same visit) occurred at 387 follow-up visits and accounted for 27% of all diagnoses.

Incidence of any STI diagnosis during study follow-up was 91.9 per 100 person-years, with incidences of 45.0 per 100 person-years for chlamydia, 39.0 per 100 person-years for

Table 1. Characteristics of Participants at Enrollment (N = 2981)[a]

	No. (%)[b]
Age, median (interquartile range), y	34 (28-42)
Gender identity[c]	
Male (cisgender[d] or transgender)	2958 (99.2)
Female (cisgender[d] or transgender)	10 (0.3)
Nonbinary/gender fluid	13 (0.4)
Trans or gender diverse[c]	37 (1.2)
Sexuality	
Gay/homosexual	2817 (94.5)
Bisexual	125 (4.2)
Heterosexual	9 (0.3)
Not specified	30 (1.0)
Born in Australia (n = 2187)	1557 (71.2)
Aboriginal or Torres Strait Islander (n = 2204)	65 (2.9)
Use of injection drugs (n = 2241)	
Ever	270 (12.0)
Recently (past 12 mo)	190 (8.5)
Ever accessed postexposure prophylaxis	1212 (40.7)
Currently using PrEP at enrollment	849 (28.5)
Regular partner at enrollment visit (n = 2083)	1047 (50.3)
HIV status of regular partner (n = 1047)	
Positive	179 (17.1)
Negative	786 (75.1)
Unknown	82 (7.8)
If HIV-positive, viral load of partner (n = 179)	
Undetectable	156 (87.2)
Detectable	8 (4.5)
Unknown	15 (8.4)
Diagnosed at enrollment visit	
Any sexually transmitted infection	407 (13.7)
Chlamydia	246 (8.3)
Rectal	185 (6.2)
Urethral	65 (2.2)
Pharyngeal	16 (0.5)
Gonorrhea	194 (6.5)
Rectal	100 (3.4)
Urethral	17 (0.6)
Pharyngeal	111 (3.7)
Syphilis	34 (1.1)
In the 3 mo Prior to Enrollment Visit	
Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status	1435 (48.1)
>1 Episode of condomless insertive anal intercourse with a casual male partner with HIV or of unknown HIV status	1046 (35.1)
>1 Episode of anal intercourse without correct and consistent condom use (eg, condom slipped off or broke)	918 (30.8)
Used methamphetamines	412 (13.8)
Self-reported diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis	484 (16.2)

Abbreviation: PrEP, preexposure prophylaxis.

[a] For excluded participants' comparison, see eTable 2 in Supplement 2.

[b] Indicates percentage with nonmissing responses (N=2981) unless otherwise stated.

[c] Gender identity and trans and gender diverse experience data are based on participants' self-reported gender and self-reported sex assigned at birth (eTable 1 in Supplement 2 for breakdown).

[d] Indicates a person whose gender identity corresponds with the sex the person had or was identified as having at birth.

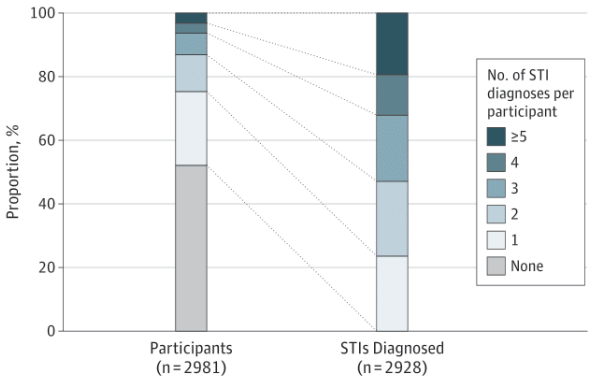
gonorrhea, and 8.0 per 100 person-years for syphilis. Rectal infections were most common for both chlamydia and gonorrhea, and the incidence of any STI was greatest among those aged 25 to 34 years (**Table 2**).

Exploratory Outcomes

Table 3 shows unadjusted and adjusted hazard ratios for factors associated with STI diagnosis during study follow-up. In bivariable Cox regression analyses, characteristics associated with greater STI risk included younger age; use of PrEP and postexposure prophylaxis prior to enrollment; diagnosis of rectal gonorrhea, rectal chlamydia or syphilis prior to enrollment; greater numbers of oral sex partners; greater numbers of anal sex partners; inconsistent or no condom use with casual partners; and participation in group sex. A total of 2058 (69%) participants had complete data for all behavioral responses included in the multivariable model and contributed to the multivariable analysis. In the multivariable model, younger age; diagnosis of rectal gonorrhea, rectal chlamydia or syphilis prior to enrollment; a greater number of anal sex partners; and participation in group sex remained significantly associated with greater STI risk, however inconsistent or no condom use with casual partners was not significantly associated with STI risk.

There were 1378 participants who had at least 1 prestudy STI test and were included in the before-and-after analysis, contributing 1347.5 person-years preenrollment and 1563.4 person-years postenrollment. Compared with the 1603 participants who were not included in the before-and-after analysis, included participants were older (mean age, 39.0 years vs 33.8 years; $P < .001$) and less likely to report injection drug use at enrollment (3.7% vs 6.5%; $P < .001$). Additionally, these same participants were more likely to report using methamphetamines (16.4% vs 11.6%; $P < .001$) and report more than 1 episode of insertive condomless anal intercourse with a partner of unknown HIV status (40.1% vs 30.8%; $P < .001$) in the 3 months prior to enrollment (see eTable 4 in Supplement 2 for comparison of participants included vs excluded in the before-and-after analysis). Among the 1378 participants included the before-and-after analysis, incidence of any STI increased from 69.5 per 100 person-years in the year prior to enrollment to 98.4 per 100 person-years during study follow-up (IRR, 1.41 [95% CI, 1.29-1.56]; incidence rate difference [IRD], 28.9/100 person-years [95% CI, 22.3-35.5]).

Figure. Distribution of Participants and STI Diagnoses by Number of Infections per Participant During Follow-up



See eTable 3 for corresponding data.

Table 2. Incidence of Sexually Transmitted Infections During Follow-up Among Included Participants (N = 2981)

	No. of Infections	Person-Years of Follow-up (n = 3185.0)[a]	Incidence Rate per 100 Person-Years (95% CI)
All STIs	2928		91.9 (88.7-95.3)
Chlamydia	1434		45.0 (42.7-47.4)
Rectal[b]	1091		34.3 (32.3-36.3)
Urethral[b]	381		12.0 (10.8-13.2)
Pharyngeal[b]	127		4.0 (3.3-4.7)
Gonorrhea	1242		39.0 (36.9-41.2)
Rectal[b]	719		22.6 (21.0-24.3)
Urethral[b]	233		7.3 (6.4-8.3)
Pharyngeal[b]	629		19.7 (18.3-21.3)
Syphilis	252	3140.8	8.0 (7.1-9.0)
Site[b]			
Rectal infections	1810		56.8 (53.4-60.4)
Urethral infections	614		19.3 (17.4-21.3)
Pharyngeal infections	756		23.7 (22.0-25.6)
Age group,y[c]			
18-24 (n = 307)	161	186.1	86.5 (74.6-101.5)
25-29 (n = 634)	554	536.3	103.3 (94.9-112.1)
30-34 (n = 620)	733	684.4	107.1 (99.8-115.3)
35-39 (n = 482)	495	593.2	83.4 (76.4-91.2)
40-44 (n = 356)	354	432.2	81.9 (73.8-90.9)
45-49 (n = 437)	486	548.0	88.7 (81.2-97.1)
≥50 (n = 145)	145	204.7	70.8 (60.2-83.4)

Abbreviation: STI, sexually transmitted infection.

[a] Number of person-years indicated unless otherwise stated.

[b] Sum is greater than all STIs total as concurrent diagnosis of same infection at multiple anatomic sites was considered a single infection in the all STIs total.

[c] Subgroup analysis indicates all STIs.

Table 3. Unadjusted and Adjusted Hazard Ratios for Factors Associated With Sexually Transmitted Infection Diagnosis Among Participants During Follow-up[a]

Characteristic	Bivariable Analysis		Multivariable Analysis (n = 2058)	
	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Age (5-y increase)	0.95 (0.93-0.98)	<.001	0.94 (0.90-0.97)	<.001
Aboriginal or Torres Strait Islander	0.92 (0.64-1.33)	.68		
Born outside of Australia	1.06 (0.95-1.18)	.28		
Ever used PrEP before enrollment	1.11 (1.00-1.22)	.04	1.10 (0.96-1.27)	.16
Ever used postexposure prophylaxis before enrollment	1.29 (1.18-1.42)	<.001	1.09 (0.96-1.25)	.20
Exchanged sex for money in past 12 mo	1.21 (0.92-1.59)	.18		
Use of injection drugs				
Ever	1.42 (1.24-1.64)	<.001	0.90 (0.64-1.26)	.54
Recently (past 12 mo)	1.53 (1.31-1.81)	<.001	1.30 (0.90-1.86)	.16
Enrollment risk criteria (≤3 mo prior to enrollment)				
Self-reported diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis	1.66 (1.49-1.85)	<.001	1.23 (1.05-1.45)	.01
Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status	1.28 (1.17-1.41)	<.001	1.17 (1.02-1.34)	.03
Used methamphetamines	1.45 (1.29-1.63)	<.001	0.90 (0.73-1.11)	.32
>1 Episode of anal intercourse without proper condom use	1.13 (1.03-1.25)	.01	1.11 (0.97-1.28)	.11
Regular partner during the last 6 mo	0.96 (0.84-1.10)	.55		
Self-reported PrEP adherence (%)[b]				
Taking PrEP daily (95.5)	1 [Reference]			
Taking PrEP 4-6 d per wk (3.4)	1.18 (0.81-1.55)	.24		
Taking PrEP 1-3 d per wk (0.4)	0.81 (0.42-1.56)	.52		
Intermittent use of PrEP (0.8)	0.67 (0.37-1.21)	.19		
No. of oral sex partners in last 6 mo (%)[b]				
1-5 (36.6)	1 [Reference]		1 [Reference]	
6-10 (26.9)	1.64 (1.38-1.95)	<.001	1.17 (0.94-1.45)	.16
11-20 (19.9)	1.97 (1.64-2.35)	<.001	0.95 (0.74-1.22)	.69
21-50 (12.8)	2.31 (1.90-2.82)	<.001	0.86 (0.63-1.17)	.33
>50 (3.9)	2.05 (1.49-2.81)	<.001	0.78 (0.30-1.87)	.59
No. of anal sex partners in last 6 mo (%)[b]				
1-5 (45.3)	1 [Reference]		1 [Reference]	
6-10 (25.3)	1.54 (1.31-1.82)	<.001	1.30 (1.06-1.59)	.01
11-20 (17.6)	2.19 (1.85-2.58)	<.001	1.91 (1.48-2.46)	<.001
21-50 (9.5)	2.32 (1.88-2.86)	<.001	2.17 (1.57-3.00)	<.001
>50 (2.4)	2.47 (1.72-3.55)	<.001	2.53 (1.58-4.03)	<.001
Condom use with regular partner in last 6 mo (%)[b]				
Always (7.3)	1 [Reference]		1 [Reference]	
Usually (>50% of the time) (19.7)	2.08 (1.37-3.15)	.001	1.27 (0.81-2.00)	.30
Sometimes (≤50% of the time) (25.5)	2.42 (1.62-3.62)	<.001	1.27 (0.82-1.98)	.29
Never (47.5)	1.84 (1.23-2.74)	.003	1.06 (0.36-1.29)	.24
Condom use with casual partners in last 6 mo (%)[b]				
Always (14.0)	1 [Reference]		1 [Reference]	
Usually (>50% of the time) (29.2)	1.82 (1.41-2.36)	<.001	1.38 (0.96-1.97)	.08
Sometimes (≤50% of the time) (38.4)	2.13 (1.67-2.71)	<.001	1.38 (0.96-1.99)	.08
Never (18.5)	1.94 (1.48-2.54)	<.001	1.31 (0.88-1.97)	.18
Group sex in last 6 mo (%)[b]				
None (40.0)	1 [Reference]		1 [Reference]	
Once or a few times (47.9)	1.89 (1.64-2.19)	<.001	1.28 (1.09-1.49)	.002
≥Monthly (10.8)	2.70 (2.22-3.29)	<.001	1.45 (1.15-1.83)	.002
≥Weekly (1.4)	3.17 (2.14-4.71)	<.001	1.67 (1.16-2.40)	.006

(continued)

Table 3. Unadjusted and Adjusted Hazard Ratios for Factors Associated With Sexually Transmitted Infection Diagnosis Among Participants During Follow-up[a] (continued)

Characteristic	Bivariable Analysis		Multivariable Analysis (n = 2058)	
	Unadjusted Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Substance use before or during sex in the last 6 mo (%)[b]				
Alcohol (49.0)	1.28 (1.13-1.46)	<.001	0.91 (0.79-1.06)	.24
Amyl nitrite (poppers) (45.8)	1.55 (1.37-1.76)	<.001	1.08 (0.94-1.26)	.26
Methylenedioxymethamphetamine (ecstasy) (16.2)	1.38 (1.18-1.62)	<.001	0.92 (0.76-1.10)	.35
Methamphetamines (13.9)	1.87 (1.62-2.16)	<.001	1.25 (0.99-1.57)	.06
Gamma hydroxybutyrate (GHB) (11.5)	1.92 (1.64-2.24)	<.001	1.25 (1.03-1.52)	.03
Cocaine (8.9)	1.49 (1.24-1.78)	<.001	1.13 (0.92-1.40)	.25

Abbreviation: PrEP, preexposure prophylaxis.

[a] There were 2058 participants with complete data for all responses who were included in the multivariable analysis. All 2981 participants provided data for at least 1 measurement in bivariable analyses.

[b] For repeated behavioral measures, % is the proportion of all nonmissing responses during follow-up, noting that participants completed different numbers of surveys.

Post Hoc Analyses

Of the 1378 participants with preenrollment testing data, 541 reported PrEP use prior to enrolling in the study, leaving 837 PrEP-naive participants. Compared with PrEP-naive participants, PrEP-experienced participants were more likely to meet the risk-based behavioral criteria at enrollment (see eTable 5 in Supplement 2 for comparison of PrEP-experienced vs PrEP-naive participants). Post hoc disaggregation of results by preenrollment PrEP use showed that STI incidence in the year prior to enrollment was significantly greater among PrEP-experienced participants (92.4/100 person-years) than PrEP-naive participants (55.1/100 person-years) (IRR, 1.68 [95% CI, 1.47-1.91]; IRD, 37.3/100 person-years [95% CI, 27.7-47.0]) (**Table 4**). Among PrEP-naive participants, incidence of any STI increased significantly to 94.2 per 100 person-years (IRR, 1.71 [95% CI, 1.49-1.96]; IRD, 39.1/100 person-years [95% CI, 31.0-47.2]) during follow-up, whereas the change in incidence among PrEP-experienced participants to 104.1/100 person-years during follow-up was not significant (IRR, 1.13, 95% CI, 0.99-1.28; IRD, 11.7/100 person-years [95% CI, −0.3 to 23.5]) (Table 4). Among PrEP-naive participants, incidence significantly increased for chlamydia (IRR, 1.84, 95% CI, 1.55-2.20; IRD, 21.3/100 person-years [95% CI, 15.5-27.1]) and gonorrhea (IRR, 1.69, 95% CI, 1.42-2.01; IRD, 16.9/100 person-years [95% CI, 11.4-22.4]) overall and at each anatomical site (Table 4) from before enrollment to during PrEP use. No significant change was observed for syphilis between preenrollment and postenrollment periods in either the PrEP-experienced (IRR, 1.32, 95% CI, 0.89-1.95; IRD, 2.4/100 person-years [95% CI, −1.1 to 5.7) or PrEP-naive (IRR, 1.24, 95% CI, 0.87-1.78; IRD, 1.5/100 person-years [95% CI, −1.0 to 4.1]) group.

The mean number of clinic visits per year increased between preenrollment and postenrollment periods from 3.2 to 4.7 among PrEP-naive participants (absolute difference, 1.5 [95% CI, 1.3-1.7]) and from 4.4 to 4.7 among PrEP-experienced participants (absolute difference, 0.3 [95% CI, 0.1-0.6]). The mean number of STI tests per year increased between preenrollment and postenrollment periods from 8.5 to 12.9 among PrEP-naive participants (absolute difference, 4.4 [95% CI, 4.1-4.7]) and from 11.7 to 13.0 among PrEP-experienced participants (absolute difference, 1.3 [95% CI, 0.9-1.7]; see eTable 6 in Supplement 2 for number of tests performed before and after enrollment).

After adjusting for change in individual STI testing frequency between periods, a significant increase across periods was observed for any STI (adjusted IRR, 1.12 [95% CI, 1.02-1.23]) and for chlamydia (adjusted IRR, 1.17 [95% CI, 1.04-1.33]) for all participants (eTable 7 in Supplement 2) and for PrEP-naive participants with any STI (adjusted IRR, 1.21 [95% CI 1.06-1.39]) and with chlamydia (adjusted IRR, 1.38 [95% CI 1.13-1.66]) (Table 4). However, after adjusting for testing frequency, the change in incidence of any STI from preenrollment to postenrollment among PrEP-experienced participants was not significant (adjusted IRR, 1.05 [95% CI 0.92-1.19]), and no significant change was observed in either group of participants for gonorrhea or syphilis (Table 4).

Discussion

This cohort of predominantly gay and bisexual men who accessed PrEP through a PrEP intervention study in Victoria experienced high rates of bacterial STIs, with STI diagnoses highly concentrated among a subgroup of participants during follow-up. STI diagnosis during follow-up was associated with reporting higher numbers of anal sex partners and participation in group sex; however, in the multivariable analysis, there was no independent association with reported levels of condom use, a factor historically strongly associated with STI risk. STI incidence increased from before to after commencing PrEP with the increase greatest for chlamydia infection. Although the incidence of bacterial STIs increased from the period before PrEP use to during PrEP use among participants commencing PrEP for the first time, the study design did not include a control group that did not receive PrEP and could not directly imply that PrEP initiation per se caused the observed increase in STI risk. The lack of association with condoms and clustering of STIs in a small group of participants suggested that commencing PrEP may be associated with unknown or unmeasured factors that drive STI risk, such as changes in the size and constituents of sexual networks or other unmeasured sexual behaviors.

Table 4. Incidence of Sexually Transmitted Infections Before and After Enrollment (n = 1378)[a]

Outcome (No. of Participants)[b]	PrEP-Experienced Participants (n = 541)						PrEP-Naive Participants (n = 837)					
	IR 1 Year Before Enrollment[c]	IR During Follow-up[c]	IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)[d]	*P* Value	IR 1 Year Before Enrollment[c]	IR During Follow-up[c]	IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)[d]	*P* Value
All STIs (n = 1378)	92.4	104.1	1.13 (0.99-1.28)	.07	1.05 (0.92-1.19)	.49	55.1	94.2	1.71 (1.49-1.96)	<.001	1.21 (1.06-1.39)	.006
Chlamydia (n = 1318)	45.8	52.4	1.14 (0.97-1.35)	.12	1.04 (0.88-1.23)	.66	25.2	46.5	1.84 (1.55-2.20)	<.001	1.38 (1.13-1.66)	.001
Rectal (n = 1240)	36.3	40.5	1.12 (0.92-1.36)	.28	0.98 (0.81-1.18)	.83	19.4	34.4	1.78 (1.44-2.19)	<.001	1.20 (0.95-1.51)	.13
Urethral (n = 1304)	13.1	14.1	1.08 (0.78-1.49)	.65	0.96 (0.69-1.33)	.80	7.6	13.9	1.83 (1.30-2.56)	<.001	1.32 (0.91-1.90)	.14
Pharyngeal (n = 1061)	2.6	4.0	1.52 (0.73-3.18)	.26	1.40 (0.66-2.95)	.38	2.6	5.1	1.99 (1.10-3.62)	.02	1.64 (0.86-3.13)	.13
Gonorrhea (n = 1324)	40.1	43.4	1.08 (0.90-1.30)	.38	0.99 (0.83-1.17)	.87	24.6	41.5	1.69 (1.42-2.01)	<.001	1.11 (0.92-1.34)	.26
Rectal (n = 1241)	24.6	25.6	1.04 (0.82-1.33)	.75	0.93 (0.73-1.19)	.57	15.1	25.2	1.67 (1.33-2.09)	<.001	1.00 (0.78-1.28)	.99
Urethral (n = 1309)	7.4	9.5	1.28 (0.88-1.86)	.20	1.17 (0.80-1.70)	.42	3.6	7.5	2.06 (1.29-3.31)	.002	1.33 (0.84-2.09)	.23
Pharyngeal (n = 1274)	17.5	19.7	1.13 (0.86-1.47)	.38	1.03 (0.79-1.34)	.83	11.6	17.7	1.53 (1.17-1.99)	.002	1.04 (0.78-1.38)	.78
Syphilis (n = 1318)	7.4	9.8	1.32 (0.89-1.95)	.17	1.28 (0.87-1.90)	.21	6.4	7.9	1.24 (0.87-1.78)	.24	0.93 (0.62-1.40)	.74
Rectal infections (n = 1243)	60.9	66.0	1.08 (0.91-1.30)	.38	0.95 (0.79-1.13)	.54	34.7	59.6	1.72 (1.44-2.05)	<.001	1.10 (0.91-1.32)	.32
Urethral infections (n = 1310)	20.7	23.6	1.14 (0.89-1.45)	.29	1.01 (0.79-1.29)	.95	11.5	21.3	1.86 (1.40-2.48)	<.001	1.26 (0.94-1.70)	.13
Pharyngeal infections (n = 1276)	20.1	23.5	1.17 (0.91-1.51)	.23	1.03 (0.80-1.32)	.85	13.8	23.1	1.67 (1.31-2.14)	<.001	1.14 (0.88-1.47)	.34

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; PrEP, preexposure prophylaxis; STI, sexually transmitted infection.

[a] Analyses of change in incidence disaggregated by PrEP-experienced vs PrEP-naive participants were post hoc. Incidence rates, IRRs, and adjusted IRRs for all 1378 participants combined are shown in eTable 7 in Supplement 2.

[b] The number of participants for each STI outcome category counts only those with a test result for that specific STI and anatomical site in the year prior to enrollment and during follow-up. Participants could contribute multiple diagnoses in each period (before enrollment and during follow-up).

[c] Values are per 100 person-years.

[d] Adjusted for change in individual testing frequency between before enrollment and during follow-up. Adjusted IRRs were calculated using negative binomial regression with robust standard errors clustered by participant.

Rates of chlamydia and gonorrhea were high during study follow-up, but were comparable to rates among other cohorts of gay and bisexual men using PrEP reported internationally.[10,11,21,22] Most STIs observed during study follow-up were diagnosed within a subgroup of participants who experienced high rates of reinfection. This finding highlights an opportunity to interrupt community-level STI transmission by offering frequent, easily accessible STI screening and other prevention strategies to PrEP users who are diagnosed with multiple STIs. A recent modeling study found that while PrEP use may lead to increased STI incidence following individual-level behavior change, the timely diagnosis and short duration of STIs among PrEP users due to high screening frequency may lead to an overall decrease in STI prevalence and incidence among the wider gay and bisexual male population.[23]

After multivariable adjustment, reporting greater numbers of recent casual sex partners and participation in group sex remained principal indicators of STI risk, and a dose-response relationship was observed between STI risk and increased partner numbers and frequency of group sex. In contrast, in the adjusted model, there was no significant difference in STI risk between participants who used condoms usually (>50% of the time), sometimes (≤50% of the time), or never with casual partners compared with those who reported always using condoms. The observation that consistent condom use was not significantly associated with decreased STI risk may be due to low-levels of consistent condom use across the cohort and the partial efficacy of condoms to prevent bacterial STI transmission. Recent work has suggested that bacterial STIs, particularly gonorrhea, are readily transmitted during oro-penile and oro-anal sex, for which gay and bisexual men rarely use condoms, and perhaps during tongue kissing.[24] While condoms continue to play an important role in STI prevention, their use among Australian gay and bisexual men has been declining in recent years,[25] and in a recent review of PrEP studies, condom use was shown to decline following initiation of PrEP.[9] Findings suggested that STI prevention campaigns should not focus solely on condom use but also on reducing the time to STI diagnosis and treatment by promoting easy access to frequent testing.

Limitations

This study has several limitations. First, early adopters of PrEP are typically individuals whose attendant STI risk is high,[21] and those enrolling into PrEP studies may not be representative of the wider population of gay and bisexual men who will use PrEP outside of a study environment. Second, participants included in the before-and-after analysis were those accessing STI screening at ACCESS clinics before enrollment, and comparative analysis found that included participants were more likely than excluded participants to report methamphetamine use and report having more than 1 episode of condomless insertive anal intercourse with a partner of unknown HIV status or a partner with HIV not taking antiretroviral treatment in the 3 months prior to enrollment. Hence, selection bias may be present in this analysis, and findings may not be generalizable to all gay and bisexual men. Third, behavioral responses relied on self-reporting, which may lead to recall or social desirability bias. However, computer-assisted self-interview methods, as used in this study, have been shown to reduce such biases in sexual behavior reporting.[26] Fourth, although participant movement between clinics participating in ACCESS was captured, it is possible that some participants sought medical treatment for STIs at nonparticipating clinics. However, given that participants were routinely attending clinics involved in the study prior to enrollment, this would have little effect on the before-and-after analysis. Fifth, as only clinical testing data were extracted, and not data on STI treatments prescribed to participants, it could not be ensured that every STI was treated effectively and that all positive diagnoses were incident infections. However, these clinics are highly experienced in managing STIs, and participating study clinics followed standard STI treatment guidelines.[15] A conservative 30-day window was used to define new infections, so results were unlikely to be affected. Sixth, we did not report on the incidence of STIs in individuals who may have been using the study medication in an on-demand fashion. Study participants were advised to take PrEP on a daily basis, and use of on-demand preexposure prophylaxis was not collected systematically throughout the study. It will be important to evaluate the incidence of STIs among individuals using on-demand preexposure prophylaxis in future studies. Seventh, it is possible that participants who were lost to follow-up may have had differential STI risk compared with those not lost to follow-up, affecting the generalizability of our findings.

Conclusions

Among gay and bisexual men using PrEP, sexually transmitted infections were highly concentrated among a subset of study participants, and receipt of PrEP after study enrollment was associated with an increased incidence of STIs compared with preenrollment. These findings highlight the importance of frequent STI testing among gay and bisexual men using PrEP.

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Author Affiliations: Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia (Traeger, Asselin, Lal, Spelman, Nguyen, Ryan, El-Hayek, Hellard, Stoové, Wright); Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia (Cornelisse, Price, Chang, Armishaw, Vujovic, Lal, Mak, Ryan, Lockwood, Hoy, Hellard, Wright); Melbourne Sexual Health Centre, Alfred Health, Melbourne, Victoria, Australia (Cornelisse, Fairley); Prahran Market Clinic, Melbourne, Victoria, Australia (Cornelisse, Roth); Central Clinical School, Monash University, Melbourne, Victoria, Australia (Cornelisse, Fairley, Chang); Northside Clinic, Melbourne, Victoria, Australia (Willcox); Centre Clinic, Thorne Harbour Health, Melbourne, Victoria, Australia (Tee); PRONTO! Clinic, Thorne Harbour Health, Melbourne, Victoria, Australia (Penn, Cundill); ERA Health, Melbourne, Victoria, Australia (Forgan-Smith, Gall); Ballarat Community Health Centre, Ballarat, Victoria, Australia (Pickett); School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (Spelman, Hellard, Stoové); The Peter Doherty Institute of Infection and Immunity, University of Melbourne, Melbourne, Victoria, Australia (Spelman, Wright); Department of Gender and Cultural Studies, University of Sydney, Sydney, New South Wales, Australia (Murphy); The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia (Murphy); Sexual Health and Viral Hepatitis Service, Department of Health and Human Services, Government of Victoria, Melbourne, Victoria, Australia (West); Thorne Harbour Health, Melbourne, Victoria, Australia (Ruth, Batrouney).

