Physical and mental health of long-term users of HIV preexposure prophylaxis in Australia

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Introduction: HIV preexposure prophylaxis (PrEP) is highly effective at preventing HIV. We aimed to assess mental and physical health among long-term PrEP users in Australia's X-PLORE cohort.

Methods: In early 2021, 1485 X-PLORE participants were emailed a survey covering demographics, sexual practices, ongoing PrEP use, physical and psychological diagnoses received since commencing PrEP, substance use, and impacts of the COVID-19 pandemic. Current anxiety and depression were assessed using GAD-7 and PHQ-9 questionnaires.

Results: Of 476 participants (completion rate 32.1%), 99.8% were cis-gender men. Median PrEP use duration was 48 months (2002 person-years), with 81.7% currently using PrEP. PrEP-related toxicity was uncommon: 2.9% reported bone fractures, 1.3% low bone density, and 4.0% reported kidney problems, largely not necessitating PrEP cessation. Most (92.0%) rated their health as 'good' to 'excellent', and 22.6% reported improved health since starting PrEP, often because of improved mental health. Only 6.2% reported deterioration in health since starting PrEP, largely unrelated to PrEP. The most common diagnoses were hypertension (9.9%), depression (13.2%) and anxiety (14.9%); 17% had PHQ-9 scores indicating current moderate-to-severe depression, which was associated with unemployment [adjusted odds ratio (aOR) 3.90], regular cannabis use (aOR 2.49), and having ceased PrEP (aOR 2.13).

Conclusion: Among long-term PrEP users, of which over 80% were currently using PrEP, self-reported PrEP toxicity was uncommon. With almost one in five PrEP users categorized as having depression, and with higher risk among those having ceased PrEP, we recommend routine screening for depression and anxiety in PrEP users and corresponding follow-up of patients no longer attending for PrEP.

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Introduction

Daily and on-demand HIV preexposure prophylaxis (PrEP) using co-formulated tenofovir and emtricitabine (TD*/FTC) are highly effective methods of HIV prevention for gay, bisexual and other MSM (GBMSM), with HIV risk reductions of up to 99% when users consume at least four pills per week [1,2]. High efficacy has been shown to be maintained with longer term use, with up to 3 years of follow-up [3,4]. The use of TD*/FTC for PrEP is generally safe, though it can be associated with a small risk of renal toxicity and bone mineral density loss [5,6]. The ANRS PREVENIR Study in France reported on the safety of longer term PrEP use, with a median follow-up period of 22.1 months (median PrEP use duration 9.6 months), totalling 5623 person-years, and found low incidence of significant renal impairment defined as estimated glomerular filtration rate (eGFR) less than 50 ml/min (0.25 cases per 100 person-years) or bone fracture (0.27 cases per 100 person-years), none of which were defined as fragility fractures nor considered to be treatment-related [4]. Mental health outcomes among long-term PrEP users have received little attention, and are especially pertinent when one considers higher rates of depression, anxiety and suicide among GBMSM compared with the general population [7,8]. Further, substance use and poor mental health are linked to increased risk of HIV acquisition among GBMSM not on PrEP [9–11], and are associated with reduced adherence to PrEP and PrEP discontinuation, potentially undermining PrEP effectiveness [12,13].

We aimed to comprehensively assess the health of participants in the X-PLORE cohort of long-term PrEP users in Australia. Participants were asked questions about PrEP continuation, adverse effects, general physical and mental health, substance use, and the impact of the COVID-19 pandemic.

Methods

PrEPX was a PrEP demonstration study in Australia that enrolled 5083 participants between July 2016 and April 2018. In 2018, 1485 PrEPX participants enrolled into the X-PLORE cohort, and at the time of enrolment, participants consented to receiving annual follow-up surveys. We administered an online survey of X-PLORE participants between 13 March and 31 May 2021, which additionally confirmed consent by explaining the nature of the questions in the survey and then asking participants whether they wished to participate. Survey questions asked about PrEP cessation and interruption, and focused on factors associated with ongoing PrEP use including adverse effects and toxicity that necessitated PrEP cessation, self-reported diagnoses of physical or mental health conditions, sexually transmitted infections (STIs) or viral hepatitis since commencement of PrEP, and asked about alcohol and substance use over the preceding six months.

