HIV incidence in people receiving government-subsidised pre-exposure prophylaxis in Australia: a whole-of-population retrospective cohort study

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Summary

Background HIV pre-exposure prophylaxis (PrEP) is highly effective and has been government subsidised in Australia since April, 2018. We examined HIV incidence over 5 years in a retrospective observational cohort of people who had received subsidised PrEP.

Methods Linked de-identified dispensing records for all government-subsidised oral PrEP, HIV antiretroviral therapy (ART), and hepatitis C treatment were used. We included all people dispensed subsidised PrEP from April 1, 2018, to March 31, 2023, and examined records up to Sept 30, 2023. Exposure was measured from date of first PrEP prescription and days covered by PrEP calculated for individuals based on quantity and date supplied. Assuming that HIV was diagnosed 30 days before ART initiation, we imputed the date of acquisition as the midpoint between the diagnosis and the later of the last PrEP prescription or 6 months before the diagnosis. We calculated HIV incidence and its predictors using Poisson regression.

Findings We included 66 206 people dispensed PrEP: 64 757 (97·8%) were men; median age was 33 years (IQR 27–43). 207 people acquired HIV, with an overall incidence of 1·07 per 1000 person-years (95% CI 0·93–1·23). Incidence was 2·61 per 1000 person-years among those dispensed PrEP once only. Using this group as a comparator, those with 60% or more days covered by PrEP had a 78·5% reduction in incidence (0·56 per 1000 person-years, p<0·0001) and those with less than 60% days covered had a 61·6% reduction (0·99 per 1000 person-years, p=0·0045). Independent predictors of HIV acquisition were a record of hepatitis C treatment (9·83 per 1000 person-years, adjusted incident rate ratio [aIRR] 8·70, 95% CI 4·86–15·56), only attending prescribers outside of areas with a high estimated prevalence of gay men (1·66 per 1000 person-years, aIRR 1·50, 1·08–2·09), age 18–29 years (1·33 per 1000 person-years, aIRR 1·56, 1·11–2·21), and earlier year of first PrEP.

Interpretation The low observed incidence of HIV among people receiving government-subsidised PrEP highlights the success of a national programme of oral PrEP scale-up in achieving sustained reduction in community HIV transmission. However, incidence varied greatly, indicating that more research is needed to understand why people were not taking PrEP at times of risk and emphasising the need for new interventions focused on this population to achieve elimination of HIV transmission. Individuals dispensed PrEP once only and less frequent users might benefit from more support.

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Introduction

Use of HIV pre-exposure prophylaxis (PrEP) among people at risk of HIV is a crucial element in global strategies to reduce HIV transmission.[1] Many countries, including Australia, the UK, and the USA, have committed to high PrEP targets to achieve elimination of HIV transmission.[2–4] In Australia, most HIV transmission occurs among gay and bisexual men (GBM), and PrEP is widely promoted to this group.[5,6] Large implementation studies between 2016 and 2018 were followed by a government-subsidised PrEP programme from April, 2018, and saw rapid uptake and high rates of PrEP use in the target population.[6,7]

In 2017, the year before the national programme began, there were 604 HIV diagnoses in GBM. By 2022, this number had fallen by 55% to 273. Over the same time, the number of GBM diagnosed with HIV classified as newly acquired (ie, with a negative HIV test or evidence of seroconversion within 12 months of diagnosis) fell by 61% from 276 to 107.[5] Despite this, Australia remains well short of its strategic goal of a 90% reduction in transmission from the 2010 baseline.[5]

Progress towards HIV prevention targets faces at least two major challenges even when PrEP uptake is high. Firstly, a key concern internationally is that effective PrEP use at times of sexual risk can be lower in

Research in context

Evidence before this study

The safety and effectiveness of HIV pre-exposure prophylaxis (PrEP) has been shown in clinical trials and in demonstration and implementation studies with large numbers of consented participants who met specified enrolment criteria. PrEP has been licensed widely for prevention of HIV. Less is known about HIV incidence in large populations of people who take PrEP during national scale-up when need, persistence, and adherence might vary over time. This knowledge gap is important because PrEP is a key part of national and global HIV prevention strategies and it is not known whether it is as effective at the population level during national scale-up and outside of observational studies, and whether protection against HIV acquisition can be sustained over time. We searched PubMed for studies published up to Feb 29, 2024, using the following search string: ((HIV incidence) OR (HIV acquisition)) AND (population) AND ((HIV pre-exposure prophylaxis) OR (PrEP)) and found no studies that reported HIV incidence rates at the national or jurisdictional level in people who had received PrEP who were not study participants. Measuring real-world population PrEP effectiveness is also complicated by a lack of an appropriate comparator group; people not taking PrEP might be at lower risk than those who do, and historical comparators might appear to be at higher risk because incidence has gone down in areas with high PrEP uptake.