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Concept and design: Traeger, Fairley, Chang, Lal, Mak, Batrouney, Lockwood, Stoové, Wright.
Acquisition, analysis, or interpretation of data: Traeger, Cornelisse, Asselin, Price, Roth, Willcox, Tee, Fairley, Chang, Armishaw, Vujovic, Penn, Cundill, Forgan-Smith, Gall, Pickett, Lal, Mak, Spelman, Nguyen, Murphy, Ryan, El-Hayek, West, Ruth, Lockwood, Hoy, Hellard, Stoové, Wright.
Drafting of the manuscript: Traeger, Fairley, Forgan-Smith, West, Stoové, Wright.
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Statistical analysis: Traeger, Tee, Spelman, Stoové.
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The PrEPX Study Team: Edwina J. Wright, MBBS, PhD (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia; Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia; and The Peter Doherty Institute of Infection and Immunity, University of Melbourne, Melbourne, Victoria, Australia), Brian Price, MBA (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia), Mark A. Stoové, Ph D (Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia; and School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia), Simon Ruth, MSSc (Thorne Harbour Health, Melbourne, Victoria, Australia), Colin Batrouney, BA (Thorne Harbour Health, Melbourne, Victoria, Australia), John T. Lockwood, BN (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia), Michael West, BA (Sexual Health and Viral Hepatitis Service, Department of Health and Human Services, Government of Victoria, Melbourne, Victoria, Australia), Dean A. Murphy, PhD (Department of Gender and Cultural Studies, University of Sydney, Sydney, New South Wales, Australia; and The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia), John de Wit, PhD (Centre for Social Research in Health, University of New South Wales, Sydney, New South Wales, Australia), Luxi Lal, B Pharm (Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia; and Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia), Jennifer Audsley, PhD (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia; and The Peter Doherty Institute for Infection and Immunity, The University of Melbourne and Royal Melbourne Hospital, Melbourne, Victoria, Australia), Christina C. Chang, MBBS, PhD (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia; and Central Clinical School, Monash University, Melbourne, Victoria, Australia), Carol El-Hayek, MEpi (Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia), Anne Mak, BPharm (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia), Alison Duncan, BPharm (The Alfred, Alfred Health, Melbourne, Victoria, Australia), Joe Sasadeusz, MBBS, PhD (Royal Melbourne Hospital, Melbourne, Victoria, Australia; The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia; and The Alfred, Alfred Health, Melbourne, Victoria, Australia), Brent Allan, MSocSc (Living Positive Victoria, Melbourne, Victoria, Australia), Michael Whelan, BA (PAN-PrEP Access Now, Melbourne, Victoria, Australia), Daniel McPhail, (PrEP'd For Change, Melbourne, Victoria, Australia), David Wilson, PhD (Burnet Institute, Melbourne, Victoria, Australia), Olga Vujovic, MBBS (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia), Martin Holt, PhD (Kirby Institute, University of New South Wales, Sydney, NSW, Australia), Chris Williams, (PrEP'd For Change, Melbourne, Victoria, Australia), Steve Wesselingh, BMBS, PhD (South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia), James Ward, PhD (South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia), Danny Gallant, MBBS (South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia), Alison Ward, MBBS (Adelaide Sexual Health Centre, Adelaide, South Australia, Australia; and Royal Adelaide Hospital, Adelaide, South Australia, Australia), Alistair Chong, BSc (The Alfred, Alfred Health, Melbourne, Victoria, Australia; and University of Melbourne, Melbourne, Victoria, Australia), Katharine McKinnon, PhD (La Trobe University, Melbourne, Victoria, Australia), Kathleen E. Ryan, PhD (Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia; and Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia), Michael W. Traeger, MSc (Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia), Christopher K. Fairley, MBBS, PhD (Melbourne Sexual Health Centre, Alfred Health, Melbourne, Victoria, Australia; and Central Clinical School, Monash University, Melbourne, Victoria, Australia), Ivette Aguirre, BPharm (The Alfred, Alfred Health, Melbourne, Victoria, Australia), Ban Kiem Tee, MBBS (Centre Clinic, Thorne Harbour Health, Melbourne, Victoria, Australia), Norman J. Roth, MBBS (Prahran Market

Clinic, Melbourne, Victoria, Australia), Vincent J. Cornelisse, (Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Victoria, Australia; Melbourne Sexual Health Centre, Alfred Health, Melbourne, Victoria, Australia; Prahran Market Clinic, Melbourne, Victoria, Australia; and Central Clinical School, Monash University, Melbourne, Victoria, Australia), Jason Asselin, BSc (Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia), Timothy Read, MBBS, PhD (Melbourne Sexual Health Centre, Alfred Health, Melbourne, Victoria, Australia), Richard Moore, MBBS (Northside Clinic, Melbourne, Victoria, Australia), Jeff Willcox, MBBS (Northside Clinic, Melbourne, Victoria, Australia), George Forgan-Smith, MBBS (ERA Health, Melbourne, Victoria, Australia), John Gall, MBBS, PhD (ERA Health, Melbourne, Victoria, Australia), Matthew Penn, MBBS (PRONTO! Clinic, Thorne Harbour Health, Melbourne, Victoria, Australia), Pauline Cundill, BM (PRONTO! Clinic, Thorne Harbour Health, Melbourne, Victoria, Australia), Helan Lau, BN (Prahran Market Clinic, Melbourne, Victoria, Australia; and Centre Clinic, Thorne Harbour Health, Melbourne, Victoria, Australia), Danielle Collins, BN (The Alfred, Alfred Health, Melbourne, Victoria, Australia), Sian Edwards, BN (Northside Clinic, Melbourne, Victoria, Australia), Susan Boyd, BN (Northside Clinic, Melbourne, Victoria, Australia), Claire Pickett, MBBS (Ballarat Community Health Centre, Ballarat, Victoria, Australia), Emma Paige, MBBS (The Alfred, Alfred Health, Melbourne, Victoria, Australia), Amanda Wade, MBBS, PhD (Geelong Hospital, Geelong, Victoria, Australia; and Barwon Health, Geelong, Victoria, Australia), Charlotte Bell, MBBS (Adelaide Sexual Health Centre, Adelaide, South Australia, Australia; and Royal Adelaide Hospital, Adelaide, South Australia, Australia), William Donohue, MBBS, MPH (O'Brien St Practice, Adelaide, South Australia, Australia), Samuel Elliot, MBBS (Riverside Family Medical Practice, St Marys, South Australia, Australia), Helen Calabretto, PhD (SHINE SA, South Australia, Australia), Louise Owen, MBBS (Sexual Health Service Tasmania, Tasmania, Australia; Clinic 60, Hobart, Tasmania, Australia; and Clinic 34, Launceston, Tasmania, Australia), Jenny Kelsall, BA (Harm Reduction Victoria, Victoria, Australia).

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Appendix C2. Changes in HIV PrEP prescribing in Australian clinical services following COVID-19 restrictions

Citation:

Traeger MW, Patel P, Guy R, Hellard M, Stoové M. Changes in HIV pre-exposure prophylaxis prescribing in Australian clinical services following COVID-10 restrictions. *AIDS*. 2021;35(1):155-157. doi:10.1097/QAD.0000000000002703

Correspondence

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Changes in HIV preexposure prophylaxis prescribing in Australian clinical services following COVID-19 restrictions

The first case of COVID-19 in Australia was diagnosed on 25 January 2020 [1]. In response, the Australian Federal and State governments implemented staged restrictions, including international and state border closures and physical distancing requirements in public spaces. Between 23 and 26 March, nonessential services, including gyms, restaurants and places of worship were closed, and, on 29 March, the government urged Australians to stay at home other than for essential reasons (i.e. care giving, exercise, and to access healthcare, food and supplies). Data from one large sexual health clinic in Melbourne showed a rapid decline in postexposure prophylaxis (PEP) dispensing following implementation of restrictions [2]. A survey of gay and bisexual men (GBM) accessing preexposure prophylaxis (PrEP) from the same clinic found that among 178 GBM reporting daily PrEP use in January to February 2020, 23% subsequently reported PrEP cessation in May (during restrictions) and 5% switched to on-demand PrEP, with participants reporting no longer engaging in casual sex and reduced number of sexual partners [3]. Although these data suggest that some GBM have reduced their PrEP use, findings are limited by self-report and it is not yet known whether these data reflect broader community trends beyond this single site.

We extracted PrEP prescribing data from 42 primary care and sexual health services across Australia participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-borne Viruses and Sexually Transmitted Infections (ACCESS) [4]. Specialized data extraction software installed at participating services extracts and links patient data across clinics over time [5]. We compared trends in weekly PrEP prescribing before (1 January 2019 to 31 March 2020) and after (1 April 2020 to 30 June 2020) the implementation of restrictions using segmented linear regression. We estimated the immediate drop in PrEP prescriptions following restrictions by comparing the predicted number of weekly PrEP prescriptions in the week starting 1 April 2020 (first week in the time-series following implementation of all restrictions) based on prerestrictions and during-restrictions trends. The ACCESS study was approved by the Alfred Hospital Ethics Committee (project 248/17).

Between 1 January 2019 and 30 June 2020, 52 596 PrEP prescriptions among 19 876 individuals (96.3% male individuals) were recorded at ACCESS clinics. Between 1 January 2019 and 31 March 2020 (prerestrictions period), there was an average of 718 PrEP prescriptions per week across the network. During this period, the weekly number of PrEP prescriptions was stable, with an estimated decline of 0.2 prescriptions per week ($P = 0.734$). PrEP prescriptions declined by an estimated 236 at the week following implementation of restrictions, representing an immediate 33.3% decline in prescriptions ($P < 0.001$). Between 1 April 2020 and 30 June 2020 (during-restrictions period), the average number of PrEP prescriptions per week was 543 (a 24.4% decline compared with the prerestrictions period overall). We then observed a nonsignificant increase of 10.6 prescriptions per week during the restrictions period ($P = 0.178$) (Fig. 1).

In New South Wales and Victoria (representing 77% of PrEP prescriptions in the study), the largest absolute declines in PrEP prescribing were observed. In Victoria, estimated weekly PrEP prescriptions fell from 294 to 188 (36% decline; $P < 0.001$); in New South Wales, estimated weekly prescriptions fell from 250 to 165 (33.9% decline; $P = 0.002$). Declines were also observed in the Australian Capital Territory (32–17; 46.9% reduction; $P = 0.001$), South Australia (50–35; 30.5% reduction; $P = 0.005$), and Tasmania (17–9; 47.1% reduction; $P = 0.002$) with no change in Western Australia ($P = 0.806$) and Queensland ($P = 0.404$).

Declines in PrEP prescribing may be due to decreased sexual activity among PrEP users or decreased attendance at clinical services, although seeking medical care was exempt from COVID-19 restrictions and many clinics provided telehealth consultations. A recent online survey found that among 940 Australian GBM, the mean number of sexual partners decreased more than 12-fold after participants first reported becoming 'concerned' about COVID-19. Further, only 16% of respondents who reported having casual sex prior to COVID-19 continued to do so following the implementation of restrictions [6].

Rapid changes in PrEP use among GBM, alongside changes in sexual behaviour mediated by the implementation of social restrictions, may have salient implications for the transmission of HIV and other sexually transmitted infections. Although we did not detect a continuing decline in PrEP prescribing during restrictions, ongoing community transmission of COVID-19 across multiple

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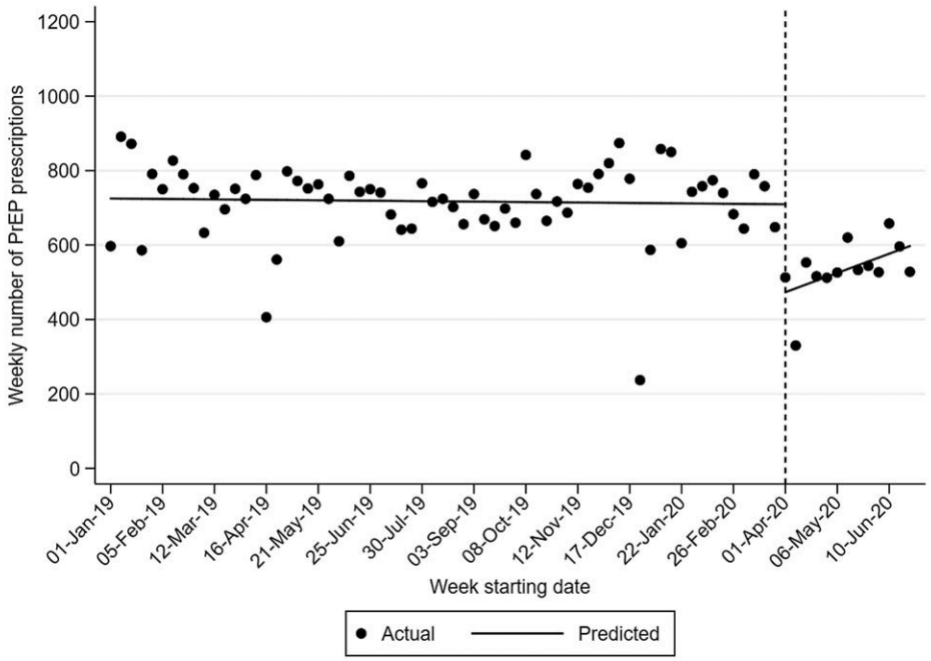

Fig. 1. Weekly preexposure prophylaxis prescriptions across 42 Australian services from January 2019 to June 2020, with segmented linear regression trends for prerestrictions (1 January 2019 to 31 March 2020)∗ and during-restrictions (1 April 2020 to 30 June 2020) periods. PrEP = preexposure prophylaxis. *Data point for week starting 24 December 2019 includes 8 days (24–31 December 2019).

Australian states suggests sustained and potentially additional restrictions are likely, with the state of Victoria already returning to lockdown status for the second time in late July. Reduced sexual activity may help interrupt community transmission of HIV and STIs. However, if sexual activity begins to return to pre-COVID-19 levels without a congruous and timely rebound in testing and PrEP use, this may create potential for increased transmission. Ongoing behavioural and epidemiological surveillance during the COVID-19 pandemic will be important in monitoring the effects of COVID-19 on HIV and STI diagnoses.

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Conflicts of interest

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Michael W. Traeger[a,b], Prital Patel[c], Rebecca Guy[c], Margaret E. Hellard[a,b,d], Mark A. Stoové[a,b], on behalf of the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS)[a]*Disease Elimination, Burnet Institute,* [b]*School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria,* [c]*Kirby Institute, UNSW Sydney, Sydney, New South Wales, and* [d]*Department of Infectious Diseases, Alfred and Monash University, Melbourne, Victoria, Australia.*

Correspondence to Michael W. Traeger, Burnet Institute, 85 Commercial Road, Melbourne VIC 3004, Australia.
Tel: +61 3 9282 2218;
e-mail: michael.traeger@burnet.edu.au

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Appendix C3. The presence of symptoms among cases of urethral gonorrhoea in men taking HIV PrEP in the PrEPX study

Citation:

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Open Forum Infectious Diseases

BRIEF REPORT

The Presence or Absence of Symptoms Among Cases of Urethral Gonorrhoea Occurring in a Cohort of Men Taking Human Immunodeficiency Virus Pre-exposure Prophylaxis in the PrEPX Study

Lucy C. Donovan,[1] Christopher K. Fairley,[2,3] Ei T. Aung,[2,3] Michael W. Traeger,[4,5] Edwina J. Wright,[4,6,7] Mark A. Stoové,[4,5] and Eric P. F. Chow[2,3,8]

[1]Prahran Market Clinic, Melbourne, Victoria, Australia, [2]Melbourne Sexual Health Centre, Alfred Health, Melbourne, Victoria, Australia, [3]Central Clinical School, Monash University, Melbourne, Victoria, Australia, [4]Disease Elimination Program, Burnet Institute, Melbourne, Victoria, Australia, [5]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, [6]Department of Infectious Diseases, Alfred Hospital, Monash Central Clinical School, Melbourne, Victoria, Australia, [7]Peter Doherty Institute, Melbourne, Victoria, Australia, [8]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia

We aimed to estimate how often urethral gonorrhoea is symptomatic among men in the Pre-Exposure Prophylaxis Expanded Victoria study. Eighty-seven percent of 213 cases of urethral gonorrhoea were symptomatic. Ensuring men with urethral gonorrhoea both recognize and present early for treatment is critical to reduce transmission.

Keywords. gonorrhoea; men who have sex with men; screening; sexually transmitted infection; urethritis.

Studies that have attempted to determine the proportion of men who develop symptoms after infection of the urethra with *Neisseria gonorrhoeae* have been subjected to considerable potential bias. Apart from one cohort analysis undertaken approximately 50 years ago, these cross-sectional studies have either been retrospective descriptions from sexual health clinics or studies screening large numbers of men [1–7]. Studies in sexual health clinics are biased towards overestimating the proportion of patients with symptoms because men who develop symptoms preferentially attend these services [8]. These clinic-based studies have estimated that 89%–94% of men with urethral *N gonorrhoeae* develop symptoms [1–3]. One cohort analysis among service men in 1974 found that 98% of men with urethral gonorrhoea developed symptoms [7]. In contrast, screening studies are biased towards underestimating the proportion of patients with symptoms because cases with symptoms have a much shorter duration and therefore are less likely to be present in cross-sectional studies. Furthermore, these screening studies have primarily screened asymptomatic men (ie, reporting that between 0% and 58% of men have symptoms) [4–6].

Estimating the proportion of men who have symptoms from urethral gonorrhoea is important because the recognition of symptoms prompt individuals to access healthcare and treatment. This allows for other important steps, such as contract tracing, which can put substantial downward pressure on transmission within populations. However, if symptoms are uncommon among men with urethral gonorrhoea, then strategies that increase symptom recognition will be less effective in reducing transmission, whereas strategies that promote regular asymptomatic screening of men at risk may be preferred.

We recently undertook a large cohort study of participants taking pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) in which 233 cases of urethral gonorrhoea occurred [9]. Data from this cohort study should provide a less biased method of determining the proportion of symptomatic cases than previous studies because participants were required to attend PrEP appointments every 3 months and sexually transmitted infection (STI) screening was required of all participants regardless of the presence of symptoms. Participants were also asked to attend their study enrollment clinic for testing and treatment should they develop STI symptoms between quarterly visits. The present study aimed to determine the proportion of men with symptomatic urethral gonorrhoea from the cohort study.

MATERIALS AND METHODS

The Pre-Exposure Prophylaxis Expanded (PrEPX) Victoria study was a multisite, single-armed, open-label intervention study of tenofovir disoproxil fumurate and emtricitabine for HIV PrEP among 4275 participants in Victoria, Australia, between July 2016 and May 2018 [9]. Men were followed up every 3 months. We conducted a retrospective analysis of the clinical records of men with linked STI testing data who developed incident urethral gonorrhoea and urethral chlamydia during the 3185 person-years of follow up in the PrEPX study. A detailed description of the PrEPX study is published elsewhere [10]. A total of 2981 PrEPX participants enrolled through 1 of 5 recruitment sites that also participate in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) project, an existing sentinel surveillance network [11], and were monitored for STI outcomes during study follow up.

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Correspondence: Lucy Donovan, MBBS, MPHTM, FRACGP, Melbourne Sexual Health Centre, 580 Swanston Street, Carlton, VIC 3053, Australia (lucy_donovan@hotmail.com).

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PATIENT CONSENT STATEMENT

Ethics approval was obtained from the Alfred Hospital Human Research Ethics Committee for the PrEPX study (projects 100/16 and 248/17) [10]. All participants provided written consent to have their medical records reviewed as part of this project when they consented to the PrEPX study.

Participants who had a positive test result from a urethral swab or first pass urine specimen for *N gonorrhoeae* by nucleic acid amplification test at 1 of the 5 recruitment sites were included in this analysis. As previously described [10], the ACCESS system uses specialized data extraction software to routinely extract clinical data from patient management systems. These data identified each case of urethral gonorrhoea among participants in the PrEPX study. Chart review for all urethral gonorrhoea cases was performed by L.C.D. and E.T.A. We reported the frequency, proportion, and corresponding 95% confidence intervals of urethral symptoms and other clinical characteristics. All statistical analyses were conducted using Stata (version 14).

RESULTS

Between July 2016 and May 2018, 233 cases of urethral gonorrhoea were diagnosed among 191 individual men. Table 1 shows the characteristics of the 191 men. Of the 191 men, 160 individuals were diagnosed with a single infection, 24 with 2 infections, 5 with 3 infections, 1 with 4 infections, and 1 with 6 infections during the study period (Table 2).

A total of 8 cases were excluded from this analysis because 2 cases (1 participant) had been excluded from the PrEPX study at enrollment after HIV was diagnosed and 6 cases did not have information on urethral symptoms in their clinical notes.

Of the 225 cases included, 176 reported urethral symptoms on the day of testing and 49 reported an absence of symptoms. Of the 176 cases who had urethral symptoms, 139 had typical urethral discharge (yellow, green, or pus like) and 30 had other urethral symptoms such as urethral discomfort, dysuria, or a nonpurulent discharge.

Among the 225 cases of urethral gonorrhoea, 222 were also tested for urethral chlamydia on the same day. Of these 222 cases of urethral gonorrhoea, 35 were coinfected with urethral chlamydia. Of the 174 symptomatic cases, 29 (17%) were also coinfected with chlamydia. Of the 48 asymptomatic cases, 6 (13%) were also coinfected with chlamydia.

Among the 49 cases that were asymptomatic, 7 were treated on the day of testing because they were sexual contacts of a known case of gonorrhoea. Of the 42 untreated asymptomatic cases, 37 had a record of them returning for treatment at 1 of the 5 recruitment sites and 5 sought treatment with a local healthcare provider. Among the 37 asymptomatic cases who returned for treatment, the time between testing and

Table 1. Characteristics of Participants With Urethral Gonorrhoea (N = 191)

Characteristics	No. (%)
Age (years), mean (standard derivation)	36.0 (10.1)
Gender	
Male	189 (99.0)
Transgender, Male	1 (0.5)
Nonbinary/Gender Fluid	1 (0.5)
Sex at Birth	
Male	189 (99.0)
Female	2 (1.0)
Sexuality	
Gay/Homosexual	180 (94.2)
Bisexual	9 (4.7)
Other	2 (1.0)
Country of Birth	
Australia	100 (52.4)
Overseas	68 (35.6)
Missing	23 (12.0)
Injecting Drug Use at Enrollment	
Yes	17 (8.9)
No	174 (91.1)
In the 3 Months Before Enrollment:	
Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status	99 (51.8)
>1 Episode of condomless insertive anal intercourse with a casual male partner with HIV or of unknown HIV status	82 (42.9)
>1 Episode of anal intercourse without correct and consistent condom use (eg, condom slipped off or broke)	59 (30.9)
Used methamphetamines	36 (18.8)
Self-reported diagnosis of rectal gonorrhoea, rectal chlamydia, or syphilis	48 (25.1)

Abbreviations: HIV, human immunodeficiency virus.

Table 2. Characteristics of 225 Cases of Urethral *Neisseria Gonorrhoeae* in the PrEPX Study

Characteristics	n/N	% (95% CI)
On Initial Presentation:		
Urethral Symptoms Present	176/225	78 (72–83)
Coinfected with urethral chlamydia*	29/174	17 (11–23)
Typical urethral symptoms	139/176	79 (72–84)
Other urethral symptoms†	30/176	17 (12–23)
Urethral Symptoms Absent	49/225	22 (17–28)
Coinfected with urethral chlamydia‡	6/48	13 (5–25)
Asymptomatic and treated on day	7/49	14 (7–27)
Asymptomatic and not treated on day	42/49	86 (72–93)
Known contact of gonorrhoea infection	21/225	9 (6–14)
Initially Asymptomatic and Returned for Treatment		
Returned to recruitment site for treatment	37/42	88 (75–95)
Urethral symptoms absent	16/37	43 (29–59)
Urethral symptoms present	9/37	24 (13–40)
Data incomplete to determine symptoms	12/37	32 (20–49)
Symptomatic at either presentation§	185/213	87 (82–91)

Abbreviations: CI, confidence interval; PrEPX, Pre-Exposure Prophylaxis Expanded.

*Two men with urethral symptoms were not tested for urethral chlamydia and therefore were excluded for coinfection analysis.

†The data on the nature of the symptoms was missing for 7 participants.

‡One man who did not have urethral symptoms was not tested for urethral chlamydia and therefore was excluded for coinfection analysis.

§The denominator excluded 7 asymptomatic individuals who were treated on the day of testing (contacts of gonorrhoea) and 5 who did not return for treatment at the 5 recruitment sites.

treatment follow up ranged from 2 to 16 days (mean = 6, median = 5 days). Nine had documentation that they had since developed some urethral symptoms, 12 cases had no documentation as to whether they were symptomatic or not, and 16 remained asymptomatic.

If the proportion of cases with symptoms includes the 176 who initially had symptoms and the 9 who later developed symptoms, then the proportion of cases with symptoms was 87% (185 of 213) (12 excluded because 7 asymptomatic cases were treated on the day of testing and 5 did not return for treatment at a recruitment site).

DISCUSSION

In this cohort study of men taking PrEP, 87% of men who acquired urethral gonorrhoea developed symptoms. This finding is relatively consistent with the estimates from most of the clinic-based studies where between 89% and 94% of men were symptomatic [1–3] and the only other cohort study where 98% of infections were symptomatic [7]. However, our findings are substantially greater than the screening studies where between 0% and 58% were symptomatic [4–6].

One of the strengths of this study is that we have managed to capture participants at 3 monthly intervals and also when symptomatic. Due to the design of this study, we have been able to combine the strengths of previous sexual health clinic studies and those of screening studies.

There are several limitations to our study. First, the data on symptoms were collected retrospectively from patient records. More importantly, however, only a few cases did not specifically mention either the presence or absence of urethral symptoms. Second, our study may have slightly overestimated the proportion of cases who were asymptomatic because 7 asymptomatic cases who were contacts of gonorrhoea were treated on the day and may have developed symptoms if they had not been treated so promptly. We may have also underestimated the proportion of men who would have developed symptoms because some men were recalled and treated within a short time frame of only a few days (median = 5 days). The cases of chlamydia coinfection may have also affected our results. Approximately 17% of the symptomatic cases were coinfected, and therefore some of these symptoms may be attributable to the chlamydia infection rather than the gonorrhoea infection.

Previous studies of men attending sexual health clinics have reported slightly higher rates of symptomatic urethral gonorrhoea. Ong et al's [1] study of 242 men who have sex with men (MSM) attendances at a sexual health clinic in Melbourne found that 89% of urethral gonorrhoea cases were symptomatic. Barbee et al's [2] case-control study of 1604 MSM attending 2 sexual health clinics in the United States found that 94% of urethral gonorrhoea cases were symptomatic. Martín-Sánchez et al's [3] study of 116 heterosexual men attending a sexual health clinic in Melbourne found that 94% of cases of urethral gonorrhoea were symptomatic. Most of these sexual health clinics have a standardized reporting form that allows for more complete sets of data. However, the nature of sexual health clinics creates a bias towards more symptomatic cases given that individuals with symptoms are prompted to attend these services by the symptoms [12].

The reported proportion of men who are symptomatic with urethral gonorrhoea varies greatly in previous screening studies. In Pack et al's [5] study of black male adolescents from detention facilities in the United States, 0 of 19 cases of urethral gonorrhoea reported symptoms. However, the study also reported 9 cases of dual chlamydia/gonorrhoea urethral infection in which 33% of males were experiencing symptoms so it is possible that 3 of 28 (11%) had symptoms. A study of 12 young men attending health centers and educational settings in the United States found that 58% of men with urethral gonorrhoea had symptoms [4]. The study included men with incidental urethral symptoms but actively excluded men who were seeking healthcare with genitourinary symptoms as their primary reason of attendance. A further study by Handsfield et al [6] of 59 men serving in the US Army reported that 32% of men with urethral gonorrhoea had symptoms. These studies have all looked at populations that were not presenting with symptoms or actively excluded symptomatic presentations, and therefore they may have biased the findings to underestimate the numbers of symptomatic infections. They are also limited by their sample

sizes, which are significantly smaller than the sexual health clinic studies. The study design of these screening studies and low sample sizes may explain why their results have differed so greatly with the results of our study.

The estimate in our cohort analysis was much closer to the previous single cohort study and the clinic studies than it was to the cross-sectional studies. This is likely to be because if most urethral gonorrhoea cases are symptomatic (ie, finding from our study), then any estimate will be driven mostly by these cases and not the small number of asymptomatic cases. The small number of studies providing asymptomatic cases may reflect how uncommon asymptomatic cases are and therefore pragmatically how difficult it is to undertake studies to identify them.

CONCLUSIONS

Our results support previous findings that the majority of men with urethral gonorrhoea are symptomatic; however, there were a clinically meaningful number of asymptomatic presentations. These findings support health promotion to improve symptom recognition and the provision of accessible sexual healthcare but also support the need for ongoing screening in asymptomatic high-risk groups. Gonorrhoea infection occurs commonly in other sites (ie, oropharynx and anorectum) apart from the urethra. Oropharyngeal and anorectal gonorrhoea infections are mostly asymptomatic, whereas urethral gonorrhoea infections are mostly symptomatic; therefore, a combination of frequent screening and symptoms awareness are important for gonorrhoea prevention and control.

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Author contributions. E. P. F. C. and C. K. F. conceived and designed the study. E. P. F. C., L. C. D., E. T. A., and C. K. F. designed the study materials. L. C. D. and E. T. A. performed the clinical audit. L. C. D. performed the statistical analyses and wrote the first draft of the manuscript. E. P. F. C. oversaw the study. M. W. T. contributed to data duration. M. A. S. helped lead the quantitative data collections for the Pre-Exposure Prophylaxis Expanded (PrEPX) study and contributed to drafting the manuscript. All authors were involved in revising the manuscript for important intellectual content and approved the final version. E. J. W. was the principal investigator of the PrEPX study and contributed to drafting this manuscript.

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Appendix C4. Trends in HIV and STI testing among gay and bisexual men after rapid scale-up of PrEP in Victoria, Australia

Citation:

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OPEN

Trends in Human Immunodeficiency Virus and Sexually Transmitted Infection Testing Among Gay, Bisexual, and Other Men Who Have Sex With Men After Rapid Scale-up of Preexposure Prophylaxis in Victoria, Australia

Kathleen E. Ryan, PhD,†‡ Jason Asselin, MEpi,† Chistopher K. Fairley, MBBS, PhD,§¶ Judy Armishaw, BNurs,* Luxi Lal, BPharm,*† Long Nguyen, MComm,† Dean Murphy, PhD,||** Michael Traeger, MSc,*‡ Margaret Hellard, MBBS, PhD,*†‡ Jennifer Hoy, MBBS,* Mark Stoové, PhD,*‡ Edwina Wright, MBBS, PhD,*†§ and on behalf of the PrEPX Study team*

Objective: Scale-up of human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) has raised concerns regarding its impact on clinic capacity and access to HIV testing. We describe enrolment in PrEPX, a large PrEP implementation study in Victoria, Australia, and the impact of PrEP uptake and maintenance on existing health services.

Methods: We describe enrolment between July 26, 2016, and March 31, 2018, and trends in HIV testing among PrEPX participating and nonparticipating gay and bisexual and other men who have sex with men (GBM) at 5 study clinics participating in a sentinel surveillance system (ACCESS). We evaluated HIV and STI testing trends using segmented linear regression across the prestudy (January 2015 to June 2016) and PrEPX study (July 2016 to March 2018) periods.