We screened for current anxiety using the GAD-7, which is a seven-item validated tool, and a GAD-7 score of 10 or greater reliably identifies moderate-to-severe anxiety [14]. We screened for depression using the Patient Health Questionnaire (PHQ-9), which is a nine-item validated tool, and a PHQ-9 score of 10 or greater reliably identifies major depression [15].

For substance use questions, participants were asked to report their frequency of use in the previous 6 months of amphetamines, gamma-hydroxybutyrate (GHB), ketamine, amyl nitrite, cannabis, ecstasy/MDMA, cocaine, psychedelics (LSD and mushrooms), and heroin, categorized as 'never', 'once or twice', 'at least monthly', or 'every week'. Participants were also asked if they had used drugs during sex over the last 6 months, and if they had injected drugs, either 'ever' or 'over the last six months'. For questions on alcohol consumption, participants were asked how many standard drinks they consume on a typical day, and how often they consumed six or more standard drinks in one sitting (hereafter referred to as a 'binge').

Most X-PLORE participants lived in Melbourne, and for context, the reporting period encompasses COVID-19 outbreaks, where notably in Melbourne, COVID-19 restrictions included extended lockdowns. These measures were enforced through most of 2020 (from March onwards) and through the first half of 2021. As the survey was conducted during the COVID-19 pandemic, participants were asked about the effects of the COVID-19 pandemic on their life and health.

Statistical analysis

Data were summarized using means ± standard deviation (SD) or medians with inter-quartile range (IQR) for continuous variables, as appropriate. Categorical variables were described using frequency and percentage (%). Comparisons between groups were made using Student's *t* test, Mann–Whitney *U* or Kruskal–Wallis test for continuous variables and chi-squared or Fisher's exact text for categorical variables.

Variables found to be associated with depression at *P* less than 0.02 in the univariate analysis were included in a multivariable logistic regression model to identify independent predictors of this outcome.

We checked for interaction between age and living in inner metro areas, as this is a common confounder but found no interaction.

Ethics approval

The 2021 X-PLORE survey edition was approved by the Alfred Hospital Ethics Committee (Approval Nr 77/21), as part of a larger survey of attitudes to SARS-CoV2 vaccines among GBMSM.

Results

Demographics, education, and employment

The survey was commenced by 534 of 1485 (36%) X-PLORE cohort participants, of whom 477 (89.3%) completed the entire survey. One participant was diagnosed with HIV during follow-up, and was excluded from further analyses. Survey completion dates ranged from 13 March to 31 May 2021, with most ($n = 353$, 74.2%) completed between 16 March and 31 March 2021. Almost all participants (99.8%) were cis-gender GBMSM, with a median age of 42 years (IQR 35–53 years). Most ($n = 345$, 72.6%) were born in Australia. Most ($n = 335$, 72%) lived in a metropolitan setting, as opposed to regional or rural settings. Most had attained a university degree ($n = 346$, 72.7%) or trade certificate ($n = 33$, 6.9%). A small minority were unemployed ($n = 34$, 7.2%) (Table 1).

Comparison of current preexposure prophylaxis users and previous preexposure prophylaxis users

Of the 476 participants, 87 (18.3%) were no longer using PrEP at the time of survey completion. Compared with participants who continued to use PrEP, participants who had ceased PrEP had used PrEP for a shorter period in total (median 36 vs. 48 months, $P < 0.001$), were less likely to be single (32.2 vs. 60.9%, $P < 0.001$), and had fewer sexual partners in the preceding six months (median 1 vs. 8, $P < 0.001$). As described below, participants who had ceased PrEP were more likely to have high depression scores (Table 1).

Relationships, sexual partners, and preexposure prophylaxis use

Over half of participants were single ($n = 265$, 55.7%), and 40% reported living alone ($n = 186$). Participants reported a median of six sexual partners (IQR 2–15) in the preceding 6 months.