Added value of this study

We examined HIV incidence among the 66 206 people in Australia who ever received government-subsidised PrEP in the 5 years from April, 2018, when it first became available, almost all of whom are thought to be gay and bisexual men (GBM). Using linked and de-identified data on dispensed subsidised PrEP and HIV antiretroviral treatment (ART), we were able to identify HIV acquisition using ART initiation because of the known high rates of HIV testing in people using PrEP and the known early initiation of ART after receipt of an HIV diagnosis. Novel aspects of this study were that it covers the entire population of people receiving PrEP through this scheme (more than 90% of Australian PrEP users) over 5 years. Also, to estimate the effectiveness of PrEP, we compared incidence in people with 60% or more of days covered by PrEP and those with less than 60% of days covered by PrEP with the group who stopped PrEP after a single dispensed supply. We found that overall incidence was low, at 1·07 per 1000 person-years. Those who received only a single PrEP supply had a higher rate of 2·61 per 1000 person-years and compared with this group, incidence was 78·5% lower in those with 60% or more days covered and 61·6% lower in those with less than 60% of days covered by PrEP.

Implications of all the available evidence

PrEP is effective as a large-scale HIV prevention strategy and the effects appear durable over time. However, the benefit is not uniform across the entire population of GBM. To push HIV incidence even lower and to achieve HIV transmission elimination targets, policy makers and health implementers should also consider people who have previously taken PrEP but might be at ongoing HIV risk. This population has not previously been a priority in HIV prevention strategies. Measures aimed at identifying those who have stopped PrEP and ensuring that people take PrEP correctly when risk occurs should be considered.

programmatic scale-up than in clinical trials and implementation studies.[8] Secondly, the lack of a direct measure of incidence and a suitable comparator population limits evaluation of the effectiveness of PrEP at the population level. For example, some studies compare incidence rates in specific clinic populations, which might not be representative of the whole population of people at risk, with the time before PrEP was available when incidence might have been higher, or with people who have not received PrEP who might be at lower risk.[9–12]

The Australian Government subsidises both PrEP and HIV antiretroviral treatment (ART) through the Pharmaceutical Benefits Scheme. The government-defined "general" subsidy sets a maximum patient copayment (currently AU$30) for a 1-month supply; and a "concessional" subsidy based on income, employment, health, disability, and yearly pharmaceutical expenditure reduces the co-payment (currently to AU$7·30 or less).[13] PrEP prescription is for up to 3 months, dispensed monthly, after which a new prescription is required (appendix p 10). Guidelines recommend HIV testing every 3 months or at every prescription.[14]

See Online for appendix

Centralised administrative records of all subsidised dispensing provide an opportunity to measure both PrEP and ART use in the same individuals. The degree of completeness in this dataset is high because most Australian eligible GBM access PrEP through this scheme and almost all ART is government subsidised.[13] ART initiation in people who have received PrEP can be used to examine and estimate HIV diagnosis, acquisition, and, hence, incidence. This is because, firstly, rates of repeat HIV testing among people who report taking PrEP are very high,[11,15] and secondly, ART is initiated rapidly after diagnosis.[5,16] People who initiate PrEP but do not continue it could also be used as a comparator because their risk is contemporaneous (unlike historical controls), because they were considered to be eligible for PrEP by their prescriber (unlike people not prescribed PrEP), and because the incidence can be estimated from the same dataset using the same methods.

Measurements of HIV incidence among people who have used PrEP (including those who have discontinued) and key subgroups are critical to understanding

the effectiveness of large-scale PrEP programmes and targeting future interventions. The aim of this study was to use Australian Government dispensing data to estimate HIV incidence in people who ever received PrEP in the national programme, to identify the predictors of HIV acquisition, and examine the relative effectiveness of ongoing PrEP use in comparison with those who initiated but received only one PrEP supply.

Methods

Study design and participants

In this retrospective cohort using observational routinely collected administrative data, we examined government records of dispensed subsidised prescriptions for PrEP from when it was first subsidised on April 1, 2018, to Sept 30, 2023, and for ART and hepatitis C treatment from Jan 1, 2015, to Sept 30, 2023. The fumarate salt of tenofovir disoproxil (tenofovir disoproxil fumarate) coformulated with emtricitabine was the first formulation licenced for HIV prevention in Australia, although bioequivalent maleate, succinate, and phosphate salts have subsequently been licensed:[14] all are included in the government subsidy and no attempt was made to distinguish between them in this study. Tenofovir alafenamide is not licensed or subsidised as PrEP in Australia, and is not included in this dataset. Post-exposure prophylaxis for HIV is not subsidised by the Pharmaceutical Benefits Scheme and is also not included in this dataset (appendix p 10).

We included all people aged 16 years and older who were dispensed government-subsidised coformulated tenofovir disoproxil with emtricitabine in Australia on at least one occasion between April 1, 2018, and March 31, 2023 (the study period) and with the PrEP indication recorded. We excluded those who only ever received this medication at the same time as raltegravir or dolutegravir (the guideline-recommended three-drug post-exposure prophylaxis regimen[17]), but included those with PrEP prescribed before or after this.

