



High Adherence to HIV Pre-exposure Prophylaxis and No HIV Seroconversions Despite High Levels of Risk Behaviour and STIs: The Australian Demonstration Study PrELUDE

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Published online: 4 October 2018
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Abstract

PrELUDE study evaluated daily pre-exposure prophylaxis (PrEP) in high-risk individuals in Australia. This open-label, single-arm study tested participants for HIV/STI and collected behavioural information three-monthly. We report trends over 18 months in medication adherence, side-effects, HIV/STI incidence and behaviour. 320 gay/bisexual men (GBM), 4 women and 3 transgender participants, followed on average 461 days, reported taking seven pills/week on 1,591 (88.5%) occasions and 4-6 pills/week on 153 (8.5%) occasions. No HIV infections were observed. STI incidence was high and stable, while gonorrhoea infections declined from 100.0 to 25.8/100 person-years between 6 and 15 months ($p < 0.001$). The number of HIV-positive and unknown-status sex partners, and condomless anal intercourse, significantly increased. In this high-risk cohort of mainly GBM, increases in risk behaviours and high STI incidence were not accompanied by HIV infections due to high adherence to daily PrEP. The study informed policy and further PrEP implementation among Australian GBM.

Keywords Gay and bisexual men · HIV prevention · Pre-exposure prophylaxis · Sexually transmitted infections · HIV/STI incidence · Side-effects · Behaviour

Introduction

In Australia and many other high-income settings, condomless anal intercourse (CLAI) and HIV diagnoses have increased among men who have sex with men (MSM) since the late 1990s [1, 2]. In New South Wales (NSW),

Australia's most populous state, widespread promotion and use of available HIV prevention interventions had little impact on the rate of new HIV infections before HIV pre-exposure preexposure prophylaxis (PrEP) was introduced [3].

The effectiveness of the daily oral antiretroviral combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) as HIV PrEP has been well documented [4].

A list of the PrELUDE study group is given in Acknowledgements section.

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Nonetheless, inadequate medication adherence may pose a major challenge for PrEP implementation [5]. Before results of the PROUD and IPERGAY trials were published [6, 7], the issue of whether PrEP was a feasible strategy to implement, still required investigation. The World Health Organisation (WHO) encouraged countries to undertake demonstration projects to facilitate the understanding of PrEP safety, effectiveness and sustainable use alongside existing HIV prevention efforts in their at-risk communities [8].

Through its “HIV prevention strategy 2012–2015: a New era”, the NSW Ministry of Health committed to implement PrEP [9] and supported a pilot PrEP demonstration project, which commenced in 2014. By that time, TDF/FTC was already approved by the Federal Drug Administration for PrEP use in the US [10], but not by the Australian Therapeutic Goods Administration for PrEP indication in Australia (which happened later, in May 2016 [11]). Therefore, PrELUDE was designed to evaluate the off-label provision of daily TDF/FTC as PrEP to HIV-negative individuals at high risk for HIV infection. The study aimed to assess the feasibility of PrEP delivery in public and private health care settings, and to evaluate factors associated with longer-term PrEP use, such as adherence to PrEP, its side-effects and behaviour on PrEP. The project was set-up to record HIV and STI infections among participants. It was also expected to develop behavioural eligibility criteria for the provision of PrEP and inform policy development regarding PrEP implementation. Here we report the PrELUDE study key outcomes related to the assessment of feasibility of PrEP delivery in NSW and factors that may influence PrEP implementation, such as adherence to PrEP, its safety, behaviour, and STI diagnoses among PrEP users.

Methods

Study Design

The PrELUDE protocol has been described previously [12]. Briefly, it was a prospective, open-label, single-arm, multi-centre study. Eight clinics in Sydney, Australia, including public and private practices, participated in the study. Prospective participants were first assessed for their behavioural risk of HIV acquisition.

The target population reflected the epidemiology of HIV in NSW and included predominantly gay and bisexually-identified MSM at high risk of sexual exposure to HIV, but transgender people and HIV-negative heterosexual women planning natural conception with their HIV-positive partners were also eligible to participate. Behavioural eligibility criteria were developed from local evidence about high HIV incidence [13]. MSM were eligible to participate if they acknowledged an ongoing nature of their risk exposure and

reported at least one of the four risk factors: (a) being a regular partner of an HIV-positive man, (b) having condomless anal intercourse (CLAI) with casual partners, (c) reporting a recent anal STI diagnosis, or (d) methamphetamine use [12]. Those who were found eligible based on behavioural eligibility criteria, were asked about their medical history, tested for HIV, sexually transmissible infections (STIs), and pregnancy (where applicable). Eligible to participate were individuals aged 18 years or older, who satisfied behavioural eligibility criteria, were HIV negative at enrolment (documented by a negative HIV test less than 7 days prior to initiating PrEP), lived or visited NSW with sufficient frequency for participation, were Medicare-eligible and proficient in written and spoken English (to be able to complete all study procedures).