Median duration of PrEP use was 48 months (IQR 36–59), with a total of 2002 person-years of PrEP use. Most participants ($n = 389$, 81.7%) were actively using PrEP at the time of survey completion, of whom 86.1% ($n = 335$) were using daily oral PrEP, 8.5% ($n = 33$) on-demand oral PrEP, and 4.9% ($n = 19$) a combination of these methods. Two participants used a different dosing regimen for oral PrEP ('T's an S's method', which involves taking PrEP only on days of the week starting with a T or an S). Approximately half of participants ($n = 215$, 55.3%) had ever interrupted their PrEP use, of whom 91.2% ($n = 196$) reported using other HIV risk reduction strategies during these PrEP interruptions: sexual abstinence ($n = 164$, 76.3%); condoms ($n = 32$, 14.9%); negotiated safety ($n = 17$, 7.9%); U = U ($n = 8$, 3.7%); serosorting ($n = 4$, 1.9%); and strategic positioning ($n = 3$, 1.4%) (Fig. 1). 'Negotiated Safety' is an approach to HIV prevention used by some male couples to mitigate HIV risk within their relationships, using the available biomedical knowledge, such as HIV testing and condom use with external sexual partners [16].

Sexually transmitted infections and other physical health diagnoses

Most participants ($n = 338$, 71.0%) reported at least one diagnosis of chlamydia ($n = 286$), gonorrhoea ($n = 258$), and/or syphilis ($n = 133$) since PrEP commencement.

PrEP-related toxicity was infrequent: while 14 participants (2.9%) reported bone fractures, only 6 (1.3%) reported low bone density (not further specified). Nineteen participants (4.0%) reported kidney problems during PrEP use; this was not otherwise specified, but 16 of these 19 participants remained on PrEP at the time of survey completion, none of whom was using on-demand PrEP.

Two participants (0.4%) were diagnosed with hepatitis A, two participants (0.4%) were diagnosed with hepatitis B, and eight participants (1.7%) were diagnosed with hepatitis C since PrEP commencement. Other self-reported diagnoses since PrEP commencement included hypertension ($n = 47$, 9.9%), liver problems ($n = 16$, 3.4%), heart problems ($n = 11$, 2.3%), and diabetes ($n = 7$, 1.5%).

Most participants ($n = 438$, 92.0%) rated their current health as generally 'good' to 'excellent'. Among current PrEP users, most ($n = 277$, 71.2%) reported no change in health since starting PrEP, and approximately one-fifth (22.6%, $n = 88$) reported improvement in health since starting PrEP, of whom 70.5% ($n = 62$) attributed this improvement to PrEP. Participants were asked to provide free text responses to describe how PrEP had improved their health, and these responses consisted of themes describing improved mental health because of reduced anxiety around sex and HIV risk, proactive engagement with their general practitioner, and healthy lifestyle changes such as increased exercise, healthy diet, and weight loss. Few participants ($n = 24$, 6.2%) reported a deterioration in health since starting PrEP, but only three participants (0.8%) attributed this deterioration to PrEP, which they specified as gastrointestinal intolerance and more STIs.

Impact of COVID-19

Many participants ($n = 188$, 39.5%) reported being worried about acquiring SARS-CoV-2 infection, but only six participants had been diagnosed with COVID-19. Most participants ($n = 351$, 73.7%) reported that the COVID-19 pandemic had a large impact on their life. Participants with moderate-to-severe depression were more likely ($P = 0.004$) to report that COVID-19 had a large impact on their life (53.1% 'totally agree') compared with participants who had no depression (26.9% 'totally agree') (Table 2), but the impact of COVID-19 was not

Table 1. Demographics of preexposure prophylaxis users.