This study was approved by the UNSW Sydney Human Research Ethics Committee (HC190682). A waiver of individual patient consent was granted as part of this approval. We report results according to the STROBE and RECORD statements.[18,19]

Procedures

We extracted data from prescriptions for PrEP, ART, or hepatitis C treatment in those included in the study. Each record represents a single instance of dispensing, and contains an anonymised code linking prescriptions in the same patient, an anonymised code linking prescriptions from the same prescriber, drug, indication (PrEP, ART, or hepatitis C treatment), date of prescription, date and quantity dispensed, subsidy level, patient age, and postcode of patient residence and of prescriber practice.[20] Multiple dispensing events for the same drug on the same day were combined.

We defined ART as two or more consecutive dispensed prescriptions for antiretroviral drugs other than coformulated tenofovir disoproxil with emtricitabine. We also excluded people dispensed other antiretroviral drugs before PrEP.

One dispensed tablet was equated to 1 day on PrEP. Using date and quantity of PrEP supplied and adjusting for PrEP carried over from previous dispensing, we calculated the number (and proportion) of days covered between the first PrEP prescription and the end of the study period or the imputed date of HIV acquisition. Because a previous analysis showed that many people were dispensed PrEP once only, and because high efficacy can be maintained in GBM taking four tablets per week (approximately 60% of days covered), we categorised PrEP use as: one supply of PrEP only, less than 60% of days covered but more than one PrEP supply, and 60% or more of days covered.[14,21] Dosing is not available in the data. No attempt was made to distinguish continuous, episodic, or event-based PrEP use, which is now recommended in Australian guidelines. The minimum event-based dosing of four tablets over 3 days would be categorised as 4 days on PrEP.[7,14,21]

Additional covariates were defined with data extracted from the dispensing record:[21] age group at first prescription (29 years and younger, 30–39 years, or 40 years and older), sex recorded at first prescription (recorded as male or female only), subsidy level (higher [concessional] benefit at any dispensing), receipt of hepatitis C treatment at any point in the dataset from Jan 1, 2015 (guidelines recommend hepatitis C testing annually for people taking PrEP and people living with HIV who are sexually active or inject drugs[14,22]), and postcode of patient residence and prescriber practice, each categorised according to the published estimate of the proportion of gay men in that postal district (low [<2%] or high [≥2%][23]). We defined a doctor's PrEP caseload as the number of individual patients they prescribed PrEP to during the study period, and assigned this to each of their patients (1–100 or >100). The categorisation of location and caseload was chosen because communities of GBM and their health services are concentrated in certain geographical areas and high caseload settings, and because PrEP promotion strategies in Australia target GBM. It was adapted from a previous published analysis of this dataset.[16,21,24] When the patient had more than one prescriber or residence, the higher caseload and proportion of gay men was assigned. We also included the study year of first PrEP as a covariate.

Outcomes

The study outcome was HIV acquisition, as indicated by ART initiation. We defined ART initiation as the first instance of dispensed ART in someone previously dispensed PrEP. We assumed that HIV testing was done each time PrEP was prescribed or twice a year if it was not, on the basis of literature showing that more than 90% of GBM taking PrEP reported two or more HIV

tests in the past year.[11,15] This assumption determined the length of the observation period (6 months) after the end of the study period (5 years).

For those who initiated ART within 60 days of the last PrEP prescription, we assumed HIV was acquired before that PrEP prescription was written and dispensed. If this was the first PrEP prescription, we excluded them from the analysis as HIV was acquired before baseline. If they had previously received PrEP, we included them in the analysis but did not use that prescription for calculation of time at risk or PrEP coverage (see below).

For the purposes of estimating time at risk in those who acquired HIV, we assumed that date of HIV diagnosis was 30 days before the date of ART initiation. This assumption is based on literature showing that more than 98% of GBM with HIV are taking ART and more than 95% initiate within 6 weeks of diagnosis.[5,16]

We imputed the date of HIV acquisition as the midpoint between assumed date of diagnosis and the later of the date of most recent previous PrEP prescription or 6 months before the assumed date of diagnosis. For those with most recent PrEP prescription more than 7 months before first ART prescription, this would be 3·5 months. We assumed that people were HIV negative at the end of the study period if they had not initiated ART during or in the 6 months after the end of the study period, or if the imputed date of HIV acquisition was after the end of the study period.

We did not account for death or loss to follow-up because of the known low permanent emigration in this population, the low death rate in this population, and because emigration data are not available and death data, although available, do not cover the entire study period.

Statistical analysis

We conducted descriptive analysis comparing those with HIV acquisition with the overall study population. Incidence rates per 1000 person-years were calculated with person-time at risk from the date of first PrEP prescription after April 1, 2018, until imputed date of HIV acquisition or March 31, 2023. We calculated 95% CIs using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. We used univariate Poisson models to derive unadjusted incident rate ratios for each pattern of PrEP use and those categories defined above. Those variables with p values less than 0·2 were included in the multivariable analysis. We chose Poisson regression models to present average rates of incidence over time, assuming proportional risk for the duration of follow-up rather than a time-dependent focus. Models were tested for overdispersion by use of the deviance statistic and by comparison to analogous negative binomial models.