All participants were prescribed daily TDF/FTC as PrEP [12]. At 1 and 3 months and then three-monthly, participants were assessed for ongoing PrEP eligibility and willingness to continue taking PrEP, tested for HIV, STIs, renal and liver function, and were assessed for adverse events and PrEP adherence (self-report) [12]. Following each study visit, all patients were invited to complete online surveys about attitudes, behaviours and adherence to PrEP.

The study was designed for an arbitrary sample of 300 participants followed for 12 months, and the follow-up period was subsequently extended to 30 months. In 2016, the NSW Ministry of Health established an Expanded PrEP Implementation in Communities in NSW (EPIC-NSW) program and all remaining PrELUDE participants ($n = 243$) were transferred to EPIC-NSW.

Participants and Measures

Participants were enrolled at eight clinics with large numbers of patients at high risk for HIV acquisition [12]. Prospective participants were identified among the established clientele of the clinics (based on information available to the clinics, including previously reported high-risk behaviour, use of post-exposure prophylaxis (PEP), or recent diagnosis of a rectal STI or syphilis), and were on a waiting list for PrEP at the time PrELUDE started, regardless of their previous history of PrEP use. Some individuals were also referred through the study website, by community organisations, by other health providers or self-referred. Enrolling participants completed a written, informed consent for all study procedures.

Electronic data capture and management system OpenClinica (OpenClinica, LLC, developed by Isovera, Inc.) was used to gather information from clinical assessments, including all results of HIV, STI, renal and liver function tests, safety events, and information about PrEP use and adherence to the study medication. Online surveys were designed using SurveyGizmo (Boulder, Colorado, USA) and collected

information on sociodemographic factors, sexual behaviour (number and type of partners and sexual practices) and pill-taking in the preceding follow-up period, as well as attitudes to PrEP and HIV prevention.

Data Analyses

Here we report the indicators of:

- (1) Study retention at Month 6 and Month 12 of follow-up.
- (2) Adherence to the study medication measured by the number of pills taken per week (measured by facilitated report to clinicians) and medication possession ratio (MPR) in the first 12 months: $MPR (\%) = [\text{number of pills dispensed between baseline and Month 9 visit (or visit preceding last follow-up if a participant did not reach Month 12 visit)}] / (\text{number of days under follow-up between baseline and Month 12 visit}) \times 100\%$.
- (3) *Safety and side effects*, specifically the incidence of HIV seroconversions among study participants, serious adverse events (SAEs) and any drug-related adverse events among the participants during the course of their follow-up. SAE was defined as any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. AEs were graded for severity using the DAIDS AE Grading Table, Version 1.0, December 2004 with clarification dated August 2009, and the DAIDS Addendum 2—Male Genital Grading Table [14].
- (4) *Behavioural effects of PrEP use*, specifically the self-reported types and numbers of the participants' partners (by HIV status of partners), frequency of condomless anal intercourse.
- (5) *STI infections* were assessed using the standard of care tests [14]. We report the incidence of three infections caused by: *Neisseria gonorrhoeae* (gonorrhoea, any location), *Chlamydia trachomatis* (chlamydia, any location) and infectious *Treponema pallidum* (infectious syphilis). Analyses of behaviour and STIs excluded women because of their small number ($n=4$) and very different patterns of behaviour.

Demographic information obtained from surveys was analysed using descriptive statistics. Behavioural data were analysed using longitudinal analytical methods. Analyses of time-to-event data were conducted using survival analysis. When presenting the results of follow-up time, events of HIV/STI diagnoses and safety events, we used Kaplan–Meier curves, incidence (hazard) rates and the Wald statistic from Cox regression for assessment of trends over time, as appropriate. Statistical analyses of trends in sexual

practices and adherence to the study medication were conducted using longitudinal regression methods for continuous and binary outcomes and time-varying exposures.

Analyses were conducted in STATA Version 14.0 (Stata-Corp, College Station, TX, USA).

Results

Study Participants and Follow-Up

Between 13 November 2014 and 13 April 2016, the study screened 363 and enrolled 327 participants (Fig. 1) whose baseline characteristics are presented in Table 1. The median age was 35 years (IQR 29–43). Most participants ($n=235$, 71.9%) reported being of European origin. Of 113 overseas-born participants, 22 (19.5%) arrived to Australia within the last 5 years. This sample included predominantly MSM, as well as four women and three transgender individuals. At the time of enrolment, most (255, 78.0%) were employed full- or part-time, and almost two thirds (65