	Overall	Current use	Not currently using	*P* value
n	476	389	87	
Median age (IQR) (years)	42.0 (35.0–52.5)	42.0 (35.0–53.0)	42.0 (35.0–51.0)	0.62
Age categories [*n* (%)]				0.89
<30	42 (8.8%)	34 (8.7%)	8 (9.2%)	
30–39	154 (32.4%)	123 (31.6%)	31 (35.6%)	
40–49	128 (26.9%)	106 (27.2%)	22 (25.3%)	
>50	152 (31.9%)	126 (32.4%)	26 (29.9%)	
Unemployed [*n* (%)]	34 (7.2%)	25 (6.5%)	9 (10.6%)	0.19
Born in Australia [*n* (%)]	345 (72.6%)	279 (71.9%)	66 (75.9%)	0.45
Median PrEP duration (IQR) (months)	48 (36–59)	48 (42–60)	36 (15–42)	<0.001
Single [*n* (%)]	265 (55.7%)	237 (60.9%)	28 (32.2%)	<0.001
Living inner metro Melbourne [*n* (%)]	335 (72.0%)	277 (72.7%)	58 (69.0%)	0.50
Education categories [*n* (%)]				0.23
High school or less	55 (11.6%)	42 (10.8%)	13 (14.9%)	
Trade	33 (6.9%)	30 (7.7%)	3 (3.4%)	
Bachelor or higher	346 (72.7%)	283 (72.8%)	63 (72.4%)	
Missing	42 (8.8%)	34 (8.7%)	8 (9.2%)	
Lives alone [*n* (%)]	186 (39.1%)	156 (40.1%)	30 (34.5%)	0.33
Works in retail [*n* (%)]	16 (4.1%)	12 (3.8%)	4 (6.1%)	0.39
Works in healthcare and social assistance (includes aged care) [*n* (%)]	67 (17.4%)	60 (18.8%)	7 (10.6%)	0.11
Works in education and training [*n* (%)]	34 (8.8%)	29 (9.1%)	5 (7.6%)	0.70
Works in arts and recreation services [*n* (%)]	18 (4.7%)	14 (4.4%)	4 (6.1%)	0.55
Median number of sex partners in past 6 months (IQR)	5.5 (2–15)	8 (3–20)	1 (1–2)	<0.001
Median number of sex partners pre-COVID (IQR)	4 (2–6)	4 (2–8)	2 (1–3)	<0.001
Median number of sex partners post-COVID (IQR)	1 (1–2)	1 (1–3)	1 (0–1)	<0.001
Median change in number of sex partners pre-COVID to post-COVID (IQR)	2 (0–4)	2 (1–4)	1 (0–2)	<0.001
I am worried about catching COVID-19				0.78
Totally disagree	51 (10.7%)	39 (10.0%)	12 (13.8%)	
Disagree	116 (24.4%)	96 (24.7%)	20 (23.0%)	
Neutral	121 (25.4%)	99 (25.4%)	22 (25.3%)	
Agree	120 (25.2%)	101 (26.0%)	19 (21.8%)	
Totally agree	68 (14.3%)	54 (13.9%)	14 (16.1%)	
The COVID-19 pandemic has had a big impact on my life				0.24
Totally disagree	7 (1.5%)	4 (1.0%)	3 (3.4%)	
Disagree	37 (7.8%)	28 (7.2%)	9 (10.3%)	
Neutral	81 (17.0%)	69 (17.7%)	12 (13.8%)	
Agree	188 (39.5%)	158 (40.6%)	30 (34.5%)	
Totally agree	163 (34.2%)	130 (33.4%)	33 (37.9%)	
During COVID-19, did you change the way you use PrEP?[a]				
Yes, I stopped using PrEP completely (and have not restarted)	5 (1.1%)	5 (1.3%)	0 (0.0%)	
Yes, I stopped PrEP and have now restarted	133 (27.9%)	133 (34.2%)	0 (0.0%)	
Yes, I switched from daily PrEP to event-based PrEP (also known as on-demand PrEP or the 2-1-1 method)	35 (7.4%)	35 (9.0%)	0 (0.0%)	
Yes, I changed my PrEP use in other ways	11 (2.3%)	11 (2.8%)	0 (0.0%)	
No, I did not change my PrEP use.	193 (40.5%)	193 (49.6%)	0 (0.0%)	
Missing	99 (20.8%)	12 (3.1%)	87 (100.0%)	
How many times have you seen a doctor in the past 12 months? [*n* (%)]	4 (3, 6)	4 (4, 6)	4 (2, 5)	<0.001
Self-perceived health good to excellent (compared with fair to poor) [*n* (%)]	438 (92.0%)	357 (91.8%)	81 (93.1%)	0.68
Weekly alcohol binges [*n* (%)]	88 (18.6%)	76 (19.7%)	12 (13.8%)	0.20
Cannabis at least monthly [*n* (%)]	54 (11.8%)	47 (12.6%)	7 (8.4%)	0.29
Chemsex at least monthly [*n* (%)]	76 (16.2%)	66 (17.2%)	10 (11.5%)	0.19
Crystal methamphetamine at least monthly [*n* (%)]	21 (4.6%)	17 (4.5%)	4 (4.8%)	0.92

IQR, interquartile range; PrEP, preexposure prophylaxis.
[a]Asked only if current PrEP user or if Yes to ever used PrEP.

significant in multivariable analysis of depression scores. The median number of sexual partners per month dropped from four (IQR 2–6) pre-COVID-19 to one (IQR 1–2) during the COVID-19 pandemic, and correspondingly, many participants changed their PrEP use: 133 participants (27.9%) stopped using daily PrEP during COVID-19 but subsequently recommenced; 35 participants (7.4%) switched from daily to on-demand PrEP; and 5 participants (1.1%) stopped using PrEP and did not re-start.