Differences in the failure function by PrEP user group were estimated using the Kaplan–Meier method and evaluated using log-rank tests. To estimate population effectiveness, we compared HIV incidence in people with 60% or more days covered and less than 60% of days covered with people who received only a single supply of PrEP. All analyses were done with Stata 17.0.

We did three sensitivity analyses. For the first, we assumed that HIV testing occurred each time PrEP was prescribed or every 12 months if it was not (compared with 6 months in the main analysis). The study period was 6 months shorter to allow 12 months' observation after the end of the study period (compared with 6 months in the main analysis). For the second sensitivity analysis, we included only those dispensed PrEP in the first year and calculated onset of risk from April 1, 2018, when the national programme began (compared with the date of first prescribed PrEP in the main analysis). This is because more than 18 000 people received PrEP through implementation studies and might have been taking PrEP before being first dispensed government-subsidised PrEP.[6] For the third sensitivity analysis, we excluded people dispensed PrEP in the first year, because those who received one supply of PrEP only in the first year might have had previous supply in implementation projects.[21] See the appendix (pp 11–17) for diagrammatic representation.

Role of the funding source

There was no funding source for this study.

Results

We included 66 206 people dispensed government-subsidised PrEP in Australia on at least one occasion in the 5 years from April 1, 2018, to March 31, 2023, after excluding 246 in whom tenofovir disoproxil with emtricitabine was not for PrEP and 24 who initiated ART within 60 days of first PrEP (with presumed baseline or prevalent HIV; appendix p 2). 64 757 (97·8%) were male and the median age was 33 years (IQR 27–43; table 1). There was a total of 193 307 person-years of follow-up and a median follow-up of 39·0 months (17·8–52·6).

207 people (0·3%) acquired HIV during the study period, and three after the end of the study period. Among the 207, there was a median of 14·1 months (IQR 7·6–22·8) between the last PrEP prescription and first ART prescription. Also, 26 people initiated ART within 60 days of a PrEP prescription that was not their first (with presumed diagnosis at re-prescribing or re-initiation). For these individuals, there was a median of 11·0 months (IQR 4·5–18·0) between the previous PrEP and first ART prescriptions.

Among 153 people with prescriptions for tenofovir disoproxil with emtricitabine plus raltegravir or dolutegravir (the guideline-recommended three-drug regimen for post-exposure prophylaxis), we included 72 who received PrEP before or subsequently to this, and excluded 81 who did not.[17] We excluded 142 individuals with previous continuous ART and 23 others (appendix p 2).

Among the 207 people who acquired HIV during the study period, 63 (30·4%) were part of the group of

	All people dispensed PrEP (n=66 206)	People dispensed PrEP who acquired HIV (n=207)
Women	1449 (2·2%)	≤10 (≤5%)*
Men	64 757 (97·8%)	≥90 (≥5%)*
Age, years†	36 (12)	34 (11)
Higher subsidy‡	12 724 (19·3%)	57 (27·5%)
Duration of follow-up, months	39·0 (17·8–52·6)	21·2 (9·5–36·8)
Time from last PrEP to first ART prescription, days	NA	14·1 (7·6–22·8)
Time from first PrEP prescription to first dispensed PrEP, days	0 (0–7)	0 (0–11)
Time from first ART prescription to first dispensed ART, days	NA	0 (0–0)
Proportion of days covered by PrEP§	29·0% (7·8–66)	21·0% (5·0–44)
PrEP usage¶		
One supply	12 582 (19·0%)	63 (30·4%)
More than one supply and <60% of days covered	35 434 (53·5%)	113 (54·6%)
More than one supply and ≥60% of days covered	18 190 (27·5%)	31 (15·0%)
Study year of first PrEP prescription		
1	23 357 (35·3%)	123 (59·4%)
2	12 982 (19·6%)	48 (23·2%)
3	8839 (13·4%)	20 (9·7%)
4	9530 (14·4%)	≤20 (≤10%)*
5	11 498 (17·4%)	≤10 (≤5%)*
Calendar year of HIV diagnosis		
2018	NA	≤10 (≤5%)*
2019	NA	≤40 (≤20%)*
2020	NA	35 (16·9%)
2021	NA	36 (17·4%)
2022	NA	63 (30·4%)
2023	NA	35 (16·9%)
(Continued from previous column)		
Estimated prevalence of gay men in postcode of patient residence‖		
Low (<2%)	31 567 (47·7%)	102 (49·3%)
High (≥2%)	34 639 (52·3%)	105 (50·7%)
Estimated prevalence of gay men in postcode of prescriber practice‖		
Low (<2%)	17 894 (27·0%)	69 (33·3%)
High (≥2%)	48 312 (73·0%)	138 (66·7%)
Maximum PrEP caseload‖**		
1–100	31 049 (46·9%)	86 (41·5%)
100	35 157 (53·1%)	121 (58·5%)
Received hepatitis C treatment	384 (0·6%)	13 (6·3%)