Findings: There were 2,049 individuals who registered interest in study participation: 72% enrolled into the study. Study clinics enrolled participants rapidly; of 4265 people enrolled in PrEPX (98% GBM), 1000 enrolled by week 3, 88% (n = 876) of whom enrolled at ACCESS sites.

Prestudy period HIV testing rates were increasing at all ACCESS sites. In the month PrEPX commenced, there was an additional 247 HIV tests among PrEPX participants ($P < 0.01$) and no significant change among non-PrEPX GBM ($P = 0.72$). Across the study period, HIV testing increased by 7.2 ($P < 0.01$) and 8.9 ($P < 0.01$) tests/month among PrEPX participants and non-PrEPX GBM, respectively. The HIV testing increased among non-PrEPX GBM at sexual health clinics (18.8 tests/month, $P < 0.01$) and primary care clinics (7.9 tests/month, $P < 0.01$). Similar trends were observed across testing for all measured STIs.

Conclusions: Rapid PrEP scale-up is possible without a reduction in HIV testing among GBM not using PrEP.

Daily use of tenofovir and emtricitabine for human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) is shown to be highly efficacious at preventing transmission among gay, bisexual and other men who have sex with men (GBM),[1,2]

From the *Department of Infectious Disease, Alfred Health and Monash University; †Burnet Institute; ‡Department of Epidemiology and Preventive Medicine, Monash University; §Melbourne Sexual Health Centre, Alfred Health and ¶Central Clinical School, Alfred Health, Melbourne; ||Department of Gender and Cultural Studies, University of Sydney, Sydney; and **Kirby Institute, University of New South Wales Kensington, Australia.

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M.S. and E.W. are joint senior authors.

Declarations: Availability of data and material. The data sets generated and/or analyzed during the current study are not publicly available due to ongoing analysis undertaken by the research team but are available from the corresponding author on reasonable request.

Conflict of interest: M.A.S. received grants from the Commonwealth Department of Health, during the conduct of the study. J.A. received grants from the Commonwealth of Australia, Department of Health, during the conduct of the study. J.H.'s institution received reimbursement for her participation in Advisory Boards for Gilead Sciences, Merck, Sharp & Dohme and ViiV Healthcare. E.J.W. has received financial support from Gilead Sciences; Abbott Laboratories; Janssen-Cilag; Boehringer Ingelheim; ViiV Healthcare; Alfred Hospital; and Merck Sharp & Dohme. Gilead Sciences donated study drug to the VicPrEP study (precursor to the PrEPX study). All other authors declare no potential conflicts of interest.

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The PREPX Study team includes: Jude Armishaw, Jason Asselin, Colin Batrouney, Alison Coelho, Vincent J Cornelisse, John De Wit, Christina C Chang, Chistopher K Fairley, George Forgan-Smith, Margaret Hellard, Jennifer Hoy, Richard Keane, Luxi Lal, Anne Mak, Dean Murphy, Long Nguyen, Anna B Pierce, Brian Price, Matthew Penn, Norman Roth, Simon Ruth, Kathleen E Ryan, Garry Sattell, Mark Stoové, Ban Kiem Tee, Michael Traeger, Olga Vujovic, Michael West, Michael Whelan, Jeremy Wiggins, Jeff Willcox, Christopher Williams, Edwina Wright.

Correspondence: Kathleen Elizabeth Ryan, 85 Commercial Rd, Melbourne, Victoria, Australia, 3004. E-mail: Kathleen.ryan@burnet.edu.au.

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heterosexuals,[3] transgender women,[4] and people who inject drugs[5] in the setting of high medication adherence. The World Health Organization recommends that daily PrEP be offered as a prevention option for people at substantial risk of HIV infection as part of a combination prevention approach and includes PrEP on their list of essential medicines.[6]

Despite these recommendations, the scale-up of PrEP has been suboptimal in many countries.[7] In Organization for Economic Co-operation and Development countries, the pace of PrEP scale-up has been slow. The overall number of people on PrEP is highest in the United States; however, coverage varies considerably by jurisdiction, race, and gender.[8] In the United Kingdom, the Netherlands, and many other European countries, there are no subsidies for PrEP, and debate in these jurisdictions has focused on health care costs of PrEP and concerns about the ability of sexual health services to meet service demands for requisite quarterly clinic visits for HIV and STI testing.[9,10] In Eastern Europe and Central Asia, where HIV incidence has risen by 30% since 2010, PrEP was available through the public health system only in the Republic of Moldova, Georgia, and the Ukraine.[11]

In Australia, HIV is highly concentrated among GBM with over 70% of annual notifications occurring within this group.[12] Preexposure prophylaxis was approved for use in HIV prevention by the Therapeutic Goods Administration in 2017, national PrEP prescribing guidelines were published in 2017,[13] and PrEP was listed on the Australia's list of subsidized medicines (Pharmaceutical Benefits Scheme [PBS]) in April 2018.[14] Before PBS subsidization of PrEP most Australian jurisdictions commenced large PrEP demonstration projects during 2016 and 2017. Personal importation of PrEP via online pharmacies and through private unsubsidized prescriptions also occurred at modest levels.[15]

There are limited data regarding the impact of PrEP scale-up on access to services among priority populations not engaged in PrEP. In this article, we describe the implementation of the PrEPX study (a large implementation study in Victoria, Australia), the rate of PrEP uptake, and the impact on HIV testing rates for nonstudy participating GBM attending study clinics.

METHODS

Study Design

The PrEPX was a prospective, population-level PrEP implementation study that commenced on July 26, 2016, and ran for 21 months. The study protocol has been described in detail elsewhere.[16] The PrEPX was designed on the basis of an a priori estimate that maintaining 2600 individuals at risk of HIV infection on PrEP would reduce state-wide HIV incidence by 25% overall and by 30% among GBM within 36 months of study commencement. In the 7 months before study commencement (January 26, 2016 to July 25, 2016), individuals could register interest in the study by completing an online form. After the study commenced on July 26, 2016, waitlisted participants were contacted and offered an enrolment appointment at their clinic of choice or at an alternative clinic if their preferred study site did not have capacity. Due to participant demand, an additional 600 study places were funded on January 19, 2017, with a further 600 study places funded on March 28, 2017, bringing the total number of available places to 3800. However, due to the staggered enrolment and study withdrawals, when study enrolment closed on March 31, 2018, because PrEP became publicly subsidized through the PBS, 4265 people had been prescribed PrEP through the study.

Each study clinic had the latitude to implement PrEPX in a manner that suited their service. The primary care clinics obtain funding for each consultation through a government rebate and may charge an additional private consultation fee. Primary care clinics incorporated PrEPX patients into their existing available appointment schedule and were paid by the study for each participant they enrolled. The 2 sexual health services receive block funding for services. The sexual health clinic developed a new system to participate in PrEPX whereupon they obtained a government rebate for each PrEP consultation, separate to their existing funding. This allowed them to establish separate clinics to enroll PrEPX participants. One sexual health clinic received funding for a nurse to support their clinic, the other received payment for each participant enrolled.

Study Visits

The PrEPX study visits were scheduled to occur every 2 months. At each study visit, participants underwent a clinical review, laboratory testing for HIV and STIs (syphilis, gonorrhea, and chlamydia), and received a 3-month PrEP prescription. Drug was dispensed from participating community and hospital study pharmacies.[17] In addition to scheduled PrEPX study visits, participants could attend their PrEPX participating site for other health care, including assessment for symptomatic STI.

Data Collection

Registration of Interest

Individuals expressed their interest in participating in the PrEPX study through an online waiting list form. Data were collected and managed using REDCap online survey manager electronic data capture tools.[18] Demographic characteristics, history of prior PrEP use, and preferred PrEPX site for study enrolment were asked as part of waiting list registration.

Enrolment and Withdrawal

At the baseline enrolment visit, the clinician completed an enrolment eligibility survey with the participant, using REDCap.[18] This questionnaire collected data on participant demographic characteristics, reasons for enrolment, previous PrEP use, HIV/STI testing history, and sexual and injecting behaviors.

Participant withdrawal forms were also completed by the clinician using REDCap,[18] and included free text information on reasons for withdrawal, which were categorized into 9 domains for this analysis.

HIV and STI Testing

Prestudy and study period HIV and STI testing was available at the 5 PrEPX study sites (3 metropolitan primary care clinics and 2 metropolitan sexual health services) that also participated in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood Borne Viruses and Sexually Transmitted Infections system (ACCESS). These ACCESS study sites enrolled 3317 (78%) of 4265 PrEPX participants. ACCESS automatically extracts deidentified HIV and STI test information from clinic patient management systems through the GRHANITE data extraction software. ACCESS collected continuous HIV and STI test data from 2013 across the 5 sites and links individuals tests within a single clinic and across clinics in the ACCESS network.[19–21]

Data Analysis

We report the monthly number of people registering their interest in PrEPX through the online waitlist between January 30, 2016, and March 31, 2018, and the monthly PrEPX participant enrolments based on enrolment survey completions between July

26, 2016, and March 31, 2018. Characteristics of all participants enrolling in PrEPX are described. Variables examined included age, gender, date of enrolment, PrEPX study site, PrEP eligibility criteria, and any previous PrEP or postexposure prophylaxis (PEP) use.

We estimated shifting demand for HIV testing services before enrolment date among PrEPX participants who enrolled at sites within the ACCESS network. We report the clinic type where they enrolled in PrEPX (sexual health service or primary care service) and the clinic type they attended for HIV testing between January 1, 2015, and their enrolment date to describe movement of study participants after their enrolment into the PrEPX study.

We assessed the impact of the PrEPX study on HIV testing by comparing the aggregated number of monthly HIV tests conducted at the 5 PrEPX study sites in the 18 months before PrEPX (prestudy; January 2015 to June 2016) and the 21 months of the PrEPX study (study; July 2016 to March 2018) using segmented linear regression. This analysis focused on 5 PrEPX clinics (2 sexual health services and 3 primary care settings) where historical HIV testing data were available through the ACCESS network. Specific regression analyses were conducted examining HIV testing at the 2 sexual health clinics and the 3 primary care clinics to determine if there was a difference in trends between the 2 clinic types. All regression analyses were disaggregated by HIV testing among PrEPX participants and non-PrEPX participant GBM. The PrEPX participants were defined as those enrolling in the first 12 months of the study, and GBM not participating in PrEPX were identified using previously defined methods.[20,22]

We repeated the analyses to assess the impact of the PrEPX study on bacterial STI testing. Each individual could contribute a maximum of 1 test event per day in each bacterial STI analysis. In Victoria, the overwhelming majority of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhea* (NG) testing are conducted using duplex testing, we therefore collapsed testing for these bacteria at any anatomical site to assess CT/NG testing. We separately assessed syphilis testing. For 1 sexual health clinic which enrolled 329 study participants, CT/NG and syphilis testing was not available before the introduction of STI testing at this clinic in February 2016.

All segmented linear regression models used Newey-West standard errors and were adjusted for a maximum of 1 lag. We report the y-intercept (β0), the prestudy trend (β1, January 2015–June 2016), the immediate change in testing at the time of study commencement (β2, PrEPX commences July 2016), and the change in trend (β3) from prestudy to study periods (β1–β3, July 2016–March 2018). All statistical analyses were performed using Stata version 14 (StataCorp LP, College Station, TX) with a significance cutoff of P less than 0.05.

Human Research Ethics

Written informed consent was obtained from all study participants at study enrolment. The study was approved by the Alfred Health Human Research and Ethics Committee (HREC100/16) and registered on the Australian New Zealand Clinical Trials Registry 2 September 2016 (ACTRN12616001215415). The ACCESS study was approved by Alfred Health Human Research and Ethics Committee (HREC248/17) and this ethics committee waived the need for the individuals' consent.[20]

Role of the Funding Source

Individuals from the Victorian Department of Health and Human Services and the Thorne Harbor Health (previously Victorian AIDS Council) were PrEPX study coinvestigators and are coauthors on this article. They had a role in the design, review, and approval of the article and in the decision to submit the article for publication.

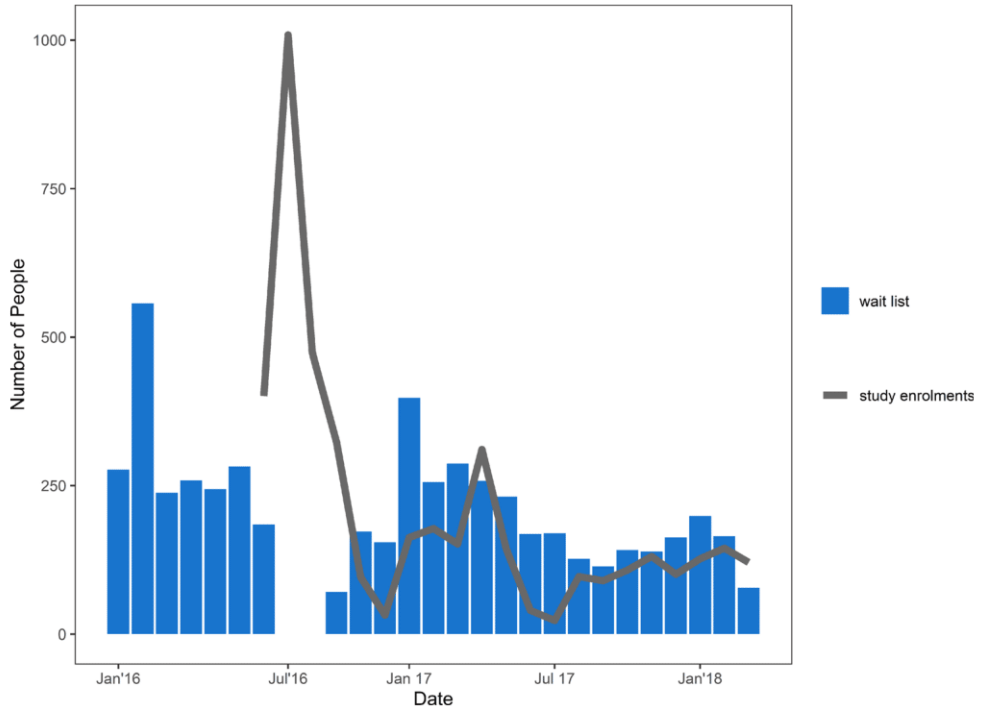

Figure 1. Registration (January 26, 2016 to March 31, 2018) and enrolment (July 16, 2016 to March 31, 2018) into PrEPX study.

RESULTS

Study Enrolment

At study commencement on July 26, 2016, 2049 individuals had registered their interest in participating in PrEPX, of whom 1471 (72%) enrolled in PrEPX within the first 12 months. An average of 183 new people registered their interest each month throughout the 21 months of the study (Fig. 1).

Between July 26 2016, and March 31, 2018, 4265 people enrolled into PrEPX in Victoria. The study recorded rapid early enrolment, with 1000 people enrolled in the first 3 weeks, 87.8% (n = 876) of whom enrolled at ACCESS sites, and 80% of the original funded number of study places (2080 of 2600) filled by week 13 (Fig. 1). Two thirds of all PrEPX participants (n = 2768) enrolled at primary care clinics (Table 1).

Participant Characteristics

The median age of the 4265 PrEPX participants at enrolment was 34 years, 99% were male, including 22 transmen, and 98% of participants identified as GBM. Approximately one quarter (26%) reported PrEP use before enrolment (Table 1).

The most common PrEP eligibility criterion reported at enrolment was GBM reporting specific behaviors that met the national PrEP prescribing guidelines[13] (78%), whereas injecting drug use (0.3%) and heterosexual sex (0.1%) were infrequently reported. Approximately 1 in 5 participants were enrolled at the clinicians' discretion, and separate analyses found that the majority of these participants reported significant risk for HIV acquisition that did not meet the formal eligibility criteria[23] (Table 1).

TABLE 1. Characteristics of PrEPX Study Participants, July 26, 2016 to March 31, 2018

Number Enrolled		4265
Age, y	18–29	1422 (33.3)
	30–39	1546 (36.3)
	40–49	857 (20.3)
	50+	430 (10.1)
	Median (IQR)	34 (28–42)
Gender identity	Male	4207 (98.6)
	Female	13 (0.3)
	Transman	15 (0.4)
	Transwoman	10 (0.2)
	Nonbinary/gender fluid	18 (0.4)
	Gender not listed	2 (0.04)
Sex at birth	Male	4236 (99.3)
	Female	29 (0.7)
Sexuality	Gay	4001 (93.8)
	Bisexual	205 (4.8)
	Heterosexual	17 (0.4)
	Other	42 (1.0)
Reason for enrolment*,†	Gay and bisexual men‡	3325 (78.0)
	Injection drug use§	14 (0.3)
	Heterosexual sex¶	6 (0.1)
	Clinicians discretion	932 (21.9)
Previous PrEP use	Yes	1104 (25.9)
	No	3161 (74.1)
Previous PEP use	Yes	1636 (38.4)
	No	2629 (61.6)
Clinic type	Primary care	2768 (64.9)
	Sexual health	846 (19.8)
	Hospital	651 (15.3)

*Not mutually exclusive.

†High risk classification in line with national PrEP prescribing guidelines.[13]

‡Reported condomless anal sex, methamphetamine use, or diagnosis with bacterial STI.

§Reported injection drug use with an HIV-positive person, with a man who has sex with men, or when there was inadequate access to safe injecting equipment.

¶Reported multiple events of condomless anal or vaginal sex with an HIV-positive partner who had detectable viral load.

Impact of the PrEPX Study on HIV Testing at Study Clinics

HIV Testing Among PrEPX Participants

Of the 3317 PrEPX participants enrolled at the 5 PrEPX sites that were also ACCESS sites, 89% (n = 2794) had attended any of these 5 ACCESS sites for HIV testing between January 1, 2015, and their study enrolment date. Among participants with a testing history at ACCESS sites, 37% (n = 1044) had tested for HIV at a clinic type other than their enrolment clinic, 91% (n = 951) of whom enrolled at a primary care clinic but had previously tested for HIV at a sexual health clinic. Of the 523 PrEPX participants that did not have previous testing history at ACCESS study sites, 79% (n = 411) enrolled at primary care clinics (Fig. 2).

HIV Testing Among GBM at ACCESS Study Clinics

In the prestudy period, there were 27,983 HIV tests recorded among 13,002 GBM. In the study period, there were 49,657 HIV tests recorded among 16,665 GBM; 19,938 tests among 3316 PrEPX participants, and 29,719 tests among 13,349 non-PrEPX participants. In January 2015, 1246 HIV tests ($\beta 0$) were conducted across the 5 ACCESS clinics, and in the prestudy period, there was a positive trend ($\beta 1$, 32.49; 95% CI, 26.19–38.80) in the monthly number of HIV tests across these study sites. In the month that PrEPX commenced (July 2016), an additional 241 HIV tests (95% confidence interval [CI], 122.75–360.76) ($\beta 2$) were conducted, and throughout the study period, the positive trend in the monthly number of HIV tests continued (postslope, 26.00; 95% CI, 14.77–37.14). There was no significant difference in the rate of increase in testing between the prestudy and PrEPX study periods ($\beta 3$, −6.54; 95% CI, −19.93 to 6.85) (Table 2, Fig. 3).

During the prestudy period, the monthly number of HIV tests increased by an average of 18 tests per month among PrEPX participants ($\beta 1$, 18.63; 95% CI, 15.77–21.48) and 13 tests per month among non-PrEPX participants ($\beta 1$, 13.87; 95% CI, 9.78–17.95). In the month that PrEPX commenced, an additional 364 HIV tests (95% CI, 291.14–438.47) were conducted among PrEPX participants and 123 fewer HIV tests (95% CI, −188.51 to −57.59) among non-PrEPX participants. In the PrEPX study period, the monthly number of HIV tests declined by an average of 1 test per month among PrEPX-participants (postslope, −0.86; 95% CI, −6.82 to 5.10) and increased by an average of 26 tests per month among non-PrEPX participants (postslope, 26.81; 95% CI, 20.20–33.43). Between the prestudy and PrEPX study periods, there was a negative change in rate of testing among PrEPX participants ($\beta 3$, −19.49; 95% CI, −26.10 to −12.88) and a positive change in the non-PrEPX participants ($\beta 3$, 12.95; 95% CI, 4.83–21.07) (Table 2, Fig. 4).

HIV testing at ACCESS Sexual Health Clinics

During the prestudy period, the monthly number of HIV tests at sexual health clinics increased by an average of 7 tests per month among PrEPX participants ($\beta 1$, 7.47; 95% CI, 5.57–9.38) and 10 tests per month among non-PrEPX participants ($\beta 1$, 10.02; 95% CI, 7.55–12.50). In the month that PrEPX commenced, an additional 118 HIV tests (95% CI, 84.24–150.91) were conducted among PrEPX participants and 53 fewer HIV tests

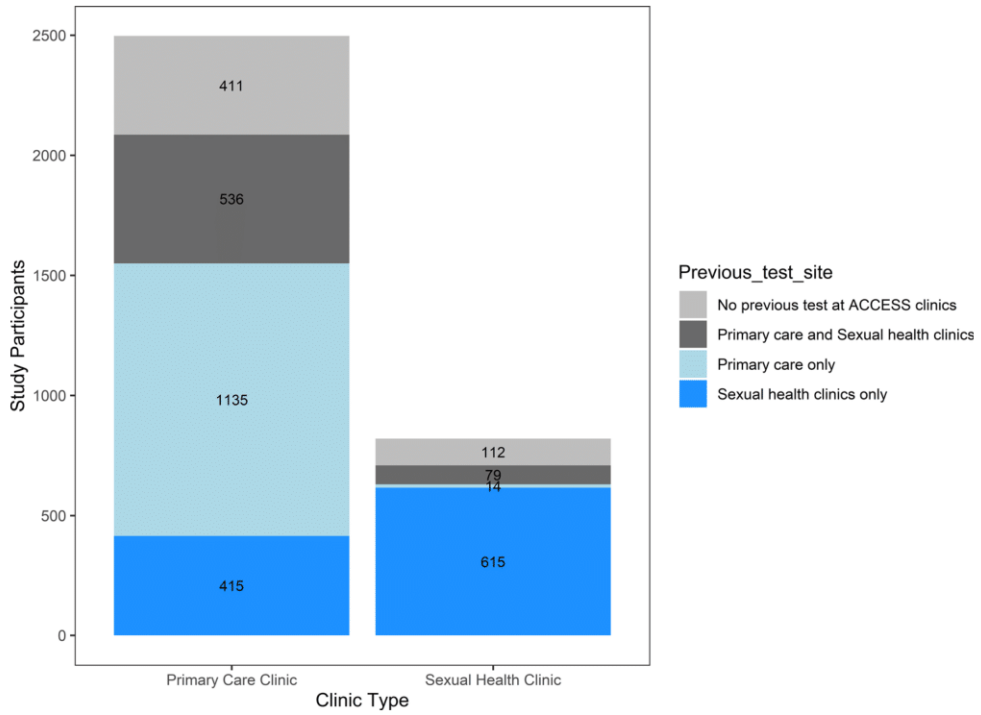

Figure 2. HIV testing among PrEPX participants attending ACCESS primary care and sexual health clinics, by their previous testing history from January 1, 2015 to enrolment at each clinic type.

TABLE 2. Segmented Linear Regression of Monthly Aggregate HIV Tests Among All GBM Attending 5 PrEPX Study Sites by PrEPX Enrolment Status, January 1, 2015 to March 31, 2018

	PrEPX Participants and Nonparticipant GBM		PrEPX Participants		GBM Not Enrolled in PrEPX	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Tests (individuals) January 2015 to June 2016	27,983 (13,002)		7493 (2183)		20,490 (10,819)	—
Tests (individuals) July 2016 to March 2018	49,657 (16,665)		19,938 (3317)		29,719 (13,349)	—
β0 intercept	1245.92 (1178.11 to 1313.73)	<0.01	239.31 (205.01 to 273.60)	<0.01	1006.61 (969.95 to 1043.24)	<0.01
β1 preslope	32.49 (26.19 to 38.80)	<0.01	18.63 (15.77 to 21.48)	<0.01	13.87 (9.78 to 17.95)	<0.01
β2 change at intervention	241.75 (122.75 to 360.76)	<0.01	364.80 (291.14 to 438.47)	<0.01	−123·05 (−188·51 to −57.59)	0.01
Postslope	26.00 (14.77 to 37.14)	<0.01	−0.86 (−6.82 to 5.10)	<0.01	26·81 (20.20 to 33.43)	<0.01
β3 change in slope	−6.54 (−19.93 to 6.85)	0.33	−19.49 (−26.10 to −12.88)	<0.01	12.95 (4.83 to 21.07)	0.03
Sexual health clinics						
Tests (individuals) January 2015 to June 2016	17,965 (9106)		3390 (1261)		14,305 (7845)	
Tests (individuals) July 2016 to March 2018	28,328 (11,402)		6797 (1518)		21,531 (9884)	
β0 intercept	816.85 (780.49 to 853.21)	<0.01	117.35 (97.39 to 137.32)	<0.01	699.50 (678.29 to 720.71)	<0.01
β1 preslope	17.50 (13.97 to 21.02)	<0.01	7.47 (5.57 to 9.38)	<0.01	10.02 (7.55 to 12.50)	<0.01
β2 change at intervention	64.60 (−8.10 to 137.30)	0.08	117.57 (84.24 to 150.91)	<0.01	−52.97 (−104.33 to 1.62)	0.04
β3 change in slope	−3.99 (−11.78 to 3.81)	0.31	−12.79 (−15.63 to 9.95)	<0.01	8.81 (2.93 to 14.69)	<0.01
Postslope	13.51 (6.90 to 20.12)	<0.01	−5.32 (−7.54 to 3.10)	<0.01	18·83 (13.76 to 23.90)	<0.01
Primary care clinics						
Tests (individuals) January 2015 to June 2016	1028 (4691)		4103 (1325)		6185 (3366)	
Tests (individuals) July 2016 to March 2018	21,329 (6688)		13,141 (2579)		8188 (4089)	
β0 intercept	426.07 (392.16 to 465.97)	<0.01	121.95 (104.90 to 139>00)	<0.01	307.11 (285.58 to 328.64)	<0.01
β1 preslope	15.00 (11.83 to 18.17)	<0.01	11.67 (9.72 to 12.60)	<0.01	3.84 (1.79 to 5.89)	<0.01
β2 change at intervention	177.15 (111.45 to 242.85)	<0.01	247.23 (192.37 to 302.09)	<0.01	−70.08 (−99.72 to 40.43)	<0.01
β3 change in slope	−2.55 (−9.37 to 4.27)	0.45	−6.70 (−11.18 to 2.21)	<0.01	4.14 (0.84 to 7.45)	0.01
Postslope	12.45 (6.60 to 18.29)	<0.01	4.46 (0.25 to 8.67)	0.04	7.99 (5.42 to 10.55)	<0.01

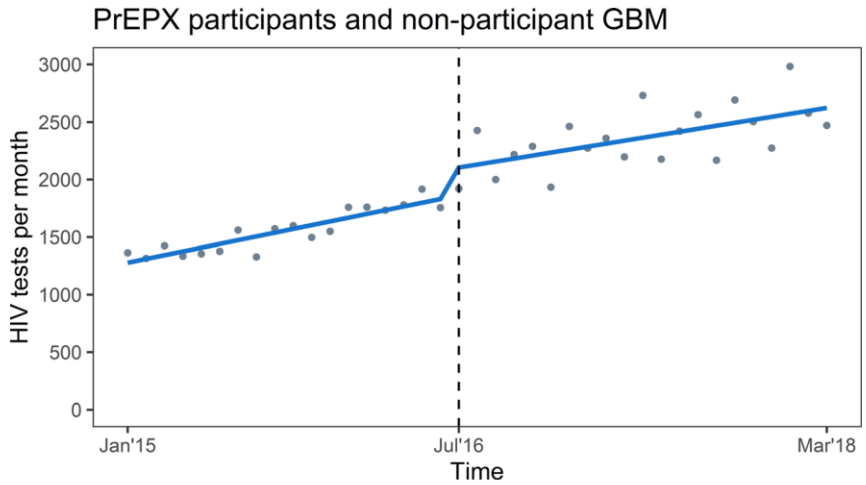

Figure 3. Segmented linear regression of monthly aggregate HIV tests among PrEPX participants and HIV-negative GBM not participating in PrEPX attending 2 sexual health and 3 primary care study sites, January 1, 2015 to March 31, 2018. Gray dots: estimated number of tests per month; Blue line: trend in testing; vertical dashed line: model interruption at PrEPX commencement July 2016.

(95% CI, −104.33 to −1.62) among non-PrEPX participants. In the PrEPX study period, the monthly number of HIV tests at sexual health clinics declined by an average of 5 tests per month among PrEPX-participants (postslope, −5.32; 95% CI, −7.54 to −3.10) and increased by 18 tests per month among non-PrEPX participants (postslope, 18.83; 95% CI, 13.76–23.90). Between the prestudy and PrEPX study periods, there was a negative change in rate of testing among PrEPX participants (β3, −12.79; 95% CI, −15.63 to −9.95) and a positive change in the non-PrEPX participants (β3, 8.81; 95% CI:, 2.93–14.69) (Table 2, Fig. 4).