Substance use

Eighty-eight participants (18.6%) reported binge drinking alcohol (defined as consuming at least six standard drinks in one sitting) at least weekly over the preceding 6 months. The number of participants who used the

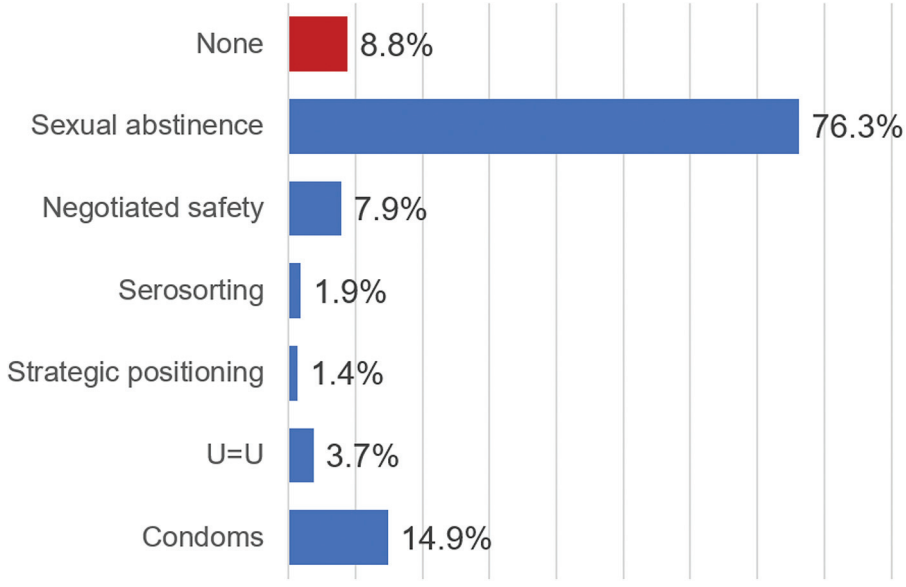

Fig. 1. HIV prevention strategies used during periods of preexposure prophylaxis interruption.

following substances at a frequency of at least once a month over the preceding 6 months was: 180 participants (37.8%) for amyl nitrite; 54 (11.8%) for cannabis; 25 (5.3%) for gamma-hydroxybutyrate (GHB); 22 (4.6%) for cocaine; 21 (4.6%) for crystal methamphetamine; 15 (4.0%) for ecstasy/MDMA; 21 (3.2%) for speed (powdered amphetamine); 12 (2.5%) for ketamine; 6 (1.3%) used psychedelics. No participants used heroin. Seventy-six participants (16.2%) used drugs during sex. The only pattern of alcohol and other substance use that showed a significant association ($P = 0.013$) with depression was the use of cannabis, where participants with moderate-to-severe depression more commonly used cannabis at least monthly (21.3% of participants) compared with participants with mild depression (9.3%) or no depression (12.2%).

Injecting drug use was infrequent, with only nine participants injecting at a frequency of at least monthly, with a further nine participants injecting at least once over the preceding 6 months.

Mental health

Mental health diagnoses made since starting PrEP included depression ($n = 63$, 13.2%) and anxiety ($n = 71$, 14.9%). Correspondingly, at the time of survey completion, 81 participants (17.0%) scored 10 or more on the PHQ-9, indicating moderate-to-severe depression, and 61 participants (12.9%) scored 10 or more on the GAD-7, indicating moderate-to-severe anxiety.

Scores on the PHQ-9 and GAD-7 were strongly correlated ($r = 0.83$), hence we describe only the associations found with PHQ-9 scores to avoid repetition (Table 2); GAD-7 scores and their associations with other factors are shown in the online supplement (Supplementary Tables 1, http://links.lww.com/QAD/D21 and 2, http://links.lww.com/QAD/D22) and are not described further here.

Among the 63 participants who reported being diagnosed with depression since PrEP commencement, ongoing symptoms of depression were common (41.3% 'moderate-to-severe'). Of the 413 participants who did not receive a formal diagnosis of depression during PrEP use, current symptoms of depression were less common (13.3% 'moderate-to-severe'), odds ratio (OR) 3.71, $P < 0.001$.