Data are n (%), mean (SD), or median (IQR). ART=antiretroviral therapy. PrEP=pre-exposure prophylaxis. NA=not applicable. *Use of Australian Government data prohibits publishing numbers of less than ten individuals or that enable cross calculation of numbers of less than ten individuals †At time of first PrEP prescription. ‡Any PrEP supply during the study period with higher (concessional) subsidy, which reduces patient copayment and is based on income, employment, health, disability, and yearly pharmaceutical expenditure. §Calculated as the number of tablets dispensed divided by the number of days from the first PrEP prescription to the end of the study period or the imputed date of HIV acquisition, adjusted for PrEP remaining from previous dispensing. All PrEP usage categories are included. ¶PrEP usage categorised as: single dispensed supply with no subsequent PrEP, more than one supply and less than 60% of days covered by PrEP, or more than one supply and 60% or more days covered by PrEP. ‖If more than one residence or prescriber, the higher estimated prevalence of gay men and higher PrEP caseload was assigned. **The number of patients prescribed PrEP by an individual's prescriber.

Table 1: **All people dispensed government-subsidised HIV PrEP in Australia between April, 2018, and March, 2023, and those with HIV acquisition**

12 582 (19·0%) people who were dispensed PrEP one time only, and 31 (15·0%) were part of the group of 18 190 (27·5%) people with 60% or more days covered by PrEP (table 1).

The overall HIV incidence rate was 1·07 per 1000 person-years (95% CI 0·93–1·23). Incidence was similar in the sensitivity analyses: 1·17 per 1000 person-years when testing was assumed at the time of PrEP prescription or every 12 months; 1·06 per 1000 person-years when including only individuals dispensed PrEP in the first year and with onset of risk at the first day of the programme; and 0.97 per 1000 person-years in the analysis excluding individuals first dispensed PrEP in the first year (table 2, appendix pp 4, 6, 8).

Incidence in individuals with a single PrEP supply was 2·61 per 1000 person-years. Compared with this group, 60% or more days covered by PrEP reduced incidence by 78·5% (0·56 per 1000 person-years, p<0·0001) and more than one supply but less than 60% of days covered by 61·6% (0·99 per 1000 person-years, p=0·0045; table 2). Kaplan–Meier survival curves also show the relative differences between the PrEP use categories (log-rank test p<0·0001; figure).

Higher incidence was also observed in individuals who received hepatitis C treatment (9·83 per 1000 person-years, 95% CI 5·71–16·93), those with higher subsidy (1·43 per 1000 person-years, 1·10–1·85), those who only attended prescribers outside of areas with a high estimated prevalence of gay men (1·66 per 1000 person-years, 1·31–2·10) and those younger than 30 years (1·33 per 1000 person-years, 1·07–1·64; table 2). Of those 13 individuals who acquired HIV and received hepatitis C treatment, nine received hepatitis treatment before initiating ART (range 212–2466 days).

In the multivariable analysis, history of hepatitis C treatment (adjusted incident rate ratio [aIRR] 8·70, 95% CI 4·86–15·56), single dispensed PrEP supply (aIRR 4·71, 2·97–7·46), less than 60% of days covered by PrEP (aIRR 1·66, 1·11–2·49), prescriber outside area with a high estimated prevalence of gay men (aIRR 1·50, 1·08–2·09), and age under 30 years (aIRR 1·56,