HIV testing at ACCESS Primary Health Care Clinics

During the prestudy period, the monthly number of HIV tests at primary health clinics increased by an average of 11 tests per month among PrEPX participants (β1, 11.67; 95% CI, 9.72–12.60) and by 4 tests per month among non-PrEPX participants (β1:1, 3.84; 95% CI, 1.79–5.89). In the month that PrEPX commenced, an additional 247 HIV tests (95% CI, 192.37–302.09) were conducted among PrEPX participants and 70 fewer HIV tests (95% CI, −99.72 to −40.43) among non-PrEPX participants. In the PrEPX study period, the monthly number of HIV tests increased by 4 tests per month among PrEPX participants (postslope, 4.46; 95% CI, 0.25–8.67) and by 8 tests per month among non-PrEPX participants (postslope, 7.99; 95% CI, 5.42–10.55). Between the prestudy and PrEPX study periods, there was a negative change in rate of testing among PrEPX participants (β3, −6.70; 95% CI, −11.18 to −2.21) and a positive change in the non-PrEPX participants (β3, 4.14; 95% CI, 5.42–10.55) (Table 2, Fig. 4).

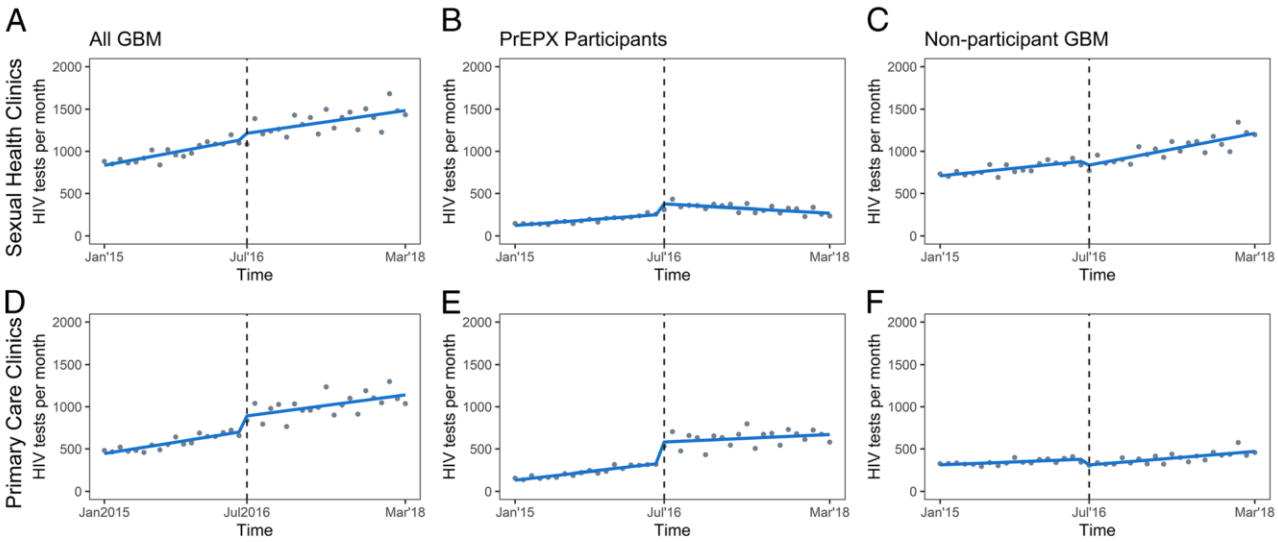

Figure 4. Segmented linear regression of monthly aggregate HIV tests among PrEPX participants and HIV-negative GBM not participating in PrEPX attending 2 sexual health and 3 primary care study sites, January 1, 2015 to March 31, 2018. Models represent testing estimates at sexual health clinics (A, B, C) and primary care clinics (D, E, F) among all GBM (A, D), PrEPX participants (B, E), and nonparticipant GBM (C, F). Gray dots: estimated number of tests per month; Blue line: trend in testing; vertical dashed line: model interruption at PrEPX commencement July 2016.

TABLE 3. Segmented Linear Regression of Monthly Aggregate CT/NG Tests Among All GBM Attending 5 PrEPX Study Sites by PrEPX Enrolment Status, January 1, 2015 to March 31, 2018

	PrEPX Participants and Nonparticipant GBM		PrEPX Participants		GBM Not Enrolled in PrEPX	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Tests (individuals) January 2015 to June 2016	27,889 (12,498)		7693 (2168)		20,196 (10,330)	
Tests (individuals) July 2016 to March 2018	53,070 (17,287)		21,426 (3320)		31,644 (13,967)	
β0 intercept	1181.99 (1094.23 to 1269.55)	<0.01	240.26 (204.79 to 275.73)	<0.01	941.63 (888.50 to 994.76)	<0.01
β1 preslope	38.68 (31.01 to 46.35)	<0.01	19.70 (16.75 to 22.65)	<0.01	18.99 (14.03 to 23.94)	<0.01
β2 change at intervention	256.89 (137.17 to 376.62)	<0.01	366.02 (293.46 to 438.57)	<0.01	−109.13 (−183.57 to −34.68)	0.01
β3 change in slope	−3.35 (−17.51 to 10.82)	<0.01	−15.72 (−22.70 to −8.75)	<0.01	12.37 (3.17 to 21.58)	0.01
Postslope	35.34 (24.14 to 46.54)	0.20	3.98 (−2.18 to 10.13)	<0.01	31.36 (23.85 to 38.87)	<0.01
Sexual health clinics						
Tests (individuals) January 2015 to June 2016	17,190 (8528)		3390 (1217)		13,800 (7311)	
Tests (individuals) July 2016 to March 2018	30,762 (12,152)		7630 (1589)		23,132 (10,563)	
β0 intercept	725.84 (669.72 to 781.97)	<0.01	108.24 (87.12 to 129.35)	<0.01	617.61 (580.89 to 654.33)	<0.01
β1 preslope	24.12 (18.93 to 29.31)	<0.01	8.43 (6.37 to 10.49)	<0.01	15.69 (12.01 to 19.29)	<0.01
β2 change at intervention	67.38 (−15.33 to 150.08)	0.11	128.50 (90.97 to 166.03)	<0.01	−61.12 (−123.76 to 1.51)	0.04
β3 change in slope	−2.79 (−11·65 to 6.07)	0.53	−11.79 (−15.22 to −8.37)	<0.01	9.00 (2.12 to 15.88)	<0.01
Postslope	21.33 (14.51 to 28.16)	<0.01	−3.36 (−6.00 to −0.72)	0.01	24.69 (18.97 to 30.42)	<0.01
Primary care clinics						
Tests (individuals) January 2015 to June 2016	10,699 (4717)		4303 (1331)		6396 (3386)	
Tests (individuals) July 2016 to March 2018	22,308 (6630)		13,796 (2578)		8512 (4052)	
β0 intercept	456.04 (419.27 to 492.82)	<0.01	132.03 (112.92 to 151.13)	<0.01	324.02 (304.03 to 344.01)	<0.01
β1 preslope	14.56 (11.32 to 17.81)	<0.01	11.27 (9.64 to 12.89)	<0.01	3.30 (1.35 to 5.24)	<0.01
β2 change at intervention	189.51 (122.32 to 256.71)	<0.01	237.52 (185.04 to 289.99)	<0.01	−48.00 (−80.24 to −15.76)	<0.01
β3 change in slope	−0.56 (−7.58 to 6.46)	0.87	−3.93 (−8.44 to 0.58)	0.09	3.37 (−0.17 to 6.91)	0.06
Postslope	14.00 (8.01 to 19.99)	<0.01	7.34 (3.19 to 11.48)	<0.01	6.67 (3.70 to 9.64)	<0.01

Bacterial STI Testing at ACCESS Clinics

Given that STI testing among GBM is routinely provided in combination with HIV testing at study clinics, similar trends were observed in the monthly number of CT/NG and syphilis tests across PrEPX participants and nonparticipant GBM attending ACCESS participating sexual health and primary care clinics (Tables 3 and 4).

DISCUSSION

The PrEPX study utilized existing health services to enroll over 2000 participants in 13 weeks and achieved one of the most rapid enrolment rates into a PrEP study reported to date.[24] Although there was concern that this increase in demand for health services would compromise HIV testing access for GBM who did not participate in PrEPX, we showed that PrEPX did not have a sustained negative impact on HIV testing among nonstudy GBM patients attending study clinics. Local modeling used to inform the PrEPX study suggested that rapid enrolment was needed to achieve prevention targets,[25] and these findings suggest that the HIV prevention impact provided by the scale-up of PrEP was not offset by changes in HIV testing capacity. Our findings also underscore the capacity of clinics to adapt service models to meet increased demand for sexual health care after the implementation of PrEP.

The PrEPX enrolment exceeded 4000 participants, and the initial rapid enrolment reflected significant interest in PrEP among Australian GBM. This rapid enrolment may be attributed to predominance of grassroots awareness raising that was driven by Victorian PrEP activists and community organizations who were study coinvestigators,[16] and establishment of an online PrEP importation assistance program.[26] These activities, and findings from a number of other studies,[27,28] suggest a highly engaged and health-literate GBM community in Victoria. Although these actions contributed to Victorian GBMs willingness for PrEP, a register of interest and use of existing services provided the structure necessary for rapid enrolment. The use of existing "client-centered" services for PrEP provision has been recommended recently,[7] and the reliance on hospital-based prescribing in France contributing to the observed limited PrEP uptake.[29] The PrEPX study used existing, highly trusted clinical services that most participants attended for HIV testing before PrEPX enrolment, and this may have further contributed to rapid enrolment and successful PrEP maintenance.

In this study, we used an existing surveillance system to assess HIV testing before and after implementation. We showed that most movement across the system was among PrEPX participants who previously tested at sexual health clinics and enrolled in primary care clinics, with the observed decline in monthly HIV tests at sexual health clinics attributable to participants moving to primary care clinics to enroll in the study. A number of factors may have contributed to primary care clinics ability to enroll greater numbers of study participants, including incorporating study participants in standard appointment slots, familiarity with federal funding for medical services, and different service priorities compared with state-funded sexual health services. The ability to accommodate a greater number of study participants contributed to movement from sexual health to primary

TABLE 4. Segmented Linear Regression of Monthly Aggregate Syphilis Tests Among All GBM Attending 5 PrEPX Study Sites by PrEPX Enrolment Status, January 1, 2015 to March 31, 2018

	PrEPX Participants and Nonparticipant GBM		PrEPX Participants		GBM Not Enrolled in PrEPX	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Tests (individuals) January 2015 to June 2016	26,219 (12,053)		7258 (2148)		18,961 (9905)	
Tests (individuals) July 2016 to March 2018	48,705 (16,374)		19,808 (3317)		28,897 (13,057)	
β0 intercept	1117.80 (1016.391 to 1219.20)	<0.01	222.79 (183.28 to 262.30)	<0.01	895.01 (831.69 to 958.33)	<0.01
β1 preslope	35.66 (26.72 to 44.61)	<0.01	18.99 (15.77 to 22.21)	<0.01	16.67 (10.64 to 22.71)	<0.01
β2 change at intervention	250.12 (113.47 to 386.77)	<0.01	356.34 (281.54 to 431.14)	<0.01	−106.22 (−189·48 to −22.97)	0.01
β3 change in slope	−8.29 (−22.97 to 6.39)	0.42	−18.67 (−25.41 to −11.93)	<0.01	10.38 (1.05 to 19.71)	0.03
Postslope	27.37 (16.15 to 38.59)	<0.01	0.32 (−5.63 to 6.28)	<0.91	27.05 (20.17 to 33.93)	<0.01
Sexual health clinics						
Tests (individuals) January 2015 to June 2016	15,850 (7996)		3158 (1186)		12,692 (6810)	
Tests (individuals) July 2016 to March 2018	27,489 (11,004)		6766 (1505)		20,723 (9499)	
β0 intercept	680.30 (616.89 to 743.71)	<0.01	100.31 (76.64 to 123.97)	<0.01	579.99 (538.05 to 621.93)	<0.01
β1 preslope	21.08 (15.05 to 27.11)	<0.01	7.91 (5.69 to 10.13)	<0.01	13.17 (8.99 to 17.35)	<0.01
β2 change at intervention	71.55 (−20.27 to 163.37)	0.11	117.58 (81.81 to 153.36)	<0.01	−46.03 (−112.18 to 20.12)	0.17
β3 change in slope	−5.42 (−14.38 to 3.54)	0.53	−12.51 (−15.48 to −9.53)	<0.01	7.09 (0.31 to 13.87)	0.04
Postslope	15.66 (9.12 to 22.20)	<0.01	−4.60 (−6.77 to 2.43)	<0.01	20.26 (15.03 to 25.49)	<0.01
Primary care clinics						
Tests (individuals) January 2015 to June 2016	10,369 (4769)		4100 (1339)		6269 (3430)	
Tests (individuals) July 2016 to March 2018	21,216 (6732)		13,042 (2577)		8174 (4155)	
β0 intercept	437.50 (394.77 to 480.22)	<0.01	122.48 (102.91 to 142.06)	<0.01	315.01 (290.54 to 339.48)	<0.01
β1 preslope	14.59 (11.06 to 18.11)	<0.01	11.08 (9.50 to 12.67)	<0.01	3.50 (1.24 to 5.76)	<0.01
β2 change at intervention	178.57 (109.17 to 247.96)	<0.01	238.75 (182.37 to 295.14)	<0.01	−60.18 (−91.57 to −28.81)	<0.01
β3 change in slope	−2.87 (−10.04 to 4.29)	0.87	−6.16 (−10.84 to −1.48)	0.01	3.29 (−0.20 to 6.78)	0.06
Postslope	11.71 (5.69 to 17.73)	<0.01	4.92 (0.57 to 9.27)	0.03	6.79 (4.16 to 9.41)	<0.01

care clinics in the PrEPX participant cohort. This movement within the testing network may have increased testing opportunities for other GBM at publically funded sexual health clinics. We also observed that before PrEPX commencement, there was an increasing trend in the monthly number of HIV tests among future PrEPX participants and non-PrEPX GBM. This increased testing may be attributed, in part, to monitoring associated with self-importation of PrEP and a positive impact of local HIV testing and prevention campaigns. These testing data show a network of sexual health and primary care services that had been able to adapt to increasing demand and shifting service needs to deliver HIV and STI testing Victorian GBM, even before PrEP was scaled up locally.

In scaling up PrEP programs, it is important to ensure that people who choose not to use PrEP are not disadvantaged in their access to sexual health care. At PrEPX implementation we observed, an immediate significant increase in the monthly number of HIV and STI tests among PrEPX participants and a decline in the number of tests among non-PrEPX participants. Importantly, the monthly number of tests among non-PrEPX participants recovered and exceeded prestudy numbers. In line with our assessment of a redistribution of HIV testing across sexual health and primary care clinics, HIV testing among non-PrEPX participants increased faster at sexual health clinics as these clinics enrolled fewer PrEPX participants and PrEPX participants moved away from sexual health clinics to enroll at primary care clinics. Recent Victorian data have shown an increasing disparity of HIV transmission, with an increased proportion of diagnoses among GBM who are not eligible for Australia's universal health care system (Medicare). These men are often diagnosed late with limited testing history, and the trend is likely driven by inequitable access to sexual health services.[30] In Victoria, sexual health clinics are state-funded, and HIV testing is provided at no cost, irrespective of Medicare eligibility, whereas services at primary care clinics are rebated through Medicare, this means that Medicare ineligible may face significant out of pocket expenses when attending such services. The redistribution of testing we observed may have increased access to free testing at sexual health care services for Medicare ineligible GBM.

This study has several limitations. Assessment of the impact of PrEPX on HIV and STI testing was restricted to 5 study sites that contribute data to ACCESS, and there may be variation in the ability of smaller clinics to accommodate PrEP users which was not measured in this study This analysis assessed shifts in absolute number of PrEP-related and unrelated tests at clinics and not the frequency of testing/retesting among GBM not accessing PrEP. Separate analysis of surveillance data collected from participating clinics suggests no meaningful change in testing frequency among GBM in response PrEP scale-up."[31] The decline in the number of tests among PrEPX participants at sexual health clinics and results from our secondary analysis which showed that some participants withdrew from the study but did not inform their study clinician[32] meant our analysis may have underestimated the number of study withdrawals. Our analysis may have underestimated the number of GBM within the ACCESS clinic who were using PrEP; our estimates are restricted to GBM enrolled in the PREPX study, however 25% of participants reported PrEP use before enrolment. However, if this is an underestimate of PrEP use, it would suggest

that the health system could adapt to even greater need for HIV and STI testing than we have assumed in this analysis. Finally, this study was undertaken in a high-income country with universal health care, and hence, the findings may not be generalizable to other settings.

The PrEPX study design incorporated close partnerships with community, clinicians, pharmacists and researchers, and PrEPX recorded a rapid enrolment of over 2000 people in less than 3 months. Clinics independently established models of PrEP delivery to suit their service models, and this enabled clinics to accommodate PrEPX study participants with no long-term impact on sexual health care among GBM attending these clinics who were not enrolled in the PrEPX study. These findings suggest that scale up of PrEP using existing health services is highly feasible and may assist the implementation and expansion of PrEP in other settings.

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Appendix C5. Low incidence of hepatitis C virus among gay and bisexual men using PrEP in Melbourne, Australia

Citation:

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Low Incidence of Hepatitis C Among a Cohort of HIV-Negative Gay and Bisexual Men Using HIV Pre-exposure Prophylaxis (PrEP) in Melbourne, Australia, and the Contribution of Sexual Transmission

Vincent J. Cornelisse, MBBS, PhD,[a,b,c,d] *Michael W. Traeger, MSc,*[e,f] *Edwina J. Wright, MBBS, PhD,*[a,b,e,g] *Dean Murphy, PhD,*[d,h] *Mark Stoové, PhD,*[e,f,i] *Margaret Hellard, MBBS, PhD,*[a,e] *Rachel Sacks-Davis, PhD,*[e,f] *Jason Asselin, BSc,*[e] *Christopher K. Fairley, MBBS, PhD,*[a,c] *Joseph Doyle, MBBS, PhD,*[a,b,e] *and Joseph Sasadeusz, MBBS, PhD*[b,g,j]

Background: PrEPX was an Australian HIV pre-exposure prophylaxis (PrEP) study conducted between 2016 and 2018. This analysis aimed to estimate hepatitis C (HCV) incidence and explore likely modes of transmission.

Setting: Cohort study of PrEP users in Victoria, Australia.

Methods: HCV tests were conducted at enrollment and every 12 months thereafter. HCV incident cases were identified from laboratory data. Likely modes of transmission were inferred from computer-assisted self-interviews, medical records, and interviews.

Results: Among 3202 PrEPX participants tested for HCV at baseline, HCV RNA-positive prevalence was 0.22% (95% confidence interval: 0.09 to 0.45). Among participants testing HCV antibody-negative or RNA-negative at baseline, 2058 had at least one follow-up HCV test. Eight incident HCV cases were identified during 2111 person-years of follow-up (incidence 0.38/100 person-years); all were primary infections in men who had sex with men. Clinical, laboratory, and computer-assisted self-interviews data were available for all, and 6 cases were interviewed. Three cases were attributable to injecting drug use (IDU). A fourth case reported IDU, but his HCV was attributable to sexual transmission. Four other cases reported no IDU and probably acquired HCV sexually. Most cases reported anal trauma in the context of condomless receptive anal intercourse during group sex at sex-on-premises venues.

Conclusions: In PrEPX, HCV incidence was low compared to international PrEP studies, and most cases were transmitted sexually. Our findings highlight the need for HCV prevention messaging by clinicians, in sex-on-premises venues, and on digital platforms used to arrange group sex; and the need for HCV screening among some PrEP-using men who have sex with men.

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From the [a]Central Clinical School, Monash University, Melbourne, Australia; [b]Department of Infectious Diseases, the Alfred Hospital, Melbourne, Australia; [c]Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia; [d]Kirby Institute, UNSW, Sydney, Australia; [e]Burnet Institute, Prahran, Australia; [f]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; [g]Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Australia; [h]Department of Gender and Cultural Studies, University of Sydney, Sydney, Australia; [i]School of Psychology and Public Health, La Trobe University, Bundoora, Australia; and [j]Royal Melbourne Hospital, Melbourne, Australia.

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V.J.C. designed this analysis, conducted interviews, analyzed the data and wrote the first draft, subsequent draft, and the final version of this manuscript. M.W.T. analyzed data from the ACCESS network to calculate HCV incidence. E.J.W. is the principal investigator of the PrEPX study and contributed to each draft and the final version of this manuscript. D.M. assisted with interpretation of qualitative data and contributed to each draft and final version of this manuscript. M.S., M.H., R.S.-D., J.A., C.K.F., and J.D. all contributed to each draft and the final version of this manuscript. J.S. conceptualized this analysis, secured funding to conduct this analysis, and contributed to each draft and the final version of this manuscript.

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Data sharing: The raw data underpinning this analysis contains potentially highly sensitive information that cannot be adequately deidentified by nature of its highly personal content. As such, the authors have not deposited these raw data in a publically accessible data repository.

Correspondence to: Vincent J. Cornelisse, MBBS, PhD, Kirketon Road Centre, 100 Darlinghurst Road, Kings Cross, NSW, Australia 2010 (e-mail: Vincent.cornelisse@health.nsw.gov.au).

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INTRODUCTION

HIV pre-exposure prophylaxis (PrEP) using once-daily co-formulated tenofovir disoproxil* and emtricitabine (TD*/FTC) is highly efficacious at preventing HIV among cisgender men who have sex with men (MSM).[1,2] However, MSM who use PrEP are at high risk of other sexually transmissible infections (STIs),[3–5] and this risk may include hepatitis C virus (HCV) infection. Sexual transmission of HCV has been observed among HIV-positive MSM,[6–10] and observational cohort data suggest that HCV may also be transmitted sexually among HIV-negative MSM using PrEP.[11–15]

Health promotion messaging on HCV prevention and HCV testing recommendations for MSM using PrEP need to be informed by context-specific HCV incidence data that include the risk of sexual transmission.

The PrEPX study was an Australian population-level PrEP study conducted in Victoria, South Australia, and Tasmania that enrolled more than 5000 participants between 2016 and 2018. Enrollment was open to any persons who were at risk of HIV, regardless of gender, but as previously described, the majority (99%) were men who have sex with men.[4] We aimed to determine the incidence of HCV among PrEPX participants and to describe each incident case in detail to determine the likely mode of HCV transmission.

METHODS

We analyzed HCV diagnoses among PrEPX participants in Victoria who enrolled at Melbourne Sexual Health Centre (MSHC) or at general practice (GP) clinics that participated in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillanc (ACCESS) Network. The PrEPX protocol has been published previously.[16] Baseline visits were conducted between June 29, 2016 and March 29, 2018. For this analysis, participants were censored at their last HCV test before April 1, 2018.

HCV Testing

The PrEPX enrollment assessment included an HCV test, usually HCV antibody (Ab), or for participants with a known history of HCV, an HCV RNA test. Any positive HCV Ab tests were followed by a HCV RNA test. In this article, "HCV test" refers to either a HCV Ab test, HCV RNA test, or both, depending on the participant's HCV history. Liver enzyme testing was not routinely required by the PrEPX protocol but permitted at clinicians' discretion. Participants were routinely followed up every 3 months for clinical and laboratory monitoring and for repeat prescriptions for TD*/FTC. Clinicians were asked to perform a repeat HCV test every 12 months but had discretion to test more frequently if clinically indicated.

Calculation of HCV Prevalence and Incidence

To calculate HCV prevalence at baseline, we defined the denominator as the number of PrEPX participants who had an HCV test at enrollment and the numerator as the number of PrEPX participants who had a positive HCV RNA test at enrollment. To calculate HCV incidence during the study, we defined the denominator as person-time accrued during the study, which was the sum of individual participants' person-time starting at their first recorded negative HCV test through to their last recorded negative HCV test or until HCV diagnosis. We defined incident HCV cases as participants who were HCV Ab-negative at baseline and subsequently tested positive for HCV Ab and RNA during follow-up or participants who had a positive HCV Ab test and negative RNA test at baseline and subsequently tested RNA-positive during follow-up. Participants who tested HCV RNA-positive at baseline were excluded from the incidence calculation because including them would have been difficult given different RNA clearance rates among these participants. Confidence intervals were calculated in STATA using the quadratic approximation to the Poisson log likelihood for the log rate parameter.

Behavioral Data

Behavioral data were collected at enrollment and follow-up visits by computer-assisted self-interview (CASI). For every incident HCV case, we reviewed CASI data and medical records and sought to conduct interviews using a predefined set of questions (see Supplemental Digital Content, http://links.lww.com/QAI/B645). Interviews were conducted in-person for 4 participants and by telephone for 2 participants. Our results denote these data sources as CASI surveys$^{(S)}$, medical records$^{(M)}$, and interviews$^{(I)}$.

RESULTS

Demographics and Behavioral Data at Baseline

Of the total PrEPX cohort, 3464 participants enrolled at MSHC or ACCESS GP clinics, of whom 3202 (92.4%) had a valid HCV test result at baseline (see Box 1, Supplemental Digital Content, http://links.lww.com/QAI/B645). Their median age was 35 years (interquartile range 28–42 years). According to clinician-completed enrollment surveys, 99.1% had a male gender identity, 98.7% identified as gay or bisexual, 4.9% currently injected drugs, 13.5% had used methamphetamines in the preceding 3 months, and 48.2% had condomless receptive anal sex with casual partners in the preceding 3 months. At enrollment, 2669 participants (83.4%) completed CASI, among whom 61.5% reported recent condomless anal intercourse with casual partners, 5.7% reported recent injecting drug use (IDU), and 9.9% reported ever IDU. Reported recent use of substances in the context of sex (chemsex) included use of methamphetamine (13.2%), gamma-hydroxybutyrate (GHB, 9.9%), amyl nitrite (36.8%), and alcohol (42.0%) (Table 1).

TABLE 1. Behavioral Data at Baseline for PrEPX Participants Enrolled at GP Clinics and MSHC

	GP Clinics	MSHC
Total	2230	439
Condom use with casual partners*		
No anal sex	133 (6.0%)	239 (54.4%)
Always used a condom	550 (24.7%)	42 (9.6%)
Did not always use a condom	1485 (66.6%)	155 (35.3%)
Unanswered	62 (2.8%)	3 (0.7%)
Recreational injecting drug use		
No	1987 (89.1%)	400 (91.1%)
Yes, ever†	225 (10.1%)	39 (8.9%)
Yes, within the past 12 mo	146 (6.6%)	6 (1.4%)
Missing	18 (0.8%)	0 (0.0%)
Methamphetamine use in the context of condomless anal intercourse‡		
Yes	294 (13.2%)	
No	1931 (86.8%)	
GHB use in the context of condomless anal intercourse§		
Yes	221 (9.9%)	
No	2004 (90.1%)	
Amyl nitrite use in the context of condomless anal intercourse		
Yes	818 (36.8%)	
No	1407 (63.2%)	
Alcohol use in the context of condomless anal intercourse		
Yes	935 (42.0%)	
No	1290 (58.0%)	

*Condom use with casual partners references the past 6 months at GP clinics or the past 3 months at MSHC.

†"Ever" includes participants who reported injecting drugs within the past 12 months.

‡Only participants who attended GP clinics were asked about the use of drugs or alcohol in the context of anal intercourse. These questions all relate to the previous 6 months.

§Five participants declined to answer the question on GHB use in the context of condomless anal intercourse.

HCV Prevalence at Baseline

Among 3202 participants with a valid HCV test at baseline, 14 participants were HCV Ab-positive, of whom 7 were HCV RNA-positive, producing an HCV RNA prevalence of 0.22% [95% confidence interval (CI): 0.09 to 0.45] (see Box 1, Supplemental Digital Content, http://links.lww.com/QAI/B645). All of these participants were successfully treated during the study period, and none had evidence of reinfection during the study.

HCV Incidence During Follow-Up

Among 3188 PrEPX participants who had a negative HCV Ab or RNA test at baseline, 2058 participants had at least one follow-up test during the study, with a median follow-up period of 1.03 years (interquartile range 0.84—1.33 years), accumulating 2111 person-years (PY) of follow-up. Eight HCV incident cases (RNA-positive) were identified, producing an incidence rate of 0.38/100PY (95% CI: 0.19 to 0.76). All HCV incident cases were primary infections (no previous HCV) (see Box 2, Supplemental Digital Content, http://links.lww.com/QAI/B645).

Potential Contributors to HCV Transmission for Incident Cases

All participants with incident HCV infections were MSM. Clinical, laboratory, and survey data were available for all cases, and 6 cases were available for interview. For each of these cases, clinical data relating to HCV are listed in Table 2, alongside data on potential contributors to HCV transmission. Each case is described in more detail in the online results, Supplemental Digital Content, http://links.lww.com/QAI/B645.

DISCUSSION

In PrEPX, HCV incidence was low, with an incidence rate of 0.38/100PY, in a study population with low baseline HCV RNA-positive prevalence of 0.22%. All incident HCV infections occurred in people without previous HCV. Of 8 HCV incident cases, 3 (37.5%) were attributable to IDU and 5 (62.5%) were attributable to condomless receptive anal intercourse, often in a context of anal trauma, chemsex, and group sex at sex-on-premises venues (SOPVs). One of the participants with sexually acquired HCV was simultaneously diagnosed with HIV, which has been shown epidemiologically to increase the risk of sexually acquired HCV.

Our findings represent the lowest incidence of HCV infection reported in a cohort of MSM using PrEP. The AmPrEP study in Amsterdam reported an HCV incidence of 2.30/100PY among 350 PrEP-using MSM[17] on a baseline HCV prevalence of 4.8%,[18] 6 times higher than our HCV incidence. AmPrEP participants diagnosed with incident HCV had higher numbers of receptive condomless anal sex acts with casual partners (median 10 vs 3, in 3 months) were more likely to have been diagnosed with anal STIs (36% vs 13%) and more commonly injected drugs (40% vs 5%) or shared straws during intranasal drug use (60% vs 29%), compared with HCV-negative participants.[17]

The PROUD study in London reported an HCV incidence of 1.9/100PY among 409 PrEP-using MSM on a baseline prevalence of 2.1%, 5 times higher than our HCV incidence. Among 25 participants with incident HCV, IDU was reported by 11, denied by 12, and unknown for 2 participants.[19] Risk factors for incident HCV were otherwise not described in detail.