In univariate analysis, factors associated with greater likelihood and severity of depression in univariate analysis included younger age ($P < 0.001$); unemployment ($P < 0.001$); having ceased PrEP ($P = 0.017$); living outside of metropolitan areas ($P = 0.016$); and reporting that COVID-19 had a significant effect on their life ($P = 0.004$) (Table 2).

In multivariable analysis, factors associated with increased risk of moderate-to-severe depression were younger age (under 30: aOR 4.36, 95% CI 1.72–11.05), unemployment (aOR 3.90, 95% CI 1.69–8.96), monthly cannabis use (aOR 2.49, 95% CI 1.23–5.05), no longer using PrEP (aOR 2.15, 95% CI 1.18–3.92), and living outside of inner metro areas (aOR 1.80, 95% CI 1.03–3.12) (Table 3). Depression scores had a borderline association ($P = 0.07$) with impact of COVID-19 in the multivariate model. The impact of COVID-19 was also correlated with employment: those who were unemployed were more likely to report an impact from COVID-19. It is likely that adjustment for employment attenuated the effect of the impact of COVID-19 on depression.

Table 2. Summary of questionnaire responses by PHQ categories.

	Overall	None	Minimal to mild	Moderate to severe	*P* value
N	476	78	317	81	
Median age (IQR) (years)	42.0 (35.0–52.5)	46.0 (37.0–54.0)	43.0 (36.0–53.0)	38.0 (33.0–45.0)	<0.001
Age categories [*n* (%)]					0.005
<30	42 (8.8%)	3 (3.8%)	26 (8.2%)	13 (16.0%)	
30–39	154 (32.4%)	19 (24.4%)	102 (32.2%)	33 (40.7%)	
40–49	128 (26.9%)	29 (37.2%)	80 (25.2%)	19 (23.5%)	
>50	152 (31.9%)	27 (34.6%)	109 (34.4%)	16 (19.8%)	
Unemployed [*n* (%)]	34 (7.2%)	4 (5.3%)	16 (5.1%)	14 (17.3%)	<0.001
Born in Australia [*n* (%)]	345 (72.6%)	56 (71.8%)	227 (71.8%)	62 (76.5%)	0.69
Current PrEP use [*n* (%)]	389 (81.7%)	69 (88.5%)	262 (82.6%)	58 (71.6%)	0.017
Median PrEP duration (IQR) (months)	48 (36–59)	48 (38–56)	48 (37–60)	48 (36–57)	0.41
Single [*n* (%)]	265 (55.7%)	43 (55.1%)	169 (53.3%)	53 (65.4%)	0.15
Living inner metro Melbourne [*n* (%)]	335 (72.0%)	65 (83.3%)	221 (71.5%)	49 (62.8%)	0.016
Education categories [*n* (%)]					0.96
High school or less	55 (11.6%)	10 (12.8%)	35 (11.0%)	10 (12.3%)	
Trade	33 (6.9%)	6 (7.7%)	21 (6.6%)	6 (7.4%)	
Bachelor or higher	346 (72.7%)	53 (67.9%)	235 (74.1%)	58 (71.6%)	
Missing	42 (8.8%)	9 (11.5%)	26 (8.2%)	7 (8.6%)	
Lives alone [*n* (%)]	186 (39.1%)	33 (42.3%)	119 (37.5%)	34 (42.0%)	0.62
Works in retail [*n* (%)]	16 (4.1%)	1 (1.6%)	10 (3.8%)	5 (8.5%)	0.15
Works in healthcare and social assistance [*n* (%)]	67 (17.4%)	16 (26.2%)	41 (15.4%)	10 (16.9%)	0.13
Works in education and training [*n* (%)]	34 (8.8%)	6 (9.8%)	25 (9.4%)	3 (5.1%)	0.54
Works in arts and recreation services [*n* (%)]	18 (4.7%)	1 (1.6%)	14 (5.3%)	3 (5.1%)	0.47
Median # sex partners in past 6 months (IQR)	5.5 (2–15)	6 (3–15)	5 (2–15)	5 (1–15)	0.49
Median number of sex partners pre-COVID (IQR)	4 (2–6)	4 (2–6)	4 (2–6)	4 (2–8)	0.93