	N	Follow-up, person-years (thousands)*	HIV incidence per 1000 person-years (95% CI)	uIRR (95% CI)	p value	aIRR (95% CI)	p value
All†	207	193·31	1·07 (0·93–1·23)	..	..	..	..
Age‡							
18–29 years	85	63·96	1·33 (1·07–1·64)	1·54 (1·10–2·16)	0·012	1·56 (1·11–2·21)	0·011
30–39 years	66	64·26	1·03 (0·81–1·31)	1·19 (0·84–1·70)	0·33	1·28 (0·89–1·83)	0·18
≥40 years	56	65·09	0·86 (0·66–1·12)	1 (ref)	..	1 (ref)	..
Hepatitis C treatment							
No	194	191·99	1·01 (0·88–1·16)	1 (ref)	..	1 (ref)	..
Yes	13	1·32	9·83 (5·71–16·93)	9·73 (5·55–17·06)	<0·0001	8·70 (4·86–15·56)	<0·0001
Higher subsidy§							
No	150	153·35	0·98 (0·83–1·15)	1 (ref)	..	1 (ref)	..
Yes	57	39·96	1·43 (1·10–1·85)	1·46 (1·07–1·98)	0·015	1·28 (0·94–1·76)	0·12
PrEP usage¶							
One supply	63	24·18	2·61 (2·04–3·33)	4·66 (3·03–7·16)	<0·0001	4·71 (2·97–7·46)	<0·0001
More than one supply and <60% of days covered	115	113·70	0·99 (0·83–1·20)	1·78 (1·19–2·64)	0·0045	1·66 (1·11–2·49)	0·013
More than one supply and ≥60% of days covered	29	55·43	0·56 (0·39–0·80)	1 (ref)	..	1 (ref)	..
Year of initiation							
1	123	106·29	1·16 (0·97–1·38)	1 (ref)	..	1 (ref)	..
2	48	45·59	1·05 (0·79–1·40)	0·91 (0·65–1·27)	0·58	0·70 (0·50–0·98)	0·040
3	20	21·64	0·92 (0·60–1·43)	0·80 (0·50–1·28)	0·35	0·58 (0·36–0·94)	0·028
4	≤20‖	14·21	0·91 (0·53–1·58)	0·79 (0·45–1·40)	0·42	0·51 (0·29–0·92)	0·026
5	≤10‖	5·59	0·54 (0·17–1·66)	0·46 (0·15–1·46)	0·19	0·27 (0·09–0·86)	0·027
Estimated prevalence of gay men in postcode of patient residence**							
Low (<2%)	102	83·31	1·22 (1·01–1·49)	1·28 (0·98–1·68)	0·073	0·93 (0·68–1·26)	0·63
High (≥2%)	105	110·00	0·95 (0·79–1·16)	1 (ref)	..	1 (ref)	..
Estimated prevalence of gay men in postcode of prescriber practice**							
Low (<2%)	69	41·64	1·66 (1·31–2·10)	1·82 (1·36–2·43)	<0·0001	1·50 (1·08–2·09)	0·017
High (≥2%)	138	151·67	0·91 (0·77–1·08)	1 (ref)	..	1 (ref)	..
PrEP caseload**††							
1–100	86	86·89	0·99 (0·80–1·22)	0·87 (0·66–1·15)	0·33	NA‡‡	..
>100	121	106·41	1·14 (0·95–1·36)	1 (ref)	..	NA‡‡	..

uIRR=unadjusted incidence rate ratio. aIRR=adjusted incidence rate ratio. PrEP=pre-exposure prophylaxis. NA=not applicable. *Exposure time from date of first PrEP prescription to end of study period or imputed date of HIV acquisition, assuming that people are tested each time PrEP is prescribed and every 6 months if not. †All people dispensed government-subsidised PrEP during the study period. ‡At time of first PrEP supply. §Any PrEP supply during the study period with higher (concessional) subsidy. ¶PrEP usage categorised as: single dispensed supply with no subsequent PrEP, more than one supply and less than 60% of days covered by PrEP, or more than one supply and 60% or more days covered by PrEP. Proportion of days covered calculated as the number of tablets dispensed divided by the number of days from the first PrEP prescription to the end of the study period or the imputed date of HIV acquisition. ‖Use of Australian Government data prohibits publishing numbers of less than ten individuals or that enable cross calculation of numbers of less than ten individuals. **If more than one residence or prescriber, the higher estimated prevalence of gay men and higher PrEP caseload was assigned. ††The number of patients prescribed PrEP by an individual's prescriber. ‡‡Not included in the multivariable analysis because p≥0·2 in the univariable analysis.

Table 2: **HIV incidence in people dispensed PrEP between April, 2018, and March, 2023, using Poisson regression**

1·11–2·21) were independently associated with HIV acquisition. In the multivariable analysis, later study year of first PrEP was associated with lower incidence of HIV (table 2).

In the three sensitivity analyses, the predictors and adjusted and unadjusted incident ratios were similar in magnitude and the same in direction as the main analysis, with the exception of year of first PrEP. Kaplan–Meier curves show that incidence is ongoing and are also similar across the main analysis and subanalyses (appendix pp 5, 7, 9).

Discussion

In this whole-of-population study, we found a low overall HIV incidence rate of 1·07 per 1000 person-years in people who ever received PrEP in the first 5 years of the Australian national programme. A higher incidence rate of 2·61 per 1000 person-years was observed in the 19·0% of the study population who received subsidised PrEP only once. Compared with this group, high PrEP usage (60% or more days covered) reduced HIV incidence by 78·5% and lower PrEP usage (less than 60% of days covered) by 61·6%. PrEP users who were younger, only

obtained PrEP prescriptions outside of the inner urban areas where gay communities were located, and had evidence of hepatitis C treatment were also at increased risk of acquiring HIV. To our knowledge, this is the first national whole-of-population study to quantify HIV incidence and its predictors during national PrEP scale-up and after transition away from implementation studies and clinical trials.