A French hospital-based cohort of 1049 PrEP-using MSM found an HCV incidence of 1.44/100PY on a baseline

TABLE 2. Hepatitis C-Related Clinical Data, Potential Contributors to Transmission, and Transmission Classification

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Interviewed	Yes	Yes	No	Yes	Yes	No	Yes	Yes
ALT result (U/L), reference < 35 U/L	590	1140	1548	445	3249	612	454	103
HCV genotype	1a	1a	1a	1a	3	3	3	3
Drug use during sex	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Injecting drug use	No	No	No	Yes	Yes	Yes	No	Yes
Condomless RAI*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Group sex	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
SOPV attendance†	Yes	Yes	Not known	Yes	No	Not known	Yes	Yes
Receptive fisting	Yes	No	Not known	Yes	No	Not known	No	No
HIV‡	No	No	Yes	No	No	No	No	No
Syphilis	No	No	No	No	No	No	No	No
Anal chlamydia	No	No	No	Yes	No	No	No	No
Anal gonorrhea	No	No	Yes	Yes	No	No	No	No
Previous anal HSV	Yes, HSV2	Yes, HSV1	Not known	No	No	Not known	Yes	No
Current anal HSV	No	No	No	Yes, HSV2	No	No	No	No
Anal trauma	Yes	Yes	Not known	Yes	No	Not known	Yes	No
Inferred HCV mechanism of transmission	Sexual	Sexual	Sexual	Likely sexual	Injecting	Injecting	Sexual	Shared injecting

Behavioural descriptors (eg, "group sex") and STI data presented in Table 2 relate to the period of likely HCV acquisition, as determined by cases' HCV testing pattern.
*Condomless anal intercourse refers to intercourse with casual partners.
†SOPV attendance refers to attendance at a sex-on-premises venue at the likely time of HCV acquisition.
‡Case 3 was initially HIV-negative and was diagnosed with HIV at the same time as his HCV diagnosis.
ALT, alanine aminotransferase; HSV, herpes simplex virus; RAI, receptive anal intercourse.

prevalence of 0.86%, 4-fold higher than our HCV incidence.[12] Their 7 incident cases included 5 that were attributed to sexual transmission and 2 related to intranasal rather than injecting drug use. The authors did not comment on IDU among these HCV incident cases.

The ANRS Prevenir study in Paris reported an HCV incidence of 0.67/100PY and 0.60/100PY among participants who used PrEP daily and on-demand, respectively,[20] but they did not describe HCV risk factors in detail.

The French ANRS IPERGAY PrEP trial reported an HCV incidence of 1.40/100PY on a low baseline HCV prevalence of 0.23%. Participants with incident HCV infections reported a greater number of sexual partners and were more likely to have ingested drugs (not IDU), compared with HCV-negative participants.[21]

One possible explanation for the low incidence of HCV in PrEPX is that government-subsidized DAA treatment for HCV became available 4 months before commencement of the PrEPX study, followed by rapid uptake of HCV treatment.[22] This resulted in microelimination of HCV among MSM, particularly in Victoria, where DAA treatment was targeted toward HIV–HCV co-infected individuals.[23] Such microelimination is particularly relevant if HIV-negative men on PrEP and HIV-positive men are involved in the same HCV transmission networks, as indicated by phylogenetic analyses from the United Kingdom, France, and Amsterdam.[17,24,25]

Of our 5 cases classified as sexually transmitted HCV, all reported receptive condomless anal intercourse with casual sexual partners and participation in group sex and all who were interviewed reported attending a SOPV around the time of their HCV acquisition. Four participants reported non-injecting drug use during sex, 2 reported receptive brachioproctic sex (ie, "fisting"), 4 reported anal trauma around the time of their HCV acquisition, and one experienced an initial outbreak of anal HSV2 after which he attended a group sex event at a SOPV. The role of anal trauma and sex at a SOPV in the acquisition of HCV was also highlighted in a 2010 survey involving 13,111 European MSM, among whom 70% were HIV-negative, which found that a recent diagnosis of HCV was independently associated with visiting a SOPV and practicing receptive fisting.[26]

Some limitations need to be considered when interpreting our findings. First, although ACCESS captures participant movement between participating clinics, some PrEPX participants may have been diagnosed with HCV elsewhere. However, such diagnoses would have been detected at subsequent study visits when participants returned for their PrEP prescriptions. Second, the PrEPX "protocol" and "stipulated" annual HCV screening, but some participants enrolled less than 12 months before termination of the PrEPX study, and hence some of them did not have a follow-up HCV test. Of the 3202 participants included in the baseline analysis, 916 enrolled less than 12 months before study closure. However, 335 of them nonetheless had an HCV test (sooner than the protocol-stipulated 12-month mark), leaving 518 participants who did not have a follow-up HCV test after enrollment, and hence were not included in the incidence calculation. In addition, by testing for HCV annually rather than every 3 or 6 months, we may have slightly underestimated HCV incidence by overestimating person-time at risk. Another limitation of our HCV testing protocol is the use of HCV antibody screening (rather than HCV RNA) in participants who had no known history of HCV, and hence we may have missed early HCV infections because of

possible delays in HCV Ab seroconversion. Third, we included only participants who attended ACCESS clinics; we did not include participants at clinics that did not collect the same level of behavioral data. This may have introduced a degree of selection bias. Fourth, observational studies have suggested that sharing of noninjecting drug use equipment, such as straws for intranasally administered drugs, may be a risk factor for HCV transmission,[9] and this is a possible alternative mechanism for some of our cases of sexually acquired HCV. Finally, we were not able to interview 2 incident cases, but we did have multiple data sources for all cases.

Our study indicates that incident HCV among Australian PrEP-using MSM is less frequent than seen in Amsterdam, the United Kingdom, and France. Available data on behavioral risk factors for HCV were broadly similar between these studies, suggesting that the observed difference in HCV incidence is likely the result of differences in HCV prevalence among MSM populations in different parts of the world, rather than due to behavioral differences. Most of the incident HCV cases in PrEPX seem to have resulted from sexual transmission, in the context condomless receptive anal intercourse at a SOPV or other group sex settings, anal trauma, and chemsex. This presents a health promotion opportunity for clinicians and for HCV awareness campaigns, which should be promoted to MSM who attend a SOPV and on digital platforms used to arrange group sex. Such campaigns should discuss the HCV risk associated with anal trauma, discuss the importance of HCV testing, and provide information on HCV treatment availability.

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Appendix C6.Incidence of hepatitis C among gay and bisexual men in Australia, 2009 - 2019

Citation:

Harney BL, Sacks-Davis R, van Santen DK, **Traeger MW**, Wilkinson A, Asselin J, El-Hayek C, Fairley CK, Roth N, Bloch M, Matthews G, Donovan B, Guy R, Stoové M, Hellard ME, Doyle JS. The incidence of hepatitis C among gay, bisexual and other men who have sex with men before and after the availability of direct acting antivirals in Australia, 2009-2019. *Clinical Infectious Diseases.* Online 25 October 2021. doi: 10.1093/cid/ciab720

Clinical Infectious Diseases

MAJOR ARTICLE

The Incidence of Hepatitis C Among Gay, Bisexual, and Other Men Who Have Sex With Men in Australia, 2009–2019

Brendan L. Harney,[1,2,3] Rachel Sacks-Davis,[1,2] Daniela K. van Santen,[1,2] Michael Traeger,[1,2] Anna L. Wilkinson,[1,2] Jason Asselin,[1] Carol El-Hayek,[1,2] Christopher K. Fairley,[4,5] Norman Roth,[6] Mark Bloch,[7] Gail Matthews,[8] Basil Donovan,[8] Rebecca Guy,[8] Mark Stoové,[1,2] Margaret E. Hellard,[1,2,3,a] and Joseph S. Doyle[1,3,a]; for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood-borne Viruses (ACCESS)

[1]Disease Elimination Program, Burnet Institute, Melbourne, Australia; [2]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; [3]Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, Australia; [4]Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia; [5]Central Clinical School, Monash University, Melbourne, Australia; [6]Prahran Market Clinic, Melbourne, Australia; [7]Holdsworth House Medical Practice, Sydney, Australia; and [8]Kirby Institute, University of New South Wales Sydney, Sydney, Australia

Background. Hepatitis C virus (HCV) infection has been reported among gay, bisexual, and other men who have sex with men (GBM) globally including GBM with human immunodeficiency virus (HIV) and HIV-negative GBM, particularly those using HIV preexposure prophylaxis (PrEP). In Australia, HCV direct-acting antiviral treatment (DAA) was government-funded from 2016. Large implementation studies of PrEP also began in 2016. We examined HCV incidence among GBM to assess whether HCV incidence has changed since 2015.

Methods. Data were drawn from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance. We included GBM who tested HCV antibody negative at their first test and had ≥1 subsequent test. Generalized linear modeling (Poisson distribution) was used to examine HCV incidence from 2009 to 2019 stratified by HIV status, and among HIV-negative GBM prescribed PrEP from 2016 to 2019.

Results. Among 6744 GBM with HIV, HCV incidence was 1.03 per 100 person-years (PY). Incidence declined by 78% in 2019 compared to 2015 (incidence rate ratio [IRR], 0.22 [95% confidence interval {CI}: .09–.55]). Among 20 590 HIV-negative GBM, HCV incidence was 0.20/100 PY, with no significant change over time. Among 11 661 HIV-negative GBM prescribed PrEP, HCV incidence was 0.29/100 PY. Compared to 2016, incidence among GBM prescribed PrEP declined by 80% in 2019 (IRR, 0.20 [95% CI: .06–.64]).

Conclusions. HCV incidence among GBM living with HIV declined following DAA availability. There was no observed change in HCV incidence among HIV-negative GBM overall. Among GBM prescribed PrEP, incidence declined since the early years of PrEP implementation in Australia. Australia is on track to eliminate HCV among GBM before global 2030 targets.

Keywords. hepatitis C; HIV; preexposure prophylaxis; incidence.

Hepatitis C virus (HCV) infection has been reported among gay, bisexual, and other men who have sex with men (GBM) globally, and GBM with human immunodeficiency virus (HIV) are disproportionally affected [1]. Prior to the introduction of direct-acting antivirals (DAAs), treatment for HCV was suboptimal with treatment lasting for a year and many side-effects reported, with only 50%–60% of people being cured [2]. With the advent of DAA treatment, >90% of people who undergo treatment are cured, with HIV status not affecting treatment efficacy [3, 4]. This has led to optimism that hepatitis C can be eliminated, and the World Health Organization has set a number of goals, including an 80% reduction in incidence by 2030 relative to a 2015 baseline [5]. It has also been suggested that elimination could be achieved more quickly in key subgroups (known as micro-elimination), including GBM with HIV [6, 7]. Mathematical modeling of HCV incidence in Australia suggests that significant reductions in HCV incidence are feasible among GBM [8]. This is supported by empirical data from primary care clinics in Melbourne, Australia, involved in a real-world study of HCV treatment among people living with HIV, most of whom were GBM [9].

There are few studies with national-level data available to assess changes in HCV incidence among GBM with HIV following the introduction of DAA treatments. A study from the Netherlands in 2018 reported a 51% decrease in incidence in the first year among GBM with HIV following the introduction of HCV DAAs in 2015 [10]. A follow-up study confirmed these initial findings but showed minimal declines in incidence after 2016 [11]. Among GBM with HIV enrolled in the Swiss HIV Cohort, following the removal of HCV treatment restrictions, incidence declined from 0.53/100 PY in 2014 to 0.12/100 PY in 2019 in this group [12]. An analysis of data from 5 clinics in England reported a similar decline in HCV incidence between 2015 and 2018 among GBM with HIV following wider access

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[a]M. E. H. and J. S. D. contributed equally to this work as co–senior authors.
Correspondence: B. Harney, Burnet Institute, 85 Commercial Rd, Melbourne, Victoria 3004, Australia (brendan.harney@burnet.edu.au).
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to DAA treatment [13]. Conversely, among GBM with HIV enrolled in a French cohort study, the incidence of HCV was reported to have increased from 0.32/100 PY in 2012 to 0.84/100 PY in 2018 [14]. While HCV infection is more common among GBM with HIV [1], there have also been reports of HCV infection among HIV-negative GBM acquired via sexual contact, in particular those using HIV preexposure prophylaxis (PrEP) [9, 15, 16]. A systematic review reported a pooled incidence of 1.48/100 PY among HIV-negative GBM using PrEP [1]. To our knowledge, there have been no published studies examining the incidence of HCV among HIV-negative GBM before and after the introduction of HCV DAAs and HIV PrEP.

DAA treatment was subsidized by the Australian government through the Pharmaceutical Benefits Scheme (PBS) (maximum patient cost US$30 per month) from 1 March 2016 with no restrictions to treatment based on liver disease stage or substance use, and reinfection could also be treated through the PBS. Furthermore, treatments were able to be prescribed by nonspecialist primary care providers and were available in general practices and sexual health clinics. HIV PrEP was scaled up in Australia in early to mid-2016 through large implementation trials enrolling 3700 and 3800 predominately GBM [17, 18], and on 1 April 2018, PrEP became widely available through the PBS and could be prescribed by any general practitioner. To understand the impact of DAA treatment on hepatitis C incidence among GBM with HIV, and the impact of PrEP on HCV incidence among HIV-negative GBM, we examined HCV incidence among GBM with HIV from 2009 to 2019, HIV-negative GBM from 2009 to 2019, and GBM prescribed HIV PrEP from 2016 to 2019.

METHODS

Data Source

Data were drawn from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood-borne Viruses (ACCESS), described in detail previously [19, 20]. In brief, ACCESS collates blood-borne virus and sexually transmitted infection (STI) testing data and demographic data from clinics and laboratories, linking data within individuals over time, including between services participating in ACCESS. Ethical approval for ACCESS was received from the Alfred Hospital, University of Tasmania, and Menzies School of Health Research. Ethical reviews were also undertaken by community organizations representing key populations including gay and bisexual men and people living with HIV. The requirement for individual-level consent was waived by all ethics committees.

For these analyses, we utilized data from ACCESS clinics in 7 of 8 Australian states and territories; no HCV testing data among GBM were available from clinics based in the Northern Territory. Data were from males who were defined as being GBM based on being recorded as gay or bisexual in patient management systems and/or reporting 1 or more male partners in the previous 12 months in behavioral surveys at sexual health clinics. A previously validated method based on males having a rectal STI swab for chlamydia or gonorrhea recorded in ACCESS was also used to identify GBM [21]. GBM were defined as being HIV positive if they had a record of an HIV-positive test or a record of an HIV viral load test at a date prior to the HCV test event. GBM were classified as HIV negative at an HCV test event if they had a negative HIV test result recorded at the time of the HCV test or at any time after or within the 12 months prior to the HCV test. GBM whose HIV status was unable to be determined on this basis were excluded (Figure 1).

Incidence of HCV Infection Analysis

The outcome for all incidence analyses was a primary (first) incident HCV infection. A primary HCV incident infection was defined as a positive HCV antibody or RNA test following a negative antibody test. GBM were included in the incidence analyses if they tested HCV antibody negative at their first HCV antibody test and had at least 1 subsequent HCV test (antibody or RNA). Depending on HIV status history, GBM could potentially be included in both the HIV-negative and HIV-positive HCV incidence analyses (Supplementary Figure 1*A*). Those who had a missing or indeterminate HCV antibody test result at their first test were included provided they had a subsequent antibody negative test and an additional test result. GBM entered the incidence analyses on the date of their first confirmed HCV antibody–negative test and were censored at their last HCV test if they remained HCV negative. Specific to the analyses among HIV-negative GBM, those who subsequently had an HIV-positive test result were censored at their previous HCV test event. GBM who were defined as an HCV incident case were censored at a randomly imputed date between their last negative HCV test and diagnosis test date (Supplementary Figure 1*B*). Due to the date of infection being unknown, the time between tests being variable and overlapping calendar years, the date of infection was randomly imputed 1000 times as has been done previously [22]. The results reported—that is, incidence rates or incidence rate ratios (IRRs)—are the mean of these 1000 imputations, with Rubin's rules used to calculate confidence intervals (CIs) [23].

Statistical Analyses

Generalized linear modeling (Poisson distribution) was used to examine overall HCV incidence and HCV incidence by calendar year, stratified by HIV status. We then repeated the same analysis with 2015 as a reference category as this was the last year preceding widespread HCV DAA treatment availability and large-scale PrEP implementation in Australia. Finally, we incorporated a piecewise function to examine trends in

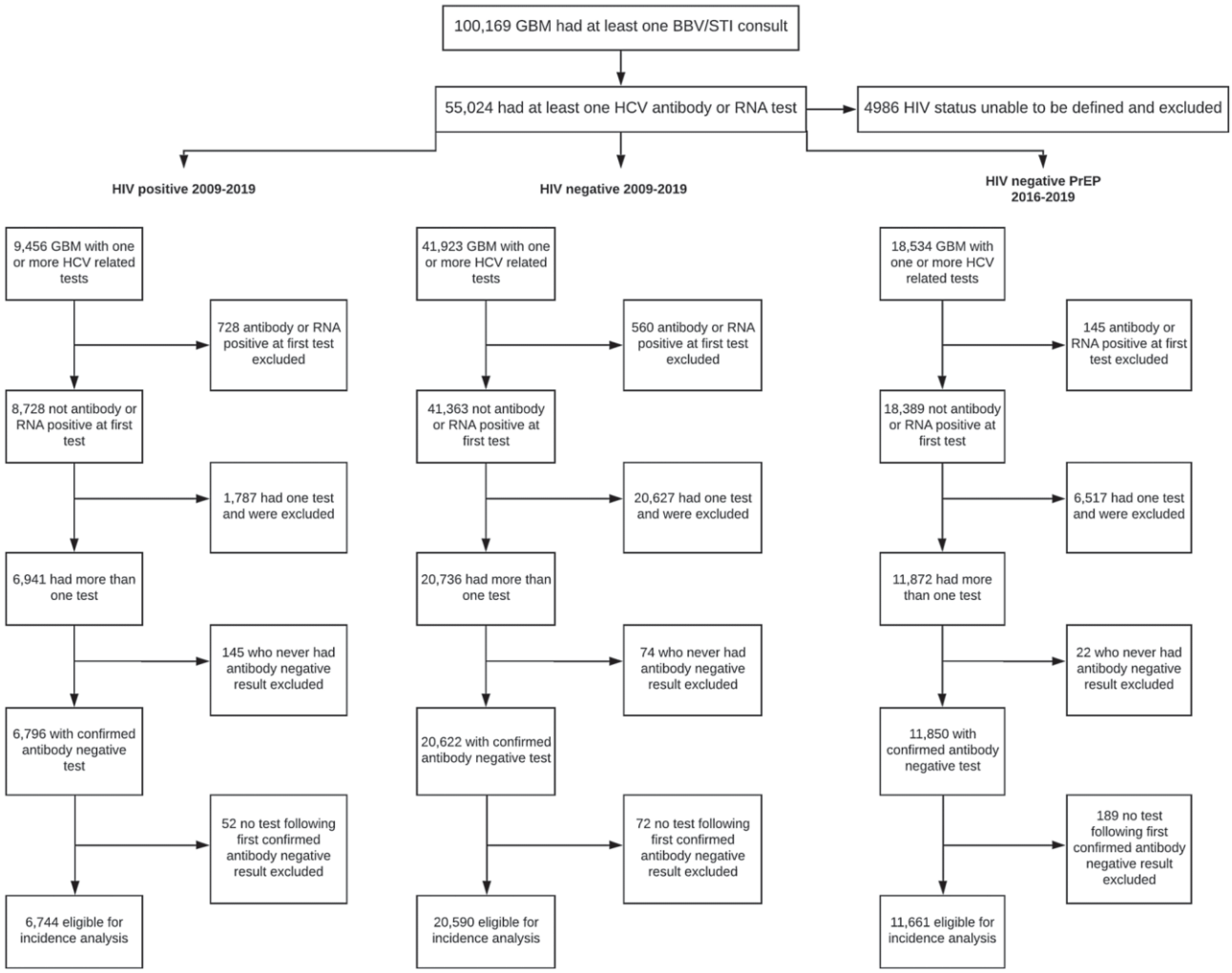

Figure 1. Gay, bisexual, and other men who have sex with men (GBM) included in hepatitis C virus incidence analyses. GBM can be included in >1 analysis depending on their testing history. Abbreviations: BBV, blood-borne virus; GBM, gay, bisexual, and other men who have sex with men; HCV, hepatitis C virus; HIV, human immunodeficiency virus; STI, sexually transmitted infection.

incidence by continuous calendar year for the periods 2009–2015 and 2016–2019 and to examine any change in the trend between the 2 periods.

HIV Preexposure Prophylaxis

To understand the impact of PrEP on HCV incidence among HIV-negative GBM in more detail, we performed an analysis focused specifically on GBM prescribed PrEP from 2016 to 2019. We included GBM from the year they first had evidence of prescription and in subsequent years, regardless of whether they had evidence of PrEP prescription in the subsequent years (Supplementary Figure 2*A*). This was done as, from mid-2016 until April 2018, PrEP could primarily only be accessed through implementation studies that included many clinics included in the ACCESS network. However, from April 2018, PrEP was available through any general practitioner, and these prescription data may not have been captured if the clinic was not part of the surveillance system. We also conducted a sensitivity analysis where HCV tests were only included in that year if there was also evidence of PrEP prescription within the surveillance system data in the same year (Supplementary Figure 2*B*).

For the PrEP-specific analyses, the analyses were the same as the main analyses except the time period was limited to 2016 to 2019, and 2016 was used as a reference category instead of 2015. The trend in incidence rate was assessed from 2016 to 2019 with calendar year included as a continuous variable.

All statistical analyses were performed using Stata S/E 16.1 software (College Station, Texas).

RESULTS

Of 100 169 GBM attending an included clinic, 55 024 had at least 1 HCV antibody or RNA test recorded between 2009 and 2019. HIV status could not be defined for 4986 GBM (9%) and they were excluded from the analysis. An additional 27 757 were

excluded from incidence analyses based on either being HCV antibody and/or RNA positive at their first test or only having 1 HCV test, leaving a total of 27 267 GBM attending 42 clinics eligible for incidence analyses (Figure 1). Most GBM (75.5%) were from general practices that specialize in the healthcare of gay and bisexual men as well as gender-diverse people. Another 19.5% were from sexual health clinics. The remaining 5% were from a hospital-based clinic, community health clinic, or general practice.

HCV Incidence Among GBM With HIV

Of 9456 GBM with HIV with at least 1 HCV test, a total of 6744 GBM with HIV were eligible for the incidence analysis (Figure 1). The median time between HCV tests was 10.7 months (interquartile range [IQR], 6.3–16.3 months) with a median of 5 tests (IQR, 3–8) per person. The median time between the previous negative test and diagnosis of an incident case was 8.6 months (IQR, 4.9–17.2 months). There were 33 150 person-years (PY) of follow-up with 290 incident HCV infections identified, resulting in an overall incidence rate of 1.03/100 PY (95% CI: .67–1.60). Incidence was highest in 2010 at 2.12/100 PY and lowest in 2019 at 0.22/100 PY (Figure 2).

Compared to 2015, incidence declined by approximately 60% in 2017 (IRR, 0.40 [95% CI: .22–.74]), 45% in 2018 (IRR, 0.55 [95% CI: .32–.95]), and 78% in 2019 (IRR, 0.22 [95% CI: .09–.5]) (Table 1). Results from the piecewise linear trend analysis indicate that there was no significant continuous year-on-year change in incidence from 2009 to 2015 (IRR, 0.89 [95% CI: .60–1.30]) nor from 2016 to 2019 (IRR, 0.80 [95% CI: .41–1.55]). Similarly, there was no significant change in the overall HCV incidence trend between 2009–2015 and 2016–2019 (IRR, 0.90 [95% CI: .46–1.78]).

Hepatitis C Incidence Among HIV-Negative GBM

Among 41 923 HIV-negative GBM with at least 1 HCV test, 20 590 HIV-negative GBM were eligible for the incidence analysis (Figure 1). There was a median of 3 (IQR, 2–5) tests per person and the median time between tests was 9.5 months (IQR, 4.2–17.7 months); the median time between a previous negative test and diagnosis of an incident HCV infection was 7.3 months (IQR, 3.3–21.9 months). Over 60 512 PY of follow-up there were 122 incident infections, for an overall incidence of 0.20/100 PY (95% CI: .09–.57). Incidence fluctuated between 0.49/100 PY in 2009 and 0.07/100 PY in 2019 (Figure 3).

Compared to 2015, there was no change in incidence in 2016 (IRR 1.44 [95% CI: .63–3.29]), 2017 (IRR, 1.92 [95% CI: .91–4.00]), or 2018 (IRR, 0.91 [95% CI: .39–2.10]) (Table 2). In the piecewise linear regression analyses, there was no continuous change in the incidence trend from 2009 to 2015 (IRR, 0.84 [95% CI: .47–1.48]) nor from 2016 to 2019 (IRR, 0.70 [95% CI: .36–1.37]). Compared to the trend from 2009 to 2015, there was no change in the trend from 2016 to 2019 (IRR, 0.84 [95% CI: .40–1.76]).

Hepatitis C Incidence Among HIV-Negative GBM Using HIV PrEP

From 2016 to 2019, a total of 23 373 GBM were defined as being prescribed PrEP and 18 534 (79.3%) had at least 1

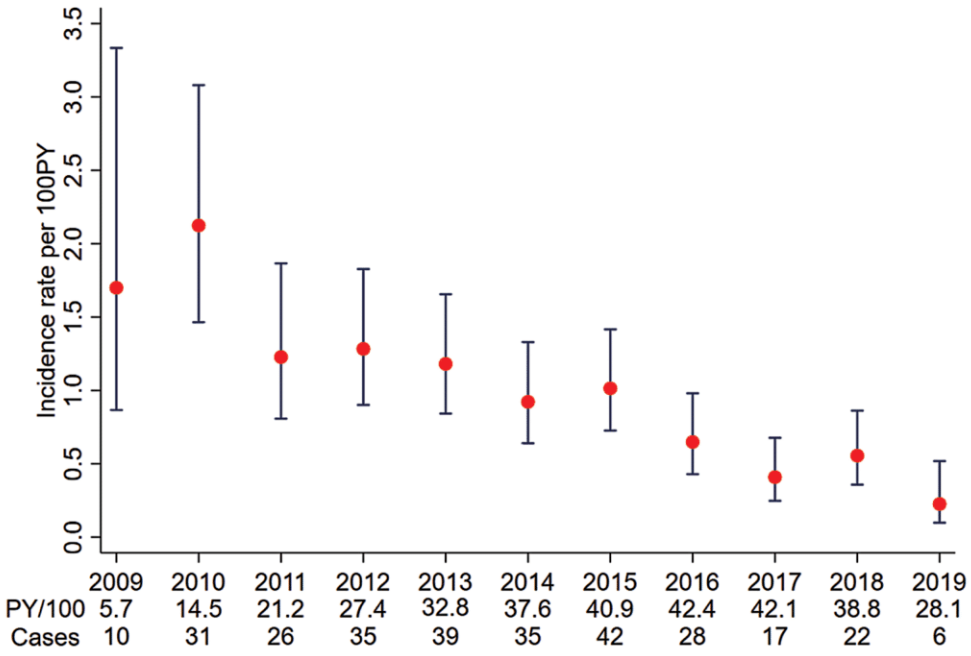

Figure 2. Hepatitis C virus incidence among gay, bisexual, and other men who have sex with men living with human immunodeficiency virus in Australia attending clinics included in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood-borne Viruses (ACCESS), 2009–2019. Abbreviation: PY, person-years.

Table 1. Hepatitis C Incidence Among Gay, Bisexual, and Other Men Who Have Sex With Men Living With Human Immunodeficiency Virus in Australia, 2009–2019

Year	Cases[a]	PY/100[a]	Incidence Rate (95% CI)	IRR[b] (95% CI)
2009	9.8	5.73	1.70 (.87–3.33)	1.68 (.79–3.55)
2010	30.8	14.49	2.12 (1.46–3.08)	2.09 (1.27–3.45)
2011	26.1	21.17	1.23 (.81–1.87)	1.21 (.71–2.07)
2012	35.3	27.44	1.28 (.90–1.83)	1.27 (.78–2.05)
2013	38.8	32.78	1.18 (.84–1.66)	1.16 (.72–1.88)
2014	34.7	37.56	0.92 (.64–1.33)	0.91 (.54–1.52)
2015	41.5	40.88	1.01 (.73–1.42)	1
2016	27.6	42.38	0.65 (.43–.98)	0.64 (.37–1.12)
2017	17.3	42.13	0.41 (.25–.68)	0.40 (.22–.74)
2018	21.6	38.80	0.56 (.36–.86)	0.55 (.32–.95)
2019	6.4	28.14	0.23 (.10–.52)	0.22 (.09–.55)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PY, person-years.

[a]Estimated mean from imputed datasets.

[b]IRR relative to 2015.