Median number of sex partners post-COVID (IQR)	1 (1–2)	1 (1–3)	1 (1–2)	1 (0–3)	0.29
Median change in number of sex partners pre to post-COVID (IQR)	2 (0–4)	2 (0–4)	2 (1–4)	2 (0–5)	0.49
I am worried about catching COVID-19					0.17
Totally disagree	51 (10.7%)	11 (14.1%)	29 (9.1%)	11 (13.6%)	
Disagree	116 (24.4%)	20 (25.6%)	83 (26.2%)	13 (16.0%)	
Neutral	121 (25.4%)	19 (24.4%)	83 (26.2%)	19 (23.5%)	
Agree	120 (25.2%)	22 (28.2%)	78 (24.6%)	20 (24.7%)	
Totally agree	68 (14.3%)	6 (7.7%)	44 (13.9%)	18 (22.2%)	
The COVID-19 pandemic has had a big impact on my life					0.004
Totally disagree	7 (1.5%)	1 (1.3%)	6 (1.9%)	0 (0.0%)	
Disagree	37 (7.8%)	7 (9.0%)	27 (8.5%)	3 (3.7%)	
Neutral	81 (17.0%)	21 (26.9%)	50 (15.8%)	10 (12.3%)	
Agree	188 (39.5%)	28 (35.9%)	135 (42.6%)	25 (30.9%)	
Totally agree	163 (34.2%)	21 (26.9%)	99 (31.2%)	43 (53.1%)	
During COVID-19, did you change the way you use PrEP?[a]					0.87
Yes, I stopped using PrEP completely (and have not restarted)	5 (1.1%)	0 (0.0%)	4 (1.3%)	1 (1.2%)	
Yes, I stopped PrEP and have now restarted	133 (27.9%)	20 (25.6%)	94 (29.7%)	19 (23.5%)	
Yes, I switched from daily PrEP to on-demand PrEP	35 (7.4%)	7 (9.0%)	23 (7.3%)	5 (6.2%)	
Yes, I changed my PrEP use in other ways	11 (2.3%)	3 (3.8%)	7 (2.2%)	1 (1.2%)	
No, I did not change my PrEP use.	193 (40.5%)	39 (50.0%)	123 (38.8%)	31 (38.3%)	
Missing	99 (20.8%)	9 (11.5%)	66 (20.8%)	24 (29.6%)	
How many times have you seen a doctor in the past 12 months? [*n* (%)]	4 (3–6)	4 (4–6)	4 (3–6)	4 (3–6)	0.91
Self-perceived health good to excellent (compared with fair to poor) [*n* (%)]	438 (92.0%)	77 (98.7%)	297 (93.7%)	64 (79.0%)	<0.001
Weekly alcohol binges [*n* (%)]	88 (18.6%)	10 (12.8%)	60 (19.2%)	18 (22.2%)	0.29
Cannabis at least monthly [*n* (%)]	54 (11.8%)	9 (12.2%)	28 (9.3%)	17 (21.3%)	0.013
Chemsex at least monthly [*n* (%)]	76 (16.2%)	13 (16.9%)	48 (15.4%)	15 (18.5%)	0.78
Crystal methamphetamine at least monthly [*n* (%)]	21 (4.6%)	4 (5.3%)	13 (4.3%)	4 (5.0%)	0.91

IQR, interquartile range; PrEP, preexposure prophylaxis.
[a]Asked only if current PrEP user or if Yes to ever used PrEP.

Discussion

After a median duration of 4 years since starting PrEP, over 80% of PrEP initiators were still using PrEP, and those who interrupted their PrEP use did so mainly while practising sexual abstinence during COVID-19 restrictions. The vast majority were satisfied with their general health, and one quarter reported an improvement in general health since starting PrEP, often attributed to active engagement with healthcare, and reduced HIV anxiety. Self-reported fractures, osteopenia, and renal disease were very uncommon. The most frequent self-reported physical comorbidity was hypertension (10%), and 71% reported diagnoses of bacterial STIs during

Table 3. Multivariate model of associations with moderate-to-severe depression (PHQ-9 score of 10 or more) compared with participants with none-to-mild depression (PHQ-9 of 9 or less).