The overall incidence rate in PrEP users was reassuringly low at 1·07 per 1000 person-years. This compares with 3·74 per 1000 person-years in a national clinic-based cohort of men who have sex with men attending genitourinary medicine services in Scotland,[9] 1·61 per 1000 person-years in long-term follow-up in Australia's largest PrEP implementation study,[11] and 1·3 per 1000 person-years in the UK national PrEP implementation study.[12]

In 2022 in Australia, there were 107 HIV diagnoses that were classified as newly acquired (with a negative HIV test or evidence of seroconversion within 12 months of diagnosis), which was 61% lower than in 2017 when government-subsidised PrEP first became available.[5,25] This study identified 63 diagnoses in the calendar year 2022 (table 1), which we believe to have been recently acquired; this was more than half of the total notified in Australia that year.[5] To drive incidence down further, programmes must also focus on long-term persistence, adherence, and correct timing of PrEP in the large and growing numbers who have already received it.

In-depth interviews of GBM who stopped PrEP have shown that although most did so because they felt they no longer needed it, some reported subsequent risk which they had not predicted.[7,26] Our results also suggest that there are indeed groups of individuals who, despite having initiated PrEP, are not taking it correctly or at all when experiencing subsequent risk. These findings can inform support services for PrEP users at increased risk, such as active recall of those who do not return for repeat PrEP supply, recommendations and guidelines to support persistence and adherence, different models of PrEP delivery, and access to long-acting injectable PrEP formulations.

In Australia, gay communities are concentrated in urban centres, as are the large gay-friendly primary care services, gay community health promotion organisations, and publicly funded sexual health clinics which are a prominent feature of the Australian HIV response.[23,24] Large differences in PrEP discontinuation associated with prescriber PrEP caseload, prescriber location, and patient location have been observed in this same population using the same data source.[21] In this study, only prescriber location outside of areas with a high estimated prevalence of gay men was associated with higher HIV incidence. Prescriber factors, such as quality of care, accessibility, and ease of renewing prescriptions, or patient factors, such as engagement with gay community and supportive services, exposure to health promotion

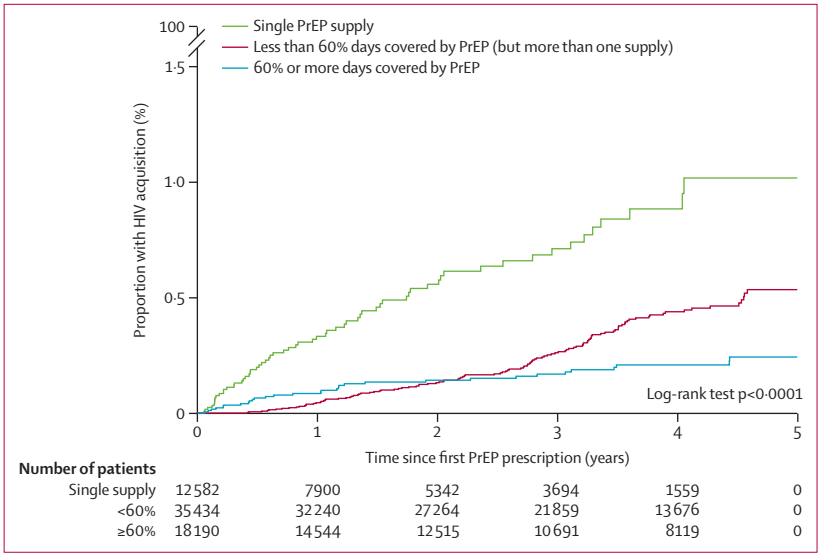

***Figure*: Kaplan–Meier graph showing HIV acquisition in people dispensed PrEP between April, 2018, and March, 2023, with a single PrEP supply, less than 60% of days covered by PrEP, or 60% or more days covered by PrEP**

PrEP=pre-exposure prophylaxis.

materials, or capacity to navigate to specialist or GBM-oriented services might explain these differences and warrant investigation.[7,21]

In Australia, sexual transmission of hepatitis C virus in GBM who take PrEP is low,[5,14,22] and HIV transmission is uncommon in people who inject drugs who are not GBM. A national anonymous biobehavioural surveillance survey among people who access needle syringe programmes shows that HIV prevalence ranged from 1·5% to 2·5% between 2018 and 2022;[27] Although not large numbers, the higher observed incidence in people who have received treatment for hepatitis C most likely reflects intersectionality of factors associated with hepatitis C and HIV risk, in particular sexualised drug use, which has been observed in Australia and elsewhere.[5,14,22]

Although not an independent predictor, incidence was higher in the 19·5% of PrEP users who received a higher concessional subsidy based on income, employment, health, disability, or yearly pharmaceutical expenditure. This highlights the need to consider contextual factors and social determinants of health when designing programmes and targeting interventions.

There are several limitations to consider when interpreting our findings. First, a general consideration for cohort studies is that all covariates might be subject to unmeasured confounding. That is, factors not accounted for in the analysis might be associated both with those covariates that were included and with the observed outcomes. Although we interpreted results cautiously, our findings need to be confirmed and replicated by other studies and study types.