Table 2. Hepatitis C Incidence Among Human Immunodeficiency Virus–Negative Gay, Bisexual, and Other Men Who Have Sex With Men in Australia, 2009–2019

Year	Cases[a]	PY/100[a]	Incidence Rate (95% CI)	IRR[b] (95% CI)
2009	2.6	5.24	0.49 (.13–1.82)	2.92 (.68–12.56)
2010	4.8	13.58	0.34 (.11–1.01)	2.00 (.56–7.11)
2011	5.5	21.13	0.25 (.09–.73)	1.47 (.42–5.18)
2012	8.1	33.54	0.24 (.11–.52)	1.41 (.51–3.93)
2013	6.7	44.17	0.15 (.06–.35)	0.88 (.30–2.60)
2014	7.3	55.62	0.13 (.06–.29)	0.76 (.26–2.26)
2015	11.4	66.73	0.17 (.09–.32)	1
2016	20.7	84.80	0.24 (.15–.39)	1.44 (.63–3.29)
2017	34.2	105.56	0.32 (.23–.46)	1.92 (.91–4.00)
2018	15.5	100.93	0.15 (.09–.26)	0.91 (.39–2.10)
2019	5.2	73.82	0.07 (.03–.18)	0.41 (.13–1.27)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PY, person-years.

[a]Estimated mean from imputed datasets.

[b]IRR relative to 2015.

HCV-related test; 11 661 GBM were eligible for the incidence analysis (Figure 1). There were 56 incident cases over 20 886 PY for an overall incidence of 0.29/100 PY (95% CI: .17–.50). As shown in Figure 4, following rates of 0.41/100 PY and 0.44/100 PY in 2016 and 2017, incidence declined to a low of 0.08/100 PY in 2019.

Relative to 2016, incidence declined by approximately 80% in 2019 (IRR, 0.20 [95% CI: .06–.64]) (Table 3). There was no continuous trend in incidence among GBM prescribed PrEP from 2016 to 2019 (IRR, 0.60 [95% CI: .29–1.24]). The sensitivity analysis included GBM only with evidence of PrEP prescription in the same year as HCV testing and there was little difference in results to the primary analysis among GBM using PrEP (Supplementary Table 1).

DISCUSSION

In our national analysis of HCV incidence from 2009 to 2019 among GBM attending 42 clinics across Australia, we found that HCV incidence among 6744 GBM with HIV declined by 78% in 2019 compared to 2015. There was no significant change

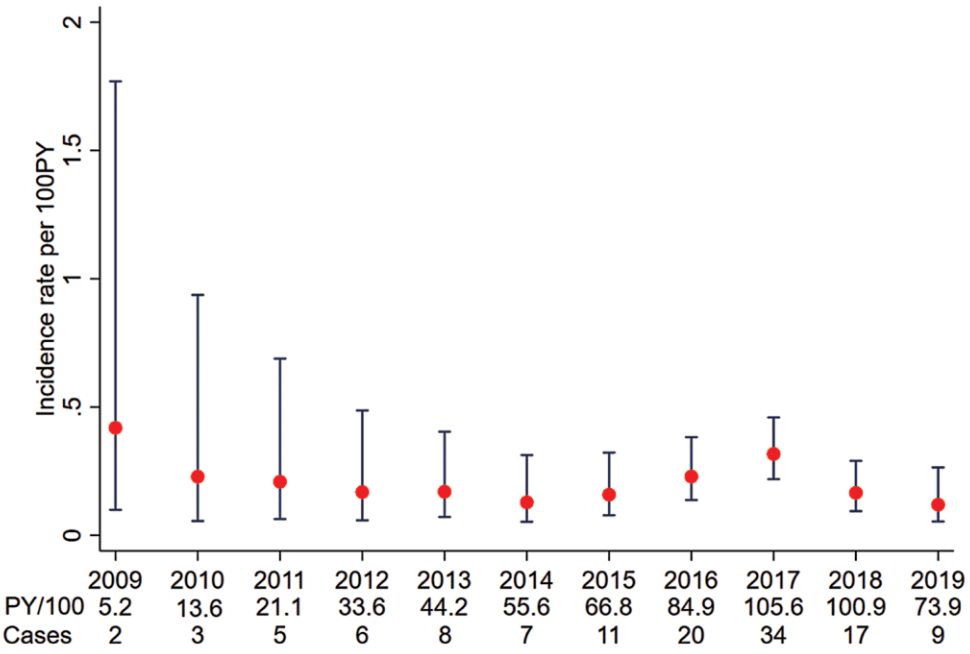

Figure 3. Hepatitis C virus incidence among human immunodeficiency virus–negative gay, bisexual, and other men who have sex with men in Australia attending clinics included in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood-borne Viruses (ACCESS), 2009–2019. Abbreviation: PY, person-years.

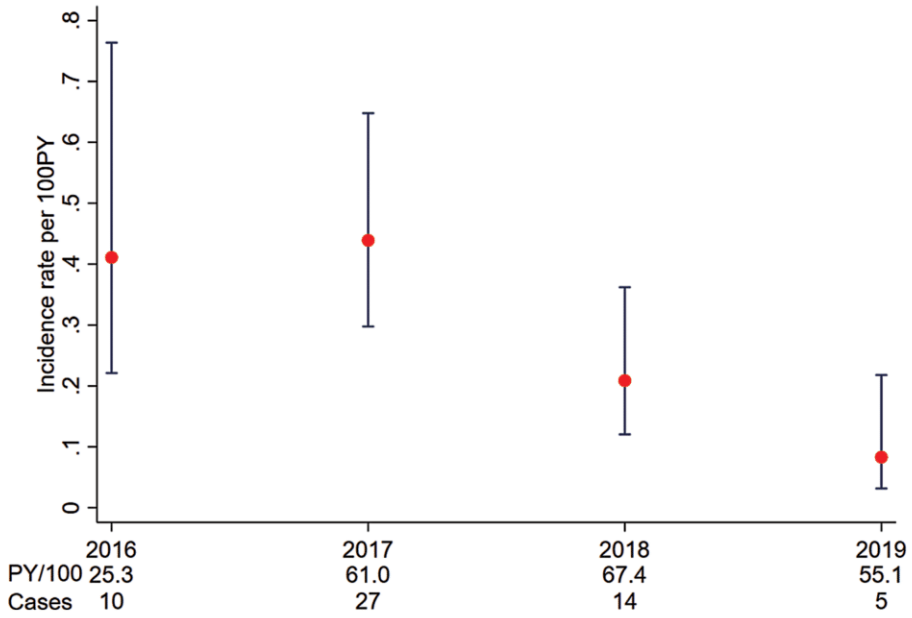

Figure 4. Hepatitis C virus incidence among human immunodeficiency virus–negative gay, bisexual, and other men who have sex with men prescribed preexposure prophylaxis in Australia attending clinics included in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood-borne Viruses (ACCESS), 2009–2019. Abbreviation: PY, person-years.

in HCV incidence among 20 590 HIV-negative GBM over this time. From 2016 onward, among 11 661 GBM prescribed PrEP, following a peak in the early years of implementation, incidence declined by 80% in 2019 compared to 2016.

Our results among GBM with HIV are consistent with reports from England, the Netherlands, and Switzerland that observed declines in HCV incidence following DAA treatment availability [10, 12, 13]. These data suggest that Australia is on track to achieving HCV micro-elimination, based on an 80% reduction in incidence, among GBM before 2030. While this is encouraging, there continued to be new HCV infections in 2019. Furthermore, like England and the Netherlands, incidence appears to be stabilizing albeit at a low level [11, 13]. This suggests an ongoing need to engage GBM with HIV in routine HCV testing. In addition, immediate treatment of newly diagnosed infections is likely required to achieve further reductions and sustain elimination, as waiting for spontaneous clearance will likely result in further transmission, including potentially reinfection [24].

Table 3. Hepatitis C Incidence Among Gay, Bisexual, and Other Men Who Have Sex With Men Using Human Immunodeficiency Virus Preexposure Prophylaxis in Australia, 2016–2019

Year	Cases[a]	PY/100[a]	Incidence Rate[a] (95% CI)	IRR[b] (95% CI)
2016	10.4	25.33	0.41 (.22–.76)	1
2017	26.8	60.97	0.44 (.30–.65)	1.07 (.51–2.24)
2018	14.1	67.49	0.21 (.12–.36)	0.51 (.22–1.16)
2019	4.6	55.06	0.08 (.03–.22)	0.20 (.06–.64)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PY, person-years.

[a]Estimated mean from imputed datasets.

[b]IRR relative to 2016.

To date there are limited data comparing HCV incidence among HIV-negative GBM, including both GBM prescribed and not prescribed PrEP, before and after the introduction of HCV DAA treatment and/or HIV PrEP. While not significant, we found that incidence re-peaked among all HIV-negative GBM in 2017 following a period of stable incidence from 2010–2011 to 2016. This may be the result of increased sexual mixing among GBM using PrEP and GBM with HIV. However, a renewed focus on HCV testing among GBM using PrEP is also likely to play a role given that it was part of the protocol for PrEP implementation studies [17, 18]. Specific to GBM prescribed PrEP, from 2016 to 2019 overall incidence was 0.29/100 PY with incidence peaking in 2017 at 0.44/100 PY. Encouragingly this declined to 0.08 cases/100 PY by 2019, which aligns with what was reported among HIV-negative GBM in Australia before HIV PrEP and HCV DAA treatment were available [25]. Our findings align with those from a recent Australian study limited to 4 sites; among 2058 GBM, HCV incidence was 0.38/100 PY [9]. These findings suggest that universal, unrestricted HCV treatment among GBM with HIV may also have a treatment-as-prevention benefit for GBM more broadly. Our findings, however, contrast with those in Europe. HCV incidence among 350 GBM using PrEP in the Netherlands has been reported to be 1.27/100 PY [15], and analysis of HCV incidence from the Pre-exposure Option for Reducing HIV in the UK (PROUD) study in England reported an overall incidence

of 1.9/100 PY among 490 GBM [22]. It is likely that HCV among GBM using PrEP is concentrated among a subgroup of GBM who engage in a range of sexual behaviors, including drug use before and/or during sex [9, 15], and these earlier, smaller studies are more representative of these groups than our larger population-level study.

This disparity in findings between Australian and European settings needs to also be interpreted accounting for the broader context of both HCV DAA treatment and PrEP availability. As noted previously, HCV treatment was funded in Australia from March 2016 with no treatment restrictions, including for reinfection. Large-scale PrEP implementation studies enrolling approximately 3700 [18] and 3800 [17] mainly GBM also commenced in mid-2016. The PROUD study from England enrolled people from late 2012 to early 2014; the study from the Netherlands enrolled people from mid-2015 to mid-2016. HCV DAA treatment was not broadly available at the time of the English study and treatment for HCV reinfection was not government-funded in England until late 2019 [13]. HCV DAA treatment was funded nationally in the Netherlands from 2015 and while high treatment uptake was reported among GBM with HIV, this predominately occurred in the first quarter of 2016 [26]. This potentially provided a time period where there may have been increased sexual mixing among GBM using PrEP and GBM with HIV who were yet to be treated for HCV. This is shown in phylogenetic analyses with high overlap of HCV among both GBM with HIV and HIV-negative GBM using PrEP [15].

Our analyses have some limitations that need to be considered. First, although these analyses indicate that among people who are retesting the time between tests is often within 12 months, not all GBM with HIV tested annually as recommended, which may limit the generalizability of our findings to the broader population of GBM with HIV. Second, a considerable number of HIV-negative GBM only had 1 test recorded including 35% of GBM prescribed PrEP; therefore, our findings may not be representative of all GBM using PrEP. Third, although we have data for many people who were prescribed PrEP, we cannot make confident assumptions that all HIV-negative GBM without these data were not using PrEP, thus limiting our ability to directly compare HCV incidence among HIV-negative GBM using and not using PrEP. Finally, while this is the largest and most representative study of HCV incidence among GBM in Australia undertaken to date, most data are from New South Wales and Victoria. In addition, most sites are in urban areas, with the remainder being in large regional areas. Although this is largely representative of the geographic distribution of GBM in Australia [27], further work may be justified to explore geographic differences in HCV awareness, testing, and incidence among GBM.

CONCLUSIONS

HCV incidence among GBM living with HIV has declined significantly in Australia following the introduction of DAA treatment. Despite concerns in other countries, incidence among HIV-negative GBM has declined since renewed peaks following large real-world PrEP implementation studies. These data are indicative of Australia being on track to achieve HCV elimination among GBM before 2030.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: B. L. H., R. S.-D., M. S., M. E. H., J. S. D. Methodology: B. L. H., R. S.-D., D. K. v. S., M. T., A. L. W. Data analysis: B. L. H. Data interpretation: B. L. H., R. S.-D., M. E. H., J. S. D. Data collection: C. K. F., N. R., M. B. Data curation: M. T., J. A., C. E.- H. Funding acquisition: B. D., R. G., M. S., M. E. H. Writing of the original draft: B. L. H. Review and editing of the manuscript: All authors.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Appendix D Protocol papers for the ACCESS surveillance system

Appendix D1. The ACCESS Study protocol

Citation

Callander D, Moreira C, El-Hayek C, Asselin J, van Gemert C, Watchirs Smith L, et al. Monitoring the Control of Sexually Transmissible Infections and Blood-Borne Viruses: Protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). JMIR Res Protoc. 2018;7(11):e11028.

Protocol

Monitoring the Control of Sexually Transmissible Infections and Blood-Borne Viruses: Protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS)

Denton Callander[1*], PhD; Clarissa Moreira[2*], MSc; Carol El-Hayek[2,3], MSc; Jason Asselin[2], BSc (Hons), GradDipHlthPrm; Caroline van Gemert[2,3], PhD; Lucy Watchirs Smith[1], BA, MPH; Long Nguyen[2], BCom, GradCertSc; Wayne Dimech[4], BAppSci, MBA; Douglas IR Boyle[5], PhD; Basil Donovan[1,6], MD; Mark Stoové[2,3], PhD; Margaret Hellard[2,3*], MD, PhD; Rebecca Guy[1*], PhD

[1]Kirby Institute, University of New South Wales Sydney, Sydney, Australia

[2]Burnet Institute, Melbourne, Australia

[3]School of Public Health and Preventative Medicine, Monash University, Melbourne, Australia

[4]National Reference Laboratory, Melbourne, Australia

[5]Research Information Technology Unit, Health and Biomedical Information Centre, Department of General Practice, University of Melbourne, Melbourne, Australia

[6]Sydney Sexual Health Centre, Sydney Hospital, Sydney, Australia

[*]these authors contributed equally

Corresponding Author:
Denton Callander, PhD
Kirby Institute
University of New South Wales Sydney
Wallace Wurth Building
Sydney, 2052
Australia
Phone: 61 293859958
Email: d.callander@unsw.edu.au

Abstract

Background: New biomedical prevention interventions make the control or elimination of some blood-borne viruses (BBVs) and sexually transmissible infections (STIs) increasingly feasible. In response, the World Health Organization and governments around the world have established elimination targets and associated timelines. To monitor progress toward such targets, enhanced systems of data collection are required. This paper describes the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS).

Objective: This study aims to establish a national surveillance network designed to monitor public health outcomes and evaluate the impact of strategies aimed at controlling BBVs and STIs.

Methods: ACCESS is a sentinel surveillance system comprising health services (sexual health clinics, general practice clinics, drug and alcohol services, community-led testing services, and hospital outpatient clinics) and pathology laboratories in each of Australia's 8 states and territories. Scoping was undertaken in each jurisdiction to identify sites that provide a significant volume of testing or management of BBVs or STIs or to see populations with particular risks for these infections ("priority populations"). Nationally, we identified 115 health services and 24 pathology laboratories as relevant to BBVs or STIs; purposive sampling was undertaken. As of March 2018, we had recruited 92.0% (104/113) of health services and 71% (17/24) of laboratories among those identified as relevant to ACCESS. ACCESS is based on the regular and automated extraction of deidentified patient data using specialized software called GRHANITE, which creates an anonymous unique identifier from patient details. This identifier allows anonymous linkage between and within participating sites, creating a national cohort to facilitate epidemiological monitoring and the evaluation of clinical and public health interventions.

Results: Between 2009 and 2017, 1,171,658 individual patients attended a health service participating in ACCESS network comprising 7,992,241 consultations. Regarding those with unique BBV and STI-related health needs, ACCESS captured data on 366,441 young heterosexuals, 96,985 gay and bisexual men, and 21,598 people living with HIV.

Conclusions: ACCESS is a unique system with the ability to track efforts to control STIs and BBVs—including through the calculation of powerful epidemiological indicators—by identifying response gaps and facilitating the evaluation of programs and interventions. By anonymously linking patients between and within services and over time, ACCESS has exciting potential as a research and evaluation platform. Establishing a national health surveillance system requires close partnerships across the research, government, community, health, and technology sectors.

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KEYWORDS

Australia; blood-borne viruses; public health; sentinel surveillance; sexually transmissible infections

Introduction

Globally, sexually transmissible infections (STIs) and blood-borne viruses (BBVs) are associated with significant morbidity, mortality, health costs, and social stigma. Indeed, these infections represent a major public health burden. There are, for example, nearly 37 million people currently infected with HIV and >1 million associated deaths per year [1], while an estimated 70 million people live with hepatitis C, from which nearly half a million die each year [2]. Regarding hepatitis B, >250 million people live with this infection, which causes >800,000 deaths annually [3,4]. Around the world, there are >350 million new cases of curable STIs every year—chlamydia, gonorrhea, syphilis, and trichomoniasis [5]—and human papillomavirus (HPV) is responsible for nearly all cases of cervical cancer, the fourth most common malignancy worldwide [6].

In Australia, the control and elimination of some BBVs and STIs are increasingly feasible through combinations of new and existing strategies of prevention, treatment, and management. For HIV, elimination is a tantalizing possibility through regular testing in combination with pre-exposure prophylaxis among uninfected individuals and antiretroviral treatment among those living with the virus [7-9]. Achieving something as lofty as HIV elimination will, naturally, be a major challenge [10] and certainly one that requires close monitoring of biomedical prevention coverage and impact to guide the refinement of implementation strategies [11]. Similarly, curative therapy with direct-acting antivirals for hepatitis C has been made available to all infected people in Australia, representing a major advance for both individual and public health [12] but one that also requires monitoring, evaluation, and adaptation if there is any hope of reducing infection rates [13].

For some other infections—notably hepatitis B and HPV—vaccinations have proved highly effective in reducing population incidence and prevalence. There remain, however, cohorts of people not included in vaccination schedules because of their age or who have migrated to Australia from countries where prevalence is high and vaccination programs limited. For these infections, ongoing clinical screening is required to identify unvaccinated individuals, and in the case of HPV, intervene early as a precursor to cancer. In addition, for curative STIs, frequent testing and timely treatment are fundamental components of interrupting incubation and preventing unintended onward transmission [14]. For STIs and BBVs, it is clear that ongoing efforts are required to track progress against targets, monitor population health, assess the impact of interventions, and plan into the future.

Surveillance and monitoring of BBVs and STIs are often complicated by the fact that they disproportionately affect populations defined by sexual identity, sex practice, drug use, and ethnicity [11,13,14]. Thus, their management requires a holistic and comprehensive approach to care, which in Australia and many other countries, involves sexual health clinics, targeted general practice clinics, drug and alcohol services, and hospitals. Health services like these play a vital role not only in diagnosing and managing BBVs and STIs but also in their prevention by encouraging uptake of diagnostic testing, treatment, and vaccines where available. Calculating the uptake of these initiatives, however, requires knowing the number of total attending patients—the denominator—and such information can only be sourced directly from health services. When linked between individuals' episodes of care, these data can also be used to calculate other powerful impact indicators such as incidence or the time between diagnosis and treatment.

Here, we describe ACCESS—the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance—a national system of sentinel surveillance that draws upon data from several different types of health services and pathology laboratories to inform and evaluate Australia's BBV and STI control efforts.

Methods

Overview and Aims

ACCESS is a system that routinely extracts and collates line-listed, deidentified data from health services and pathology laboratories across Australia. Through anonymous patient linkage between and within services and laboratories, ACCESS produces a retrospective and prospective cohort of patients attending participating sites. Established in 2008, ACCESS began as a sentinel system for chlamydia surveillance [15] that was expanded in 2013 to include BBVs and other STIs in some Australian jurisdictions. Through funding from the Australian Department of Health in 2016, ACCESS expanded further to encompass a greater number and a more diverse selection of sites relevant to these infections in all 8 Australian states and territories.

The overall aim of ACCESS is to support the Australian response to STIs and BBVs by monitoring the testing, diagnosis, and management of these infections. In addition, ACCESS aims to operate as an evaluative platform to measure the impact and

outcomes of relevant programs and interventions. This includes attention to Australian priority populations (gay and bisexual men and other men who have sex with men, people who use drugs, Aboriginal and Torres Strait Islander people, young heterosexuals, sex workers, and people from culturally and linguistically diverse backgrounds) and to "cascades of care" (eg, HIV) [16].

Infections

ACCESS focuses on specific infections, including HIV, hepatitis B, hepatitis C, HPV, chlamydia, gonorrhea, syphilis, and trichomoniasis. The design of ACCESS, however, allows for the addition of other infections or conditions as required into the future. Already, for example, steps have been taken to begin collecting data on *Mycoplasma genitalium*, a newly identified STI.

Sites and Recruitment

The ACCESS network seeks to include health services and pathology labs that best represent the prevention and management of BBVs and STIs nationally and in each state and territory. To be eligible, health services are required to use an electronic patient management system (ie, not based solely on paper files) and be willing to participate for a minimum of 2 years. Of note, we have encountered no health services still exclusively using paper files. In addition, health services have to see at least 50 individuals per year categorized as ≥1 of Australia's priority populations for BBVs and STIs or they have to represent a service designed specifically for the care and management of these infections (eg, sexual health clinics and HIV testing sites). Given differences in the overall population size between each state and territory—the largest contains >7.5 million people, while the smallest has just >200,000—we are flexible in our assessment of caseloads to allow for recruitment in smaller jurisdictions. For example, while a caseload of 50 patients with HIV might be considered small or medium in New South Wales, it would be considered large, if not the largest, in Tasmania.

Within these parameters, per jurisdiction, we have sought to include a minimum of 2 sites with large caseloads of people living with or at risk of HIV, 2 with large caseloads of people living with or at risk of hepatitis and 2 with a large amount of STI-related testing and care. In addition, we sought to recruit 2 pathology laboratories per jurisdiction (one public and one private) that conducted testing for BBVs and STIs. While in larger states (New South Wales, Queensland, and Victoria), it was necessary to exceed these targets and recruit larger number of sites, the opposite was true in some smaller jurisdictions. In the Australian Capital Territory, for example, the vast majority of BBV-related and STI-related tests were conducted by a single pathology laboratory, making it unnecessary to recruit a second site of this kind. Details like this one highlight the need and strength for a tailored approach to recruitment, given the significant differences between each state and territory.

As noted, ACCESS has been in operation since 2008 with recruitment taking place over many years and in different iterations. Most recently, recruitment was undertaken from 2016 through 2018 to expand the network's coverage in jurisdictions beyond New South Wales and Victoria. Over time, however, methods of identifying and recruiting sites have remained consistent; to gain jurisdictionally specific information on potential sites, we consult with local stakeholders in government, health, community organizations, and research institutes. We ask them to nominate sites that either conduct a large amount of testing for or care of BBVs and STIs, or sites that provide care for concentrations of Australia's priority populations. Where available, we also review public health data on locations of BBV and STI diagnoses (by general geographic areas) to identify health services located nearby, and we review publicly available lists of doctors licensed to prescribe treatments for HIV and hepatitis C.

When this process was undertaken in 2016 and 2017, we identified 115 health services and 24 pathology laboratories across Australia that met our eligibility criteria. Three-quarters of these sites were already involved with ACCESS, noting that since its inception in 2008, no site has ever withdrawn participation in the network. Of the remaining "new" sites identified through our scoping process, we undertook purposive sampling that deferred to sites with large caseloads and those that introduced diversity either through their location, patients' characteristics, or service model.

Table 1. Health services and pathology laboratories participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance network as of March 2018, by site type and jurisdiction.

Site type	Total	Jurisdiction							
		Australian Capital Territory	New South Wales	Northern Territory	Queensland	South Australia	Tasmania	Victoria	Western Australia
Sexual health clinic	58	1	38	3	8	1	3	2	2
General practice clinic	29	1	10	0	2	1	0	13	2
Hospital outpatient clinic	7	0	2	0	1	0	1	2	1
Community-led services	9	0	4	0	2	1	0	1	1
Drug and alcohol service	1	0	0	0	0	0	0	1	0
Private pathology laboratory	6	1	3	0	0	0	1	1	0
Public pathology laboratory	11	0	5	0	1	0	1	4	0

A total of 31 new sites were recruited to ACCESS, resulting in 92% (104/113) of health service identified nationally and 71% (17/24) of laboratories identified nationally participating in ACCESS. Participation is being negotiated with further 11 sites, 3 refused participation altogether, and 4 were not pursued because of small patient caseloads compared with other similar services in their jurisdiction. Table 1 provides an overview of sites contributing data to ACCESS as of March 2018, noting that these numbers will continue to change over time. Figure 1 depicts participating sites on a map of Australia.

Figure 1. Health services participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance network as of March 2018.

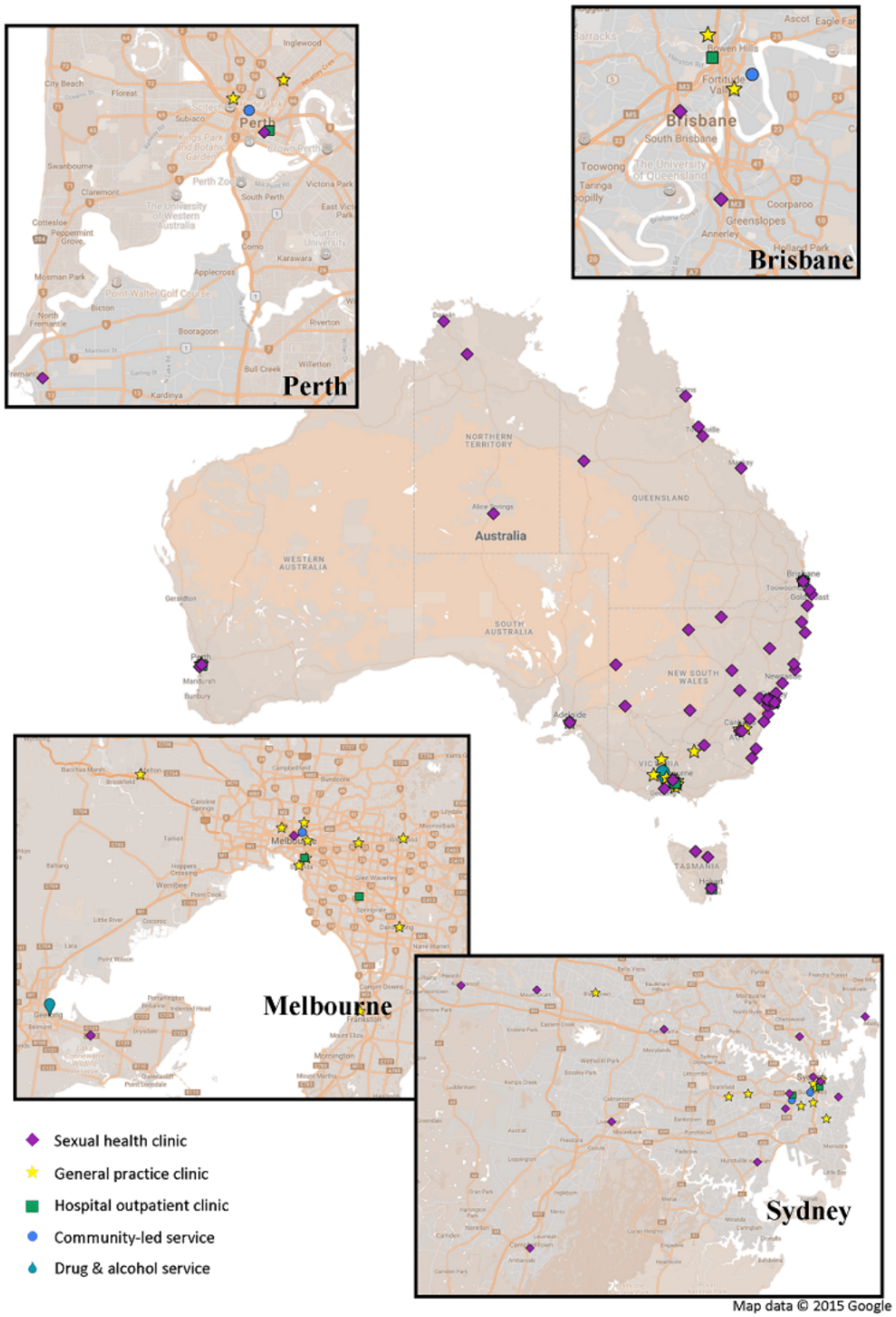

Table 2. Variables extracted (where available) from participating health services via Australian Collaboration for Coordinated Enhanced Sentinel Surveillance.

Domain	Variables
Patient information	• Age • Gender • Home postcode • Indigenous status • Country of birth • Preferred Language • Year of arrival in Australia • Sexual behavior
Consultation details	• Date • Type • Reason for attendance • Clinical diagnosis
Laboratory testing	• Tests requested • Results • Specimen type • Anatomical site
Treatment	• Drug name • Start or stop dates • Dose • Frequency • Route
Vaccination details	• Vaccination history • Vaccines administered • Type • Dose number
Behavioral: sexual practices	• Sexual partner gender(s) • Sexual partner numbers • Condom use • Sex work • Sex work location
Behavioral: drug use	• Use of injecting drugs • Shared injecting equipment • Drugs injected

Data Extraction and Management

Data are extracted from participating sites using software known as GRHANITE, which was designed specifically for the secure collection of deidentified health data. GRHANITE works by being installed on a local system at each participating site. Technical and financial costs associated with calibrating and installing GRHANITE are borne by ACCESS, making it a cost-neutral enterprise for sites. On an at least monthly basis, querying the site's database or accessing files already extracted from the database is performed. The nature of these queries is guided by schemas customized to meet the requirements and structures of each database. Because of their flexibility, GRHANITE's schemas can be deployed for use with almost any database structure to work across diverse systems ranging from established commercial platforms to unique systems built-for-purpose by individual services. Details of GRHANITE have been published previously [17,18]. Table 2 lists variables extracted for ACCESS, where available. Some sites routinely collect behavioral information from patients, and where available, these data are also extracted.