Risk factor	Adjusted odds ratio (95% CI)	*P* value
Age (years)		
50+	Reference	
40–49	1.91 (0.86–4.10)	0.099
30–39	2.99 (1.46–6.12)	0.003
<30	4.36 (1.72–11.05)	0.002
Unemployed	3.90 (1.69–8.96)	0.001
Not in inner metro area	1.80 (1.03–3.12)	0.038
Not currently using PrEP	2.15 (1.18–3.92)	0.013
Using cannabis at least monthly	2.49 (1.23–5.05)	0.011

CI, confidence interval; PrEP, preexposure prophylaxis.

PrEP use, which compares to our previously reported figure of 48% of participants in PrEPX [17]. However, a considerable proportion of respondents had PHQ-9 and GAD-7 scores indicating the presence of major depression and/or generalized anxiety disorder, respectively, and those with a known diagnosis of major depression and/or anxiety were more likely to report ongoing symptoms of depression and/or anxiety.

The main factors associated with depression were being younger, living outside of metropolitan locations, being unemployed, smoking cannabis at least monthly, and no longer using PrEP. The associations of depression with younger age, unemployment, and regular cannabis consumption have been broadly demonstrated [18–20]. GBMSM in regional or rural Australia were more likely than their metropolitan-based counterparts to have symptoms of depression, which may relate to GBMSM living in regional or rural Australia often reporting greater levels of stigma compared with their urban counterparts [21,22], and this stigma contributing to poorer mental health [23].

GBMSM who had ceased PrEP were more likely to experience symptoms of depression and anxiety. We were unable to identify the direction of causality in this relationship. It is plausible that some GBMSM may have ceased PrEP because they had stopped having sex, which could be a marker of social isolation, which is a risk factor for poor mental health [11]. Conversely, GBMSM with depression and/or anxiety are more likely to cease activities of self-care, including PrEP use [12,13]. A third possibility is that participants who ceased PrEP may have experienced a re-emergence of HIV anxiety, as PrEP use is associated with reduced HIV anxiety [24]. Whatever the mechanism, our findings indicate that cessation of PrEP use may be a marker of deteriorating mental health for some GBMSM, and hence PrEP clinicians should actively follow-up PrEP users who have not returned.

Most participants reported that COVID-19 had a large impact on their lives, and this was particularly pronounced for participants with higher depression scores. However, the impact of COVID-19 was not significant in multivariable analysis of depression scores. These findings reflect previous reports: The Australian Flux Study, which is an online cohort study of Australian GBMSM, found that for almost one-quarter of participants, levels of depression increased significantly between measures taken before and then during COVID-19, and such increases were associated with reduction in social and sexual connections and opportunities, and with being concerned about COVID-19 [25]. Similar themes emerged from a qualitative survey of 489 Australian GBMSM conducted in April 2020, early in the COVID-19 epidemic [26].

Limitations

Several limitations to our study need to be considered. Firstly, X-PLORE participants who had discontinued PrEP may have been less inclined to complete this annual survey, hence we may not be able to generalize the high PrEP continuation rate to the entire X-PLORE cohort. Secondly, we have no further data on the nature or severity of reported renal problems, however, most participants who reported renal problems had not ceased PrEP use, and hence it may be reasonable to assume that these renal problems were mild and/or transient as they had not necessitated cessation of PrEP use. Thirdly, other than mental health outcomes, which we measured with PHQ-9 and GAD-7 tools, the other health outcomes were self-reported and may be less accurate than clinician-recorded outcomes. Fourthly, we did not ask about income, which may be protective against depression and anxiety, but we did ask about education and employment. Finally, this was a cross-sectional survey with a relatively small sample, and hence our findings may not be generalizable to all Australian PrEP users.

In conclusion, cohort participants reported using PrEP effectively and safely after a median follow-up of 4 years, which is especially important as oral PrEP using TD*FTC is the most commonly available form of PrEP globally, because of the high cost of alternative PrEP modalities.

A high proportion of participants reported depression and anxiety, findings that were mirrored in participants' GAD-7 and PHQ-9 results. Although the COVID-19 pandemic is likely to have influenced survey responses, the

pandemic and its impact on social wellbeing is ongoing. Hence, we argue that mental health screening should become a routine part of PrEP care. As a corollary, we highlight the need to actively follow-up PrEP users who have ceased PrEP, because they had higher rates of depression than continuing PrEP users in this cohort, and depression may have contributed to their PrEP discontinuation.

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Conflicts of interest

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