Second, there is potential for misclassification of post-exposure prophylaxis, PrEP, and ART. In this study, the

risk in this study is low because, with rare exceptions, post-exposure prophylaxis was not included in the dataset as it is not funded by the Pharmaceutical Benefits Scheme; because regimens, durations of treatment, and dispensing quantities differ for each; and because we manually checked all ART prescriptions to validate and confirm our definitions.[13,14,17]

Third, dispensing data cannot determine when or whether the dispensed PrEP was taken, or distinguish daily from non-daily dosing.[21] 20% of surveyed PrEP users reported practising event-based dosing in 2021, and this proportion has continued to rise.[7] For this reason, we avoided classifications that could not be supported by the data or without clear definitions (such as discontinued or non-adherent) and used a straightforward classification based on the number of times PrEP was dispensed and the proportion of days covered. Other study designs will be required to examine the impact of changing HIV risk and PrEP use over time and distinguish between those who are no longer at risk, those successfully but infrequently taking event-based PrEP, and those who have stopped it despite ongoing risk.[21]

Fourth, our population-level dataset, although complete, does not include information about HIV testing or diagnosis, and therefore incidence is measured via record of ART initiation: some people who received a diagnosis might have initiated ART in another country or not at all. However, 95% of GBM initiate ART within 6 weeks of diagnosis in New South Wales, the Australian state with the largest number of diagnoses, and 100% within a year.[5,16]

Fifth, we made an assumption that people who had taken PrEP at some point continue to test for HIV. Although a behavioural survey of GBM in Sydney, the city with the largest number of HIV diagnoses, found that more than 99% of people who reported taking PrEP reported a test within the past year, 52% of people who said they did not take PrEP had not.[7] This same survey has previously indicated that people not taking PrEP who were at higher risk of HIV had more frequent HIV tests.[28] To explore the effect of assumptions about testing frequency on the study results further we conducted a sensitivity analysis with an assumption of a different testing frequency, which yielded very similar results to the main analysis.

Sixth, although later study year of first PrEP was independently and significantly associated with lower incidence in the main analysis, this association was not observed in the sensitivity analysis with an assumption of less frequent testing. We included this variable to minimise bias should there be a difference in baseline risk or a change in risk over time. Although assumptions about testing frequency made little difference to the main study results, this specific difference could indicate that this type of data might not be best suited to examining trends in incidence over time. This would include changes in behaviour, PrEP use, and HIV testing that occurred during the COVID-19 pandemic restrictions.[7,29]

Seventh, many or most of the more than 18 000 people enrolled in implementation studies before the national programme would have been taking PrEP from the start of the study period, and not just from the date of first government-subsidised PrEP. To explore the effect of earlier onset of risk on study results, we conducted a second and third sensitivity analysis assuming that transition to the national programme would have occurred in the first year. In the sensitivity analyses of incidence in those with first PrEP in the first year (measuring exposure from the first day of the programme) and in excluding those with first PrEP in the first year, overall incidence rates were very similar, as was the same strong association with PrEP usage category.

Eighth, these data do not contain any information about ethnicity, migration status, or gender affirmation or diversity other than recorded sex.

Finally, our data did not account for death or emigration. The Australian HIV Cascade assumed emigration of approximately 0·4% per year and a death rate of approximately 1·0% per year for people living with HIV.[5]

In conclusion, we found a low rate of HIV incidence in people who have ever been dispensed government-subsidised PrEP in Australia in this national whole-of-population study conducted after transition to a national programme. High PrEP use (60% or more of days covered) reduced HIV incidence by more than 78·5%, compared with discontinuation after a single supply. Our results suggest that certain groups would benefit from additional support to maintain PrEP use at times of risk: in particular, those who do not return for a second supply, those who obtain PrEP prescriptions outside of the inner urban areas where gay communities are located, younger people, and those at risk of hepatitis C. PrEP is highly effective in reducing population HIV incidence, but additional and tailored support to stay on PrEP could further reduce incidence as needed to achieve national and global elimination targets by 2030.

Contributors

NAM, HM, BRB, DF, MWT, AEG, MAS, and RJG all contributed to the conceptualisation and methodology. All authors contributed to the interpretation of the results and writing of the manuscript, and approved the final version. NAM and HM directly accessed and verified the source data and performed the statistical analyses. All authors had access to the summary data presented in this report. All authors had final responsibility for the decision to submit the manuscript.

Declaration of interests

NAM and RJG have received funding to their institution for investigator-initiated research unrelated to this work from Gilead Sciences. NAM and BRB have unpaid leadership and governance roles with ASHM and ACON, respectively. BRB has received funding to his institution for research unrelated to this work from ViiV Healthcare and Gilead Sciences, and payment, honoraria, or support for attending meetings from FHI 360, Gilead Sciences, Virology Education, and ViiV Healthcare. MWT has received funding to his institution for investigator-initiated research unrelated to this work and speaker's honoraria from

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Data sharing

The conditions under which the data are provided by the Australian Government prohibit sharing of the data with anyone other than named investigators.

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