As part of the extraction process, GRHANITE removes any data that could potentially identify a patient. While still working within a participating site, GRHANITE generates probabilistic record linkage keys (or signatures) called "hashes." These signatures are derived from, but do not contain, personal information, which means that probabilistic linkage can be safely conducted between and within participating ACCESS sites. This process makes it possible to monitor patient movement between services in a way that is anonymous and ensures that no identifiable patient details are ever transmitted beyond participating sites. Following extraction, GRHANITE encrypts the data and transmits it to a central, secure server.

Data are extracted for all patients and consultations, but pathology and treatment data are only extracted when there is evidence of testing or treatment for an STI or BBV. This approach helps limit the size of the ACCESS database by focusing on the most relevant pathology testing. In general

practice clinics, notably, the majority of testing would be unrelated to these infections, which would place an unnecessarily high technical burden on systems to fully extract all data. Thus, filters are used and regularly reviewed to ensure accuracy and completeness.

ACCESS data are processed using code that organizes pathology testing, treatment, and patient details into standardized formats. This step also involves unifying the structure of data received from different systems. Notably, because many patient management systems store pathology results as free text, computational parsing is used to identify test names, dates, and results to organize that information into consistent categories. This code is regularly reviewed for accuracy and adapted over time, as required. A similar process is used to identify patients that form part of Australia's priority populations, which involves drawing upon numerous pieces of information (eg, demographics, behavioral details, and pathology tests) to properly categorize patient files. For example, previous research has found that sexual orientation is not well recorded among men attending Australian general practice clinics [19]. To address this issue, we use history of rectal swabs for STI testing as a proximal marker indicating anal sex, which has previously been found to be effective for identifying gay and bisexual men and other men who have sex with men [20]. Definitions for organizing pathology tests and categorizing patients into priority populations were constructed in close consultation with relevant clinical and laboratory experts, as well as community representatives.

Data Quality

The quality of ACCESS data is ensured through a number of processes. Data extracted from new services are validated through a consultative process with site investigators, which includes sharing preliminary outputs to gauge the degree to which they converge (or diverge) from clinical experience. This feedback is then used to improve data processing and address gaps or errors in the extraction process. For example, to ensure data completeness, we might ask clinic staff to estimate the number of HIV-positive patients they see each year or the number of chlamydia tests they conduct in an average week, which can then be compared against extracted and processed data. This process has previously identified components missing from extracts, including pathology test names, drugs types, and demographic variables, and then used to adapt and correct extraction processes.

Beyond completeness, we also carefully attend to the accuracy of ACCESS data. This involves what is extracted as well as how we process extracted data, which is to say how variables are organized into distinct and consistent categories. Wherever possible, ACCESS data are triangulated with other sources to improve accuracy. This process includes comparing extracted health service data to that from pathology laboratories; because some participating laboratories serve participating health services, we can assess the degree to which the number of tests and results align. Comparing data in this way has allowed us to refine pathology filters and our processes for organizing results. In the past, ACCESS data have also been assessed for accuracy against passive surveillance information. For example, we previously requested information on HIV and STI notifications among sexual health clinic attendees in New South Wales to calibrate our systems for processing diagnoses in these clinics [21].

Routine data quality checks are also conducted on a quarterly basis, which focus on assessing if there are significant changes in test frequencies over time to generate alerts for significant deviations. For example, if the number of tests extracted for chlamydia doubled from one period to the next, this would be used as a point of investigation. Investigations include reviewing data processing, checking raw data, and consulting with site investigators. This kind of quality assurance is done on the dataset as a whole, by health service type and to the level of individual sites.

Dissemination and Use

ACCESS data are used for diverse purposes. Data extracted via ACCESS can be used to generate a number of powerful indicators relevant to BBVs and STIs, most commonly those related to diagnostic testing (test uptake, test frequency, test comprehensiveness, and retesting), treatment (treatment uptake and treatment success), infections (test yield, test positivity, incidence, and reinfection), and vaccinations (coverage of vaccine-acquired immunity). Indeed, indicators like these form part of ACCESS's contributions to the national surveillance of BBVs and STIs [22] and their surveillance by individual states and territories, including as stand-alone reports or as part of existing reporting mechanisms [23]. In reports such as these, ACCESS has been used to improve estimates of treatment uptake and success, which supports more accurate "cascades of care" for HIV and other infections. The automated nature of data extraction and processing facilitates timely production of reports, which in some cases are published as early as 4 weeks from the end of a reporting period. Furthermore, site-specific ACCESS data are routinely reported back to participating sites, which can include analyses of testing uptake, test positivity, and diagnosis frequency.

In addition to routine surveillance reporting, ACCESS data are used for a number of other related projects. Notably, ACCESS data have been used in stand-alone analyses of population health, for example, in studies of HIV and STIs among sex workers in Australia [24,25] and an analysis of hepatitis C testing and diagnoses among people living with HIV [26]. Moreover, ACCESS data have been used to assess the impact of syphilis testing interventions [27]. Beyond this work, ACCESS is being used increasingly to support other forms of research and evaluation. In some projects, ACCESS provides line-listed and deidentified datasets, which are and have been used to conduct a large-scale study of HIV treatment-as-prevention [28], evaluate pre-exposure prophylaxis implementation trials [29,30], and study Victoria's hepatitis C elimination response [31]. In other cases, as in the evaluation of HIV control in New South Wales [32], ACCESS has routinely provided specifically designed indicators (eg, HIV testing uptake and rates of viral suppression) to monitor and evaluate various aspects of BBV prevention and management. In many of these examples, ACCESS fills an important role by providing the kinds of data and indicators that are required for research of this kind to be conducted. Through

these projects, ACCESS demonstrates its capacity to support diverse research on STIs and BBVs, which extends beyond the realms of surveillance and monitoring.

Ethics and Governance

Ethical approval was granted by the lead human research ethics committee of Alfred Hospital in Melbourne (248/17), University of Tasmania (H0010220), and the Menzies School of Health Research (08/047). All ethics committees waived the need for consent to be collected from individual patients. Furthermore, ethical reviews were provided by organizations representing key populations, notably gay and bisexual men, people living with HIV, sex workers, and Aboriginal and Torres Strait Islander people.

To protect the identities of individual patients, access to the line-listed database is restricted to a small and select group of researchers. Where data are shared with others, potentially identifying details (eg, patient postcode) are replaced with broad categories (eg, urban/nonurban), which is a similar approach taken in any reporting of ACCESS data. Furthermore, analyses that produce cell counts of <5 individuals are suppressed.

An advisory committee was established comprising representatives from government organizations, community groups, health services and laboratories, and research institutes. This committee provides advice on the project's development and conduct; promotes its aims and objectives; and contributes to analysis, interpretation, and dissemination.

Results

Although some sites were able to provide electronic data going back as far as the 1980s, data quality and completeness tends to diminish further back in time when health services were less familiar with technologies of electronic health that dominate today. To examine a more recent period, we note that ACCESS captured data from a total of 1,171,658 individual patients who attended a participating health service at least once in the recent past between 1 January 2009 and 31 December 2017. These patients attended for a total of 7,992,241 clinical consultations or an average of 0.8 consultations per patient per year. Patient gender was evenly represented between men (597,545/1,171,658, 51%) and women (574,112/1,171,658, 49%), and records were extracted from a total of 1116 transgender patients (380/1116, 34% transgender men; 356/1116, 32% transgender women, and 380/1116, 34% unspecified gender).

Specific to Australia's priority populations, from 2009 to 2017, ACCESS captured data of 366,441 young heterosexuals aged 16-29 years. In addition, the network includes data from 96,985 gay and bisexual men and other men who have sex with men. Data were also captured from 21,598 people living with HIV, drawing upon recorded HIV diagnoses, confirmed HIV pathology results, viral load testing, and clinical attendance for "HIV management." In total, 22,089 Aboriginal and Torres Strait Islander patients attended an ACCESS health service during this period, noting that this variable was incomplete for 74% (576,219/778,674) of patients attending general practice clinics and 50% (196,490/392,984) of patients attending other services. Even though Australian guidelines recommend collecting indigenous status from all patients [33], it seems that this indicator is still not routinely collected.

As noted, sexual health clinics in Australia routinely collect enhanced behavioral data on factors associated with BBVs and STIs. This information is used by ACCESS to further identify members of priority populations. From 2009 to 2017, for example, it is possible to identify 12,111 people who attended an ACCESS site and reported injecting drug use at least once in the 12 months prior to consultation, as it is possible to identify 21,205 men and women who reported sex work in the previous 12 months. As noted, identifying members of these priority populations is not possible in settings other than sexual health and community-lead clinics, which is attributed to a lack of standardized methods for collecting and recording behavioral data. Work is ongoing to support the implementation of behavioral surveys in some general practice clinics and to develop algorithms for recognizing these populations through other means, such as through certain types and patterns of pathology tests and testing.

Discussion

In this paper, we described the methods used to establish a national sentinel surveillance system for BBVs and STIs. ACCESS seeks to complement the existing passive surveillance by tracking the uptake and impact of strategies aimed at controlling these infections. The system is highly flexible and can be adapted for use in a multitude of health contexts and evolve over time to address emerging surveillance needs. In addition, it is a project deeply rooted in collaboration, involving government, researchers, community, and clinicians from every corner of Australia. ACCESS is a unique national resource and a model with potential relevance for other countries.

A key strength of ACCESS is its ability to anonymously link patients between services and over time. In some ways, this feature makes ACCESS akin to a national retrospective and prospective cohort, which has exciting possibilities in a number of areas. ACCESS allows scrutiny of the ways that individuals move through different pathways of care, including the overall trajectory and the time it takes to move from diagnosis to viral suppression or cure. Furthermore, this linkage facilitates the calculation of powerful epidemiological markers, like incidence and test frequency and also allows for examinations of compliance with clinical guidelines associated with testing (eg, chlamydia testing among young people presenting to clinics or following past positive tests). ACCESS also makes possible detailed, individual, and large-scale evaluations of public health policy, interventions, and other strategies aimed at controlling BBVs and STIs.

Another key strength of ACCESS relates to its coverage. Specifically, the network of health services in every state and territory enables comparison between not only Australian jurisdictions but also different types of service models, such as community-based testing services, sexual health clinics, and hospitals. These comparisons are important for identifying gaps, comparing the utility of different ways for providing care and nuanced information on how BBVs and STIs are diagnosed and managed. Furthermore, by attending to the geographic

concentrations of Australia's priority populations and working with community groups and health experts, ACCESS has collated some of the largest samples of "high-risk" priority populations seen anywhere in the world.

The automated nature of ACCESS significantly reduces the resources and time required to report surveillance data, benefits that are already being realized through quarterly reporting to state health departments. Although initial enrollment of new sites to ACCESS requires some time, maintenance is minimal once established, which helps ensure the system's ongoing sustainability. Moreover, participating sites realize benefits through the publication of scientific research and the ability to more readily access their own data, including through tailored site reports that can include comparisons with aggregated data from similar sites. These strengths are reflected in the observation that in a decade of operation, no site has yet chosen to withdraw from ACCESS.

There are some limitations of the system that warrant consideration. As a surveillance network, ACCESS does not capture all new diagnoses and is, therefore, not a replacement for passive surveillance. Although we have described the process for anonymously linking patients between ACCESS sites, gaps arise when patients attend health services outside of the network. These gaps can be partly overcome through data from participating laboratories but they are inherent in the network's "sentinel" nature. Another limitation is ACCESS's inability to collect all clinical information, in particular, the free text detail contained within patient notes. Patient notes contain a wealth of details that would likely be relevant to BBVs and STIs but are not accessed by this system because they can potentially contain identifying information. Options for identifying and extracting relevant details through the use of text-recognition software are currently being assessed as a potential means of using this information confidentially. Finally, ACCESS is entirely reliant on routinely recorded health information; the quality and completeness of these details can vary between and within sites. This limitation, however, can be overcome in some cases with ACCESS's capacity for anonymous patient linkage by pooling information from multiple services and laboratories to construct a more complete picture.

ACCESS represents a new way of conducting sentinel surveillance, which adds value for government, research, clinical, and community partners. With data extraction under way across the country, over the coming years, the project will focus on new ways of providing regular feedback to health service and laboratory sites as a way to improve service delivery, sustain interest, and capitalize on the network's potential. In the future, it is imagined that ACCESS will continue to develop as a readily accessible resource for diverse stakeholders that seek to make use of it as a unique, national database.

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Conflicts of Interest

None declared.

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Abbreviations

ACCESS: Australian Collaboration for Coordinated Enhanced Sentinel Surveillance
BBV: blood-borne virus
HPV: human papillomavirus
STI: sexually transmissible infection

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Appendix D2. ACCESS linkage algorithm protocol and evaluation

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Original Paper

Privacy-Preserving Record Linkage of Deidentified Records Within a Public Health Surveillance System: Evaluation Study

Long Nguyen[1], MCom; Mark Stoové[1,2], PhD; Douglas Boyle[3], PhD; Denton Callander[4,5], PhD; Hamish McManus[4], PhD; Jason Asselin[1], MEpi; Rebecca Guy[4], PhD; Basil Donovan[4,6], MD; Margaret Hellard[1,2,7,8], MD, PhD; Carol El-Hayek[1,2], MEpi

[1]Burnet Institute, Melbourne, Australia

[2]School of Population Health and Preventive Medicine, Monash University, Melbourne, Australia

[3]Department of General Practice, HaBIC Research Technology Unit, Melbourne Medical School, University of Melbourne, Melbourne, Australia

[4]Kirby Institute, University of New South Wales, Sydney, Australia

[5]Mailman School of Public Health, Columbia University, New York, NY, United States

[6]Sydney Sexual Health Centre, Sydney, Australia

[7]Department of Infectious Diseases, The Alfred Hospital, Melbourne, Australia

[8]Doherty Institute and School of Population and Global Health, University of Melbourne, Melbourne, Australia

Corresponding Author:
Long Nguyen, MCom
Burnet Institute
85 Commercial Rd
Melbourne, 3004
Australia
Phone: 61 468689589
Email: long.nguyen@burnet.edu.au

Abstract

Background: The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) was established to monitor national testing and test outcomes for blood-borne viruses (BBVs) and sexually transmissible infections (STIs) in key populations. ACCESS extracts deidentified data from sentinel health services that include general practice, sexual health, and infectious disease clinics, as well as public and private laboratories that conduct a large volume of BBV/STI testing. An important attribute of ACCESS is the ability to accurately link individual-level records within and between the participating sites, as this enables the system to produce reliable epidemiological measures.

Objective: The aim of this study was to evaluate the use of GRHANITE software in ACCESS to extract and link deidentified data from participating clinics and laboratories. GRHANITE generates irreversible hashed linkage keys based on patient-identifying data captured in the patient electronic medical records (EMRs) at the site. The algorithms to produce the data linkage keys use probabilistic linkage principles to account for variability and completeness of the underlying patient identifiers, producing up to four linkage key types per EMR. Errors in the linkage process can arise from imperfect or missing identifiers, impacting the system's integrity. Therefore, it is important to evaluate the quality of the linkages created and evaluate the outcome of the linkage for ongoing public health surveillance.

Methods: Although ACCESS data are deidentified, we created two gold-standard datasets where the true match status could be confirmed in order to compare against record linkage results arising from different approaches of the GRHANITE Linkage Tool. We reported sensitivity, specificity, and positive and negative predictive values where possible and estimated specificity by comparing a history of HIV and hepatitis C antibody results for linked EMRs.

Results: Sensitivity ranged from 96% to 100%, and specificity was 100% when applying the GRHANITE Linkage Tool to a small gold-standard dataset of 3700 clinical medical records. Medical records in this dataset contained a very high level of data completeness by having the name, date of birth, post code, and Medicare number available for use in record linkage. In a larger gold-standard dataset containing 86,538 medical records across clinics and pathology services, with a lower level of data completeness, sensitivity ranged from 94% to 95% and estimated specificity ranged from 91% to 99% in 4 of the 6 different record linkage approaches.

Conclusions: This study's findings suggest that the GRHANITE Linkage Tool can be used to link deidentified patient records accurately and can be confidently used for public health surveillance in systems such as ACCESS.

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KEYWORDS

medical record linkage; public health surveillance; sentinel surveillance; sensitivity and specificity; data linkage; confidentiality; evaluation studies as a topic

Introduction

Background

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) of blood-borne viruses (BBVs) and sexually transmissible infections (STIs) monitors diagnostic testing and other episodes of care for priority BBVs and STIs [1,2]. ACCESS extracts deidentified patient data from a network of laboratories and clinics, including those that manage high caseloads of patients from populations with heightened risk for BBVs and STIs, including gay, bisexual, and other men who have sex with men and people who inject drugs. The main objective of ACCESS is to measure and report key indicators such as disease incidence and prevalence (measured as proportion positive) to monitor and support Australia's efforts to reduce the transmission of morbidity and mortality caused by BBV and STI [3-5].

A key challenge for ACCESS (and similar sentinel surveillance systems) is that patient outcomes can be inaccurately measured if individuals attend multiple health services, leading to potential reporting bias. For example, markers of testing frequency, an important indicator for BBV/STI prevention and management [3-5], may be underestimated if individuals test at multiple services. Accurate linkage of individuals within and between services in ACCESS provides more accurate measures of (1) the key indicators relating to Australia's BBV and STI National Strategies and (2) the effect of interventions aimed at reducing the impact of BBVs and STIs.

The linkage of deidentified ACCESS records across sites relies on specialized health data extraction software GRHANITE, which is installed at participating clinics and laboratories. GRHANITE interfaces with patient databases, securely extracting line-listed consultation, demographic, BBV and STI clinical and pathology data [6]. Before data are transferred from ACCESS sites, GRHANITE creates a unique record ID to identify an electronic medical record (EMR) and uses patient-identifying information to generate irreversible hash-coded linkage keys associated with that record. The record ID and linkage keys, rather than the personal identifiers, are transferred with the patients' clinical and pathology data to a secure data bank, preserving patient privacy [7]. A link ID is then generated [8] when the same patient is linked across different EMRs by matching linkage keys using a companion software called the GRHANITE Linkage Tool [9].

Objectives

The GRHANITE Linkage Tool has been validated to perform large-scale population-level record linkage [10] to achieve similar sensitivity and specificity data linkage profiles as per traditional person-identifiable data linkage mechanisms [9]. Given that there is variation in the available person-identifiable data at clinical and laboratory sites in ACCESS, the focus of this paper is to assess the quality of linkage results by applying different approaches to using the GRHANITE Linkage Tool in ACCESS. To evaluate the GRHANITE Linkage Tool for ongoing public health surveillance, we measured the outcomes of record linkage using the tool against gold-standard linked datasets derived from ACCESS data.

Methods

Australian Collaboration for Coordinated Enhanced Sentinel Surveillance Data Extraction and Linkage via GRHANITE

Electronic Medical Records

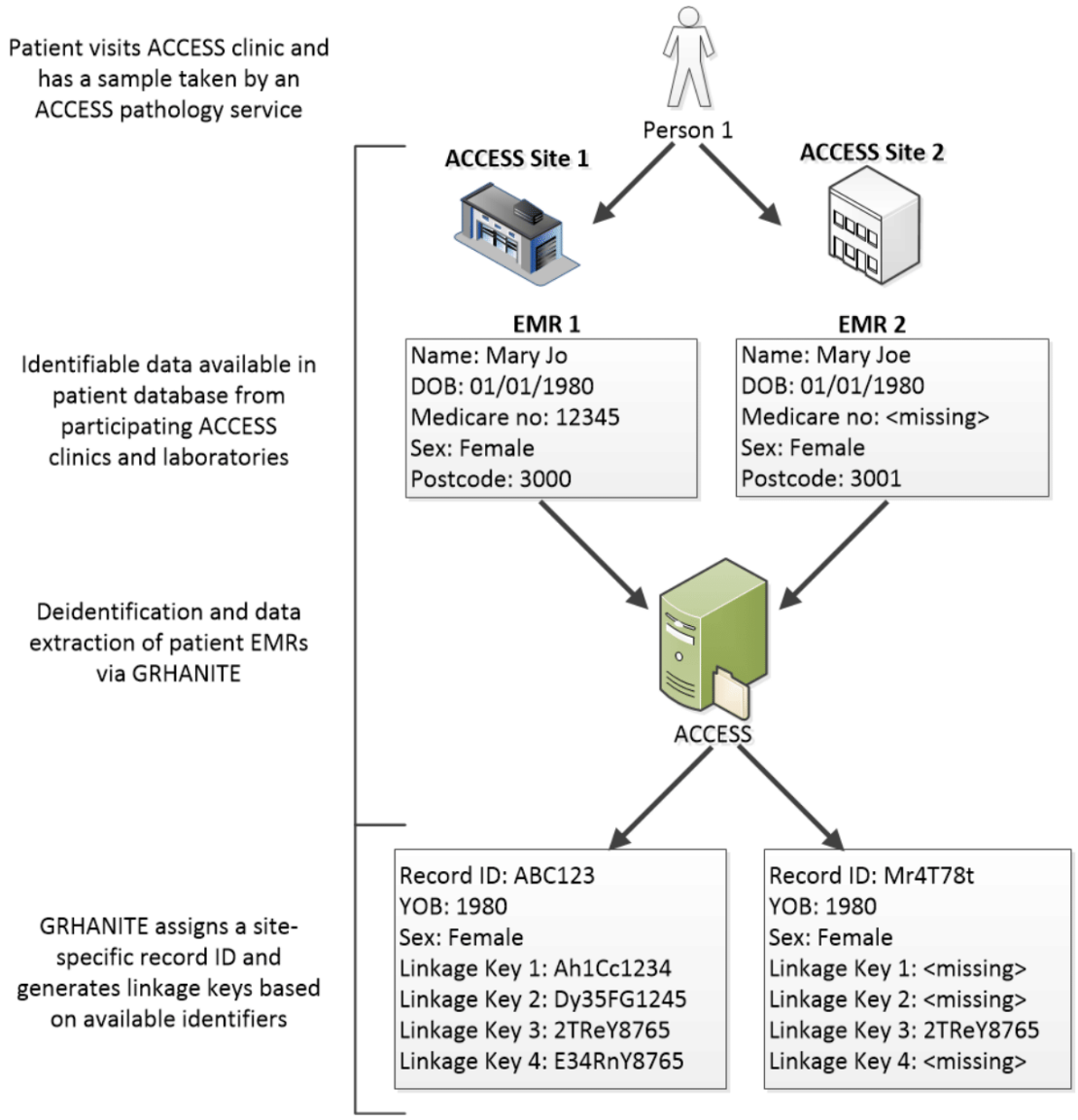
Typically, when a patient first attends a medical facility, an EMR is created in the facility's patient database, containing the patient's identifying information, including the name, date of birth, contact details, and Medicare number (an Australian government–issued health care card number used for Medicare billing). Most clinics will also have recorded other demographic information, such as preferred language, country of birth, and indigenous background in the EMR.

Every individual's EMR has a unique medical record number generated by the patient database, linking all of a patient's consultations, tests, and prescription records. Multiple EMRs may be created for one patient at the same facility if the patient's details change and are not updated, leading to the creation of a new EMR; if the patient uses an alias; or if the patient attends a clinic that allows anonymous or free testing.

Data Extraction in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance

Data were extracted from participating ACCESS clinical sites that included an EMR for every patient available in their databases at the time of extraction. GRHANITE generated a new unique record ID and up to four irreversible hash-coded linkage keys for each EMR. Personal identifying information (eg, name, date of birth, Medicare number) in the patient's EMR was passed through advanced encryption to generate both record ID and linkage keys [7]. The record ID and linkage keys were extracted by GRHANITE alongside the patient demographics, consultation, test request, pathology, and prescription information related to BBV and STI care, without the identifying information. Data extraction was similar for laboratories; however, only BBV and STI test records related to diagnosis and care and a limited set of demographic variables were available for extraction (Figure 1).

Figure 1. Data extraction in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance: using GRHANITE to deidentify electronic medical records and create linkage keys.



Record Linkage in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance

The data components used by GRHANITE to create the linkage keys include the following patient identifiers: 5 digits of the Medicare number, date of birth, sex, first name, last name, and residential postcode. However, not all EMRs have the same set of patient identifiers recorded in the same way. For example, a patient name may be recorded as *William* in one clinic with a full date of birth and *Bill* in another clinic with only a year of birth recorded. GRHANITE utilizes data preprocessing to remove unwanted characters and words and to resolve nicknames utilizing an Australian national nickname list. Phonetic encoding (double metaphone) is then employed, which permits fuzzy matching based on misspellings of the surname and forename. Transposition of day and month of birth is also supported. After preprocessing, identifiers are combined and then encrypted utilizing secret seeding keys and cryptographic hashing to generate the GRHANITE privacy-preserving cryptographic hashed linkage keys [7,9].

GRHANITE creates up to four linkage keys for each EMR, using combinations of identifying information that is recorded at each site (Textbox 1) [11]. For example, if the Medicare number was not recorded for a patient, then linkage keys that require 5 Medicare digits (Textbox 1: linkage key types 1, 2, and 4) could not be created, resulting in EMRs extracted via GRHANITE having only one linkage key (Textbox 1: linkage key 3 does not require the Medicare number; Figure 1).

Textbox 1. Types of linkage keys generated by GRHANITE.

Linkage key and components of base identifying information:

- Type 1: 5 Medicare digits; date of birth; and sex
- Type 2: 5 Medicare digits; postcode; first three characters of first name; and year of birth
- Type 3: Last name and first name (either order permitted) and fuzzy matching used; date of birth with day/month (transpositions permitted)
- Type 4: Last name and first name (either order permitted) and fuzzy matching used; 5 Medicare digits

Applying the GRHANITE Linkage Tool

There are three steps in the record linkage process in ACCESS when applying the linkage tool. The first step finds pairs of EMRs based on at least one linkage key matching and records the linkage key type/s used to match each record pair. The second step examines the strength of the link using other available data within the matched pair of records to accept or reject linked records as described in Table 1. The third step assigns an identifier (a link ID) to the accepted matched pairs to label all matched records as belonging to the same individual (Figure 2).

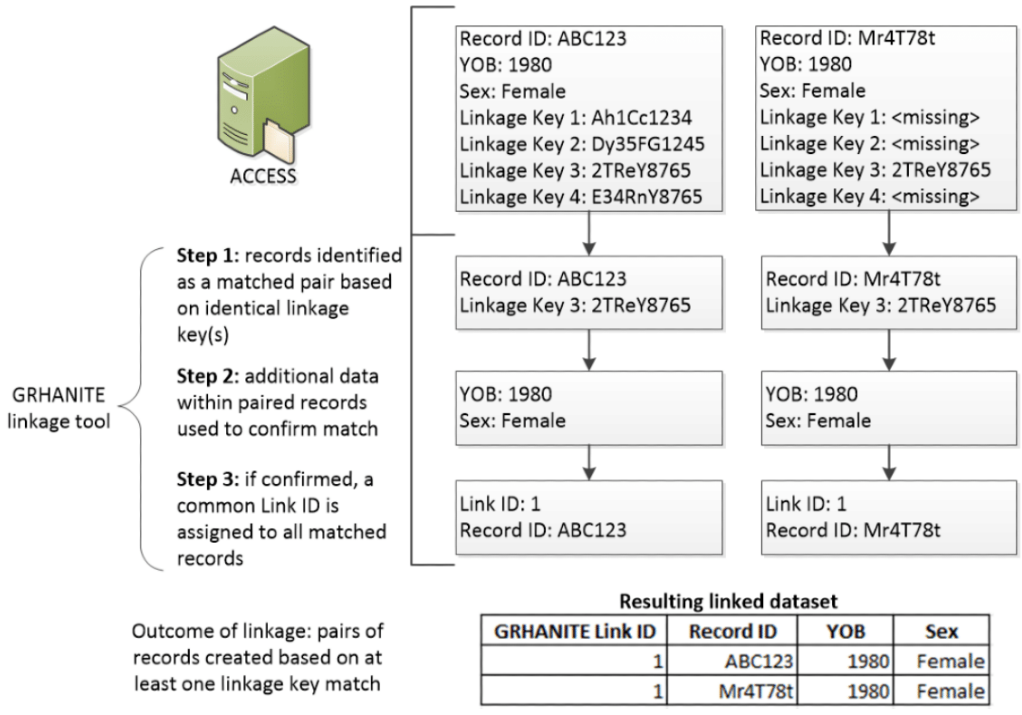
Table 1. GRHANITE Linkage Tool approaches to accepting matches.

Linkage approach	Description
Accept all	Accept all record links as determined by the linkage tool
Year of birth match	Accept only record links if year of birth matches
Sex match	Accept only record links if sex matches
Year of birth and sex match	Accept only record links if year of birth and sex match
Two or more linkage keys[a]	Accept record links only if matched on two or more linkage key types
Linkage key type 3 plus sex match[b]	Accept only record links that match on linkage key type 3 and match on sex

[a]Given that 3 out of the 4 linkage key types are generated using the Medicare number, this approach requires the Medicare number to be present in the EMR (Textbox 1).

[b]This approach only relies on linkage key type 3, which does not require the Medicare number to be present in the EMR.

Figure 2. Record linkage in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance: using the GRHANITE Linkage Tool to identify and accept matches.



Evaluating the Record Linkage

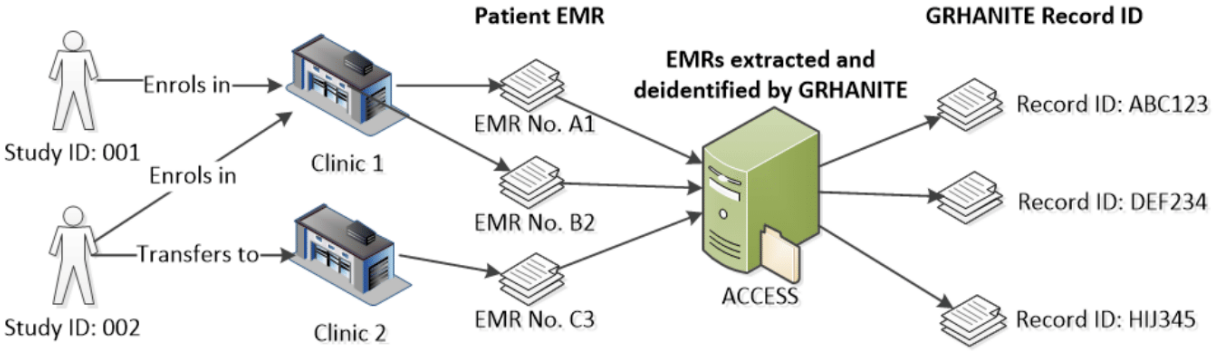
Creating the Gold-Standard Datasets

To evaluate the record linkage in ACCESS, we generated two gold-standard datasets, using a deterministic record linkage method, where the true match status could be identified [12]. To assess the outcomes of the six linkage approaches described in Table 1, using the GRHANITE Linkage Tool for matching the records in the gold-standard datasets, we measured the sensitivity, specificity, and positive and negative predictive values, where possible.

The PrEPX Gold-Standard Dataset

PrEPX is a population-level intervention study in Victoria in which HIV pre-exposure prophylaxis was made available to eligible individuals, and the study used ACCESS data to monitor participants' BBV and STI testing [13]. Eight clinical sites and one hospital clinic participating in ACCESS had PrEPX participants enrolled between July 2016 and March 2018. At enrollment, a PrEPX study ID was sequentially assigned and recorded alongside each participant's enrollment-clinic EMR number in a study database. Following enrollment in PrEPX, if a participant attended a different clinic within the network during the study period, the EMR number from the new clinic was also recorded in the study database. ACCESS had ethics approval to extract the EMR number from the participating clinics for the purpose of matching the records of participants who moved among clinics. To create the gold-standard dataset, EMRs were matched on clinic EMR number, clinic name, and clinic visit date. The gold standard included one record per PrEPX participant who attended only one clinic during the study period and multiple records per PrEPX participant who attended multiple clinics linked by study ID (Figure 3).

Figure 3. Data flow of electronic medical records in PrEPX and deterministic linkage for the gold-standard dataset.



Resulting PrEPX gold-standard dataset

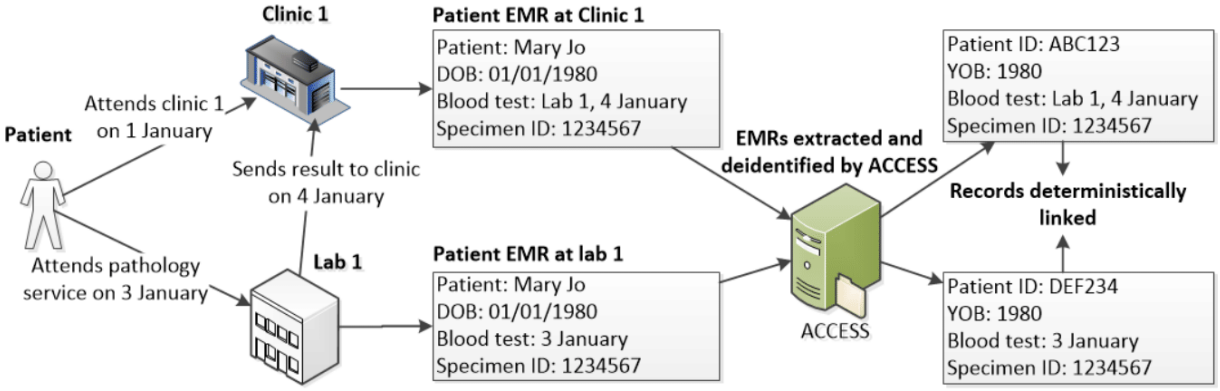
PrEPX Study ID	Clinic Name	EMR Number	GRHANITE Record ID
001	Clinic 1	A1	ABC123
002	Clinic 1	B2	DEF234
002	Clinic 2	C3	HIJ345

The Pathology Results Gold-Standard Dataset

A second and much larger gold-standard dataset was generated from the EMRs extracted from 7 clinics and 4 laboratories participating in ACCESS between January 2009 and April 2018. To be included in this dataset, patients had to have at least one specimen sent from one of the ACCESS clinics to one of the ACCESS laboratories. A unique laboratory specimen ID was assigned to the specimen at the laboratory, and when laboratories returned pathology results to the clinic, this specimen ID was also recorded at the clinic. To create the gold-standard dataset, clinic and laboratory records were matched using the laboratory specimen ID, year of birth, and test date. We allowed for a 7-day difference in test dates, as in medical records, the recorded date can commonly vary for the same specimen. Only matched records were included in the gold-standard dataset and linked using an arbitrarily assigned link identifier (Figure 4).

An EMR in the pathology results gold-standard dataset may match to many other EMRs for several reasons, including the following: individuals may have had multiple specimens sent to multiple laboratories for testing, individuals may have attended different clinics and therefore had the same test result sent from the laboratory to more than one clinic, or individuals may have had multiple EMRs at the laboratory or clinic as a result of outdated or incomplete personal identifiers.

Figure 4. Data flow of pathology results in electronic medical records and deterministic linkage for the gold-standard dataset.



Resulting pathology results gold-standard dataset

Arbitrary Link ID	Specimen ID	ACCESS site	GRHANITE record ID
0001	1234567	Clinic 1	ABC123
0001	1234567	Lab 1	DEF234

Data Analysis

Sensitivity

The sensitivity was calculated as the number of correctly linked EMRs, as identified using the GRHANITE Linkage Tool, as a percentage of the total number of linked EMRs in the gold standard dataset.

Specificity

In the PrEPX gold-standard dataset, the specificity was calculated as the number of single EMRs correctly identified as unlinked using the GRHANITE Linkage Tool as a percentage of the total number of unlinked EMRs. The positive predictive value (PPV) and negative predictive value were also calculated to provide probabilities of true matches and missed matches.

Given the deidentified nature of the ACCESS data, it was not possible to include unmatched specimen IDs in the pathology results gold-standard dataset because there was no way to confirm whether they belonged to different individuals (correctly unmatched), making it impossible to calculate specificity. Therefore, to evaluate specificity, we assessed the concordance of chronological HIV and hepatitis C test records to identify EMRs that should not have been linked. By identifying the linked EMRs with discordant results, the PPV (the proportion of linked records with concordant antibody results) could be determined. The specificity was then estimated using the PPV and the sensitivity for each linkage approach as summarized in Figure 5.

Figure 5. Estimating specificity when positive predictive value and sensitivity are known.

		Gold-Standard	
		Linked EMR	Unlinked EMR
Observed GRHANITE Linkage Result	Linked EMR	True Positive (TP)	False Positive (FP)
	Unlinked EMR	False Negative (FN)	True Negative (TN)

When PPV is known, the number of false and true positives can be derived:

- FP = (1-PPV) x Observed number of linked EMRs
- TP = Observed number of linked EMRs – FP

When sensitivity is known, the number of false and true negatives can be derived:

- FN = (TP/Sensitivity) - TP
- TN = Observed number of unlinked EMRs – FN

The number of true negative and false positives can then be used to estimate specificity:

- Specificity = [TN/(FP + TN)] × 100

Measuring Incorrect Matches Using Discordant Pathology Results

Following infection, any HIV or hepatitis C antibody test that subsequently occurs should always return a positive result. Using the pathology results gold-standard dataset provided only a small number of HIV and hepatitis C results; therefore, a dataset of linked EMRs was derived using all available EMRs from the same clinic and laboratory sites used to create the gold-standard dataset. Two datasets were created, one that contained any HIV western blot or antibody result and one that contained any hepatitis C antibody result. EMRs containing discordant results before record linkage were excluded from the sample so as not to confuse it with discordance resulting from record linkage. Records within each dataset were then linked using all six approaches (Table 1) of the GRHANITE Linkage Tool. Linked EMRs where there was no history of a positive result were removed from the sample, as a discordant test result can only be determined after an initial positive result. Therefore, in the HIV and hepatitis C datasets, only linked EMRs that contained an antibody result after an initial positive HIV western blot or hepatitis C antibody result were retained for evaluation.

To calculate the PPV, the linked EMRs were then inspected for negative antibody results occurring at least seven days after a positive test result, which were then classified as incorrectly matched. Where most subsequent antibody tests were negative, the initial and any subsequent positive results were considered incorrectly matched records.

Results

Record Linkage Using the PrEPX Gold-Standard Dataset

The PrEPX gold-standard dataset identified 28 joins among 56 EMRs, indicating 28 study participants had attended two different clinical sites during the PrEPX study period. The remaining 3644 EMRs were from participants who only attended a single clinic during the study and therefore did not have any linked records.

Over 99% of EMRs had all four linkage key types present in 8 of the 9 sites, indicating that the patient-identifying information to generate those linkage keys was near fully recorded at the clinics. One site was missing data needed to generate linkage types 1, 2, and 4 (which all require the Medicare number) in 11% (8/76) of their EMRs (Table 2).

In all linkage approaches, except the approach requiring two or more linkage keys, all pairs of EMRs from the 28 individuals who attended two sites were correctly joined (100% sensitivity). With the approach which required two or more linkage keys for matching, one pair was not identified (96% sensitivity). Specificity was 100% using all linkage approaches, without any of the remaining 3644 EMRs in the dataset being falsely linked (Table 3).

Table 2. Percentage of electronic medical records in the PrEPX gold-standard dataset by linkage key type and site.

Site	Number of electronic medical records, N	Percentage of electronic medical records with Linkage Key			
		Type 1, n (%)	Type 2, n (%)	Type 3, n (%)	Type 4, n (%)
Site 1	76	68 (89)	68 (89)	76 (100)	68 (89)
Site 2	853	853 (100.0)	853 (100.0)	853 (100.0)	853 (100.0)
Site 3	1087	1087 (100.00)	1084 (99.72)	1087 (100.00)	1087 (100.00)
Site 4	582	582 (100.0)	582 (100.0)	582 (100.0)	582 (100.0)
Site 5	40	40 (100.0)	40 (100.0)	40 (100.0)	40 (100.0)
Site 6	135	135 (100.0)	135 (100.0)	135 (100.0)	135 (100.0)
Site 7	106	106 (100.0)	103 (99.2)	106 (100.0)	106 (100.0)
Site 8	314	314 (100.0)	314 (100.0)	314 (100.0)	314 (100.0)
Site 9	507	507 (100.0)	507 (100.0)	507 (100.0)	507 (100.0)
Total	3700	3692 (99.78)	3686 (99.62)	3700 (100.00)	3692 (99.78)

Table 3. Evaluation measures derived from using the GRHANITE Linkage Tool on the PrEPX gold-standard dataset.

Linkage approach	Sensitivity (N=56), n (%)	Specificity (N=3644), n (%)	Positive predictive value (N=56), n (%)	Negative predictive value (N=3644), n (%)
Accept all	56 (100)	3644 (100.00)	56 (100)	3644 (100.00)
Year of birth match	56 (100)	3644 (100.00)	56 (100)	3644 (100.00)
Sex match	56 (100)	3644 (100.00)	56 (100)	3644 (100.00)
Year of birth and sex match	56 (100)	3644 (100.00)	56 (100)	3644 (100.00)
Two or more linkage keys	54 (96)	3644 (100.00)	54 (100)[a]	3644 (99.90)[b]
Linkage key type 3 plus sex match	56 (100)	3644 (100.00)	56 (100)	3644 (100.00)

[a]N=54.

[b]N=3646.

Record Linkage Using the Pathology Results Gold-Standard Dataset

Using the GRHANITE Linkage Tool on the pathology results gold-standard dataset created 50,484 linked records among 86,538 EMRs, with a maximum of six EMRs identified as belonging to the same individual.

A total of 99.69% (86,273/86,538) of EMRs contained at least one linkage key type, and all four linkage key types were present in 73.51% (63,610/86,538) of records, suggesting that the completion of patient-identifying information in the patient database was very high overall. However, 21.62% (18,709/86,538) of EMRs had only linkage key type 3 available for matching. One or more of linkage types 1, 2, and 4 (which all require the Medicare number) was missing in 97.42% (7914/8124) of EMRs from one public laboratory, 53.95% (5967/11,060) of EMRs from the sexual health clinic, 48.25% (1403/2908) of EMRs from a private laboratory, and 23.42% (6134/26,186) of EMRs from another public laboratory (Table 4).

For the first 4 linkage approaches, the GRHANITE Linkage Tool correctly linked 94% to 95% of EMRs in the pathology results gold-standard dataset, dropping to 66% (57,330/86,538) where two or more linkage keys are needed to form a match (Table 5). In the final linkage approach, where pairs were only accepted when matched on linkage key type 3 (which does not require the Medicare number) and sex, 89% (76,928/86,538) of records were correctly linked.

Table 4. Percentage of electronic medical records in the pathology gold-standard dataset by linkage key type and site.

Site	Number of electronic medical records, N	Number of electronic medical records with no linkage keys, n (%)	Percentage of electronic medical records with Linkage Key			
			Type 1, n (%)	Type 2, n (%)	Type 3, n (%)	Type 4, n (%)
Clinic 1	3165	0 (0.00)	3083 (97.41)	3077 (97.22)	3165 (100)	3083 (97.41)
Clinic 2	6342	0 (0.00)	6031 (95.10)	6015 (94.84)	6342 (100)	6031 (95.10)
Clinic 3	2514	0 (0.00)	2493 (99.16)	2489 (99.01)	2513 (99.96)	2492 (99.12)
Clinic 4	9679	0 (0.00)	9351 (96.61)	9322 (96.31)	9676 (99.97)	9350 (96.60)
Clinic 5	1369	1 (0.07)	1357 (99.12)	1356 (99.05)	1368 (99.93)	1357 (99.12)
Clinic 6	2489	5 (0.20)	2315 (93.01)	2288 (91.92)	2484 (99.80)	2315 (93.01)
Clinic 7 (sexual health)	11,060	9 (0.08)	5097 (46.08)	5094 (46.06)	11,049 (99.90)	5095 (46.07)
Lab 1 (public)	26,186	241 (0.92)	23,705 (90.53)	20,059 (76.60)	25,465 (97.25)	23,227 (88.70)
Lab 2 (public)	8124	8 (0.10)	215 (2.65)	210 (2.58)	8116 (99.90)	215 (2.65)
Lab 3 (private)	2908	1 (0.03)	1706 (58.67)	1509 (51.89)	2907 (99.97)	1710 (58.80)
Lab 4 (private)	12,702	0 (0.00)	12,205 (96.09)	12,203 (96.07)	12,700 (99.98)	12,203 (96.07)
Total	86,538	265 (0.31)	67,558 (78.07)	63,622 (73.52)	85,785 (99.13)	67,078 (77.51)

Table 5. Evaluation measures derived from using the GRHANITE Linkage Tool on the pathology results gold-standard dataset.

Linkage approach	Gold standard (N=86,538)	HIV results			Hepatitis C results		
	Sensitivity, n (%)	N	Positive predictive value, n (%)	Estimated specificity, (%)	N	Positive predictive value, n (%)	Estimated specificity, (%)
Accept all	82,345 (95.15)	1427	1245 (87.25)	90.52	3908	3866 (98.93)	99.32
Year of birth match	82,212 (95.00)	1412	1234 (87.39)	90.71	3817	3777 (98.95)	99.34
Sex match	81,689 (94.40)	1257	1143 (90.93)	93.20	3810	3775 (99.08)	99.42
Year of birth and sex match	81,560 (94.25)	1263	1152 (91.21)	93.42	3775	3741 (99.10)	99.43
Two or more linkage keys	57,330 (66.25)	257	256 (99.6)	99.74	2809	2795 (99.50)	99.67
Linkage key type 3 plus sex match	76,928 (88.90)	1090	984 (90.28)	92.98	3626	3596 (99.17)	99.49

Estimating Specificity Using Discordant Test Results

In the derived HIV dataset, the number of linked EMRs containing an initial positive Western blot result ranged from 1090 to 1427 with all linkage approaches except when two or more linkage keys are needed. The linkage approach which requires two or more linkage keys to match resulted in 257 linked EMRs. The PPV was between 87% and 91% for the first 4 linkage approaches and estimated specificity ranged from 90% to 93%. When fewer EMRs were linked because of the different linkage approaches, both PPV and specificity improved (Table 5).

In the derived hepatitis C dataset, with the first 4 linkage approaches, in excess of 3700 linked EMRs contained an initial positive hepatitis C antibody result, with a drop to 2809 records when two or more linkage keys are needed. The PPV was greater than 98.9% and an estimated specificity was over 99% for all six linkage approaches (Table 5).

Discussion

Principal Findings

This paper describes a comprehensive evaluation of a system of probabilistic record linkage using a privacy-preserving software tool within a large-scale health surveillance system. The results showed that this software provides a highly reliable and accurate system for linking routinely collected EMRs through the generation of linkage keys reliant on available identifying information. Optimizing the record linkage involves an appropriate balance between the sensitivity (correctly identifying records belonging to the same person) and specificity (ensuring records that belong to different people are not linked) as well as what will best suit the study design objectives and populations under study without impeding the interpretation of study results.

The high performance of the linkage tool when applied to the relatively small PrEPX gold-standard dataset was related to the data completeness for EMRs in the PrEPX trial compared with the completeness of data in the pathology results gold-standard dataset (Tables 2 and 4). Participants in PrEPX were required to have a Medicare number to be enrolled and have three monthly follow-up visits, which allowed multiple opportunities for the staff at clinics to record any missing identifying information [13]. Where the underlying identifiers are robust and duplication is at a minimum, the probability of missed matches is negligible. In addition, with the PrEPX gold-standard dataset, there was 100% specificity for all linkage approaches, indicating that the linkage tool does not falsely link records in a small sample of EMRs where there was unlikely to be individuals with similar identifying details (name, date of birth, and Medicare number).

When the linkage tool was applied to the larger pathology results gold-standard dataset, sensitivity ranged between 89% and 95% where the linkage approach relied on a single linkage key matching. However, with the approach that requires records to link on two or more linkage key types, sensitivity was reduced to 66%. This is attributable to 22% of EMRs only having a single linkage key type available for linkage, which is mostly because of the Medicare number not being available. The inclusion of laboratory records in the pathology results gold-standard dataset may contribute to a lower sensitivity as a result of patient identifier errors such as mislabeling and recording of laboratory samples [14], compared with the completeness of personal identifiers within clinic EMRs. The final linkage approach where pairs of EMRs were only linked when matched on linkage key type 3 (which does not require the Medicare number) and sex, resulted in 89% sensitivity. This approach was included in the analysis to simulate the performance of the linkage tool when the Medicare number is not available. This is important to evaluate in Australia as a significant proportion of participating sites within ACCESS are funded through jurisdictional governments and do not record patient Medicare numbers [15].

Limitations

The main challenge in evaluating the GRHANITE Linkage Tool was the development of gold-standard datasets given the deidentified nature of EMRs in ACCESS. Researchers rarely have access to gold-standard datasets on which to perform linkage validation outside large administrative health data sources, and our gold-standard dataset of 86,538 records was comparable with other published studies [16]. The gold standards required records with enough supplementary information for deterministic matching where we could be certain that matches belonged to the same individual and nonmatches belonged to different individuals. Therefore, to generate the gold-standard datasets, there were a limited number

of records we could use to accurately calculate sensitivity and specificity of the linkage tool. Although the pathology results gold-standard dataset contained over 80,000 records, one limitation of the evaluation was the inability to identify the correctly unmatched EMRs, which meant specificity could not be directly measured. However, given ACCESS is focused on the surveillance of BBV and STI, we were able to evaluate specificity within the pathology results dataset by examining the concordance of linked test results for HIV and hepatitis C. As expected, linkage specificity was inversely related to sensitivity. In addition, using discordant antibody results, we assumed that any discordant result was attributable to incorrect record linkage as opposed to an error in laboratory test results. However, given the very high sensitivity and specificity of the HIV western blot and antibody tests for HIV and hepatitis C, any testing errors would be minimal. The observed difference in PPV and estimated specificity between the HIV and hepatitis C datasets could be attributed to (1) differences in the sensitivity and specificity of the underlying laboratory tests for HIV and HCV and (2) potentially greater rates of anonymous HIV testing, whereby public laboratories do not require full names for HIV testing [15].

Beyond the false-positive record linkages identified by examining the concordance of linked test results for HIV and hepatitis C, there is potential for other false-positives to occur in cases where individuals share common patient identifiers, such as twins. Given the deidentified nature of ACCESS data, without the actual identifying demographic values, these niche cases cannot be identified. The small impact of these false-positives is not expected to impact the main purpose of public health surveillance using ACCESS. For other research projects that require a lower level of false-positive record linkage, particularly if it is known to contain a high proportion of individuals sharing common patient identifiers, then using a linkage approach that only accepts linkage based on a match of multiple linkage keys would minimize false-positives. In addition, ensuring concordance of other extracted data, such as sex, year of birth, HIV, and hepatitis C testing history, can reduce the level of false-positive record linkages to acceptable levels.

Conclusions

Evaluating record linkage is an important part of assessing the utility of surveillance and research systems for answering key population-level research questions or for accurately describing population-level trends using linked data. Our findings suggest that the GRHANITE Linkage Tool is appropriate for accurately linking individuals' episodes of care and underpins the ability for ACCESS to perform privacy-preserving linkage of patient medical records.

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Conflicts of Interest

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Abbreviations

ACCESS: Australian Collaboration for Coordinated Enhanced Sentinel Surveillance
BBV: blood-borne virus
EMR: electronic medical record
NSW: New South Wales
PPV: positive predictive value
STI: sexually transmissible infection
TAIPAN: Treatment with Antiretrovirals and their Impact on Positive And Negative men
UNSW: University of New South Wales

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Appendix E Other outputs during candidature

Appendix E1. Poster: Longitudinal changes in condom use among PrEPX participants.

Citation

Traeger M, Asselin J, Price B, Roth N, Willcox J, Tee BK, Fairley C, Penn M, El-Hayek C, Nguyen L, Ryan K, Hoy J, Ruth S, West M, Stoové M, Wright E. Longitudinal changes in condom use with casual partners among gay and bisexual men using HIV pre-exposure prophylaxis. Presented at the 10th IAS Conference on HIV Science, Mexico City, Mexico. 21-24 July 2019.

Longitudinal changes in condom use with casual partners among gay and bisexual men using HIV pre-exposure prophylaxis

Traeger M[1,2], Asselin J[1], Price B[3], Roth N[4], Willcox J[5], Tee BK[6], Fairley C[7], Penn M[8], El-Hayek C[1], Nguyen L[1], Ryan K[1,3], Hoy J[3], Ruth S[9], West M[10], Stoové M[1,2], Wright E[1,3], *on behalf of the PrEPX Study Team*

Background

- Gay and bisexual men (GBM) using PrEP are at high risk of STIs[1], however evidence for declines in condom use following PrEP initiation is mixed[2]
- The PrEPX study was a multi-site, open-label PrEP implementation study in Victoria, Australia
- PrEPX enrolled over 4,200 gay and bisexual men at high risk of HIV between July 2016 and March 2018
- Participants returned quarterly for clinical review, HIV/STI testing, to fill their PrEP scripts and complete an electronic behavioural survey
- We explore changes in condom use with casual partners among a subset of PrEPX participants with behavioural data available during follow-up

Methods

- Behavioural data were extracted via the ACCESS surveillance project
- Participants with at least 12 months follow-up were included
- Generalised estimating equation (GEE) logistic models were used to explore average change in condom use from baseline to month 12
- GEE multivariable logistic models were also used to explore factors associated with condom use during follow-up
- Responses were categorical: Always, Usually, Sometimes, or Never
- Two dichotomised outcomes were explored in GEE models;
  (1) inconsistently versus always used condoms
  (2) never versus sometimes, usually or always used condoms

Results

- 1,646 participants completed a behavioural survey at month 12 and were included
- Condom use with casual partners in the 6 months prior to baseline was lower among those reporting previous PrEP use, and declined in both groups over time (Figure)
- Odds of reporting inconsistent condom use (aOR, 1.27 [95%CI, 1.21-1.32]) and reporting never using condoms (aOR, 1.35 [95%CI, 1.29-1.42]) increased over time (Table)

	Condom use with casual partners in the last six months			
	Outcome 1: Inconsistently used condoms (versus always used)		Outcome 2: Never used condoms (versus inconsistently or always used)	
Covariate	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Visit* (per quarter)	1.27 (1.21-1.32)	<0.001	1.35 (1.29-1.42)	<0.001
Multivariable model				
Visit (per quarter)	1.31 (1.25-1.38)	<0.001	1.37 (1.29-1.44)	<0.001
Enrol date (per month increase)	0.95 (0.92-0.99)	0.028	1.03 (0.98-1.08)	0.201
Age (per 10 year increase)	1.10 (0.96-1.25)	0.171	1.24 (1.08-1.42)	0.002
Born overseas	0.68 (0.54-0.87)	0.002	0.91 (0.70-1.18)	0.492
Previous PrEP use	2.34 (1.75-3.14)	<0.001	1.66 (1.26-2.19)	<0.001
Has regular partner	0.68 (0.54-0.87)	<0.001	1.15 (0.94-1.42)	0.177
>10 anal sex partners	1.91 (1.53-2.40)	<0.001	0.76 (0.60-0.96)	0.023
Recreational drug use during sex^	Excluded[#]		2.02 (1.57-2.60)	<0.001
Reports group sex at least monthly	2.04 (1.37-3.04)	0.001	1.45 (1.08-1.96)	0.014

Table. Factors associated with inconsistent condom use (versus always used condoms) and never using condoms (versus sometimes, usually or always used condoms) with casual partners in the last six months.
*Adjusted for age and enrolment date. ^Includes use of methamphetamine, GHB/GBL, ecstasy or cocaine during sex.
[#]Zero participants who reported recreational drug use during sex reported always using condoms.

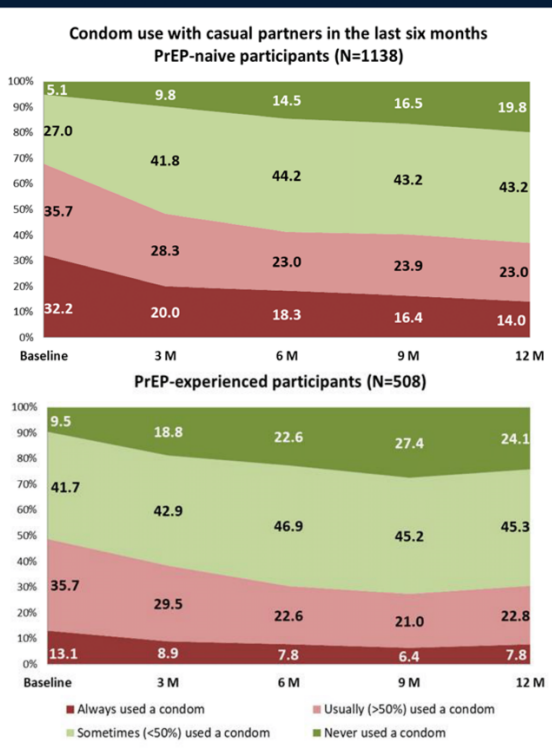

Figure. Proportion of PrEPX participants reporting frequency of condom use with casual sex partners in the last 6 months, from baseline to month 12, by whether participants reported using PrEP at enrolment

Discussion

- Reductions in condom use among GBM were greatest immediately following PrEP commencement, but still occurred during later stages of PrEP use
- Later-stage reductions in condom use may be indicative of population-level normalisation of PrEP over time[3]
- Factors associated with inconsistent condom use differed from those associated with never using condoms, highlighting the importance of consistent metrics
- Participants who enrolled in the study earlier, and participants reporting a regular partner, were more likely to always use condoms with casual partners
- Reporting more than 10 partners was positively associated with inconsistent condom use, however was negatively associated with never using condoms, which may suggest that GBM with high numbers of partners may use condoms to mitigate risk of STIs
- Continued collection of behavioural data among GBM at risk of HIV and STIs will be important for understanding how different risk reduction strategies used by GBM alter with further PrEP uptake and greater normalisation of PrEP over time
- Findings highlight the importance of ongoing, frequent monitoring of STIs among PrEP users, even among those consistently using condoms at PrEP initiation

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Author Affiliations: 1. Burnet Institute, Melbourne; 2. School of Public Health and Preventive Medicine, Monash University, Melbourne; 3. Department of Infectious Diseases, Alfred Health and Monash University, Melbourne; 4. Prahran Market Clinic, Melbourne; 5. Northside Clinic, Melbourne; 6. Centre Clinic, Thorne Harbour Health, Melbourne; 7. Melbourne Sexual Health Centre, Alfred Health, Melbourne; 8. PRONTO!, Thorne Harbour Health, Melbourne; 9. Thorne Harbour Health, Melbourne; 10. Sexual Health and Viral Hepatitis Service, Victorian Department of Health and Human Services, Melbourne

burnet.edu.au

Correspondence:
michael.traeger@burnet.edu.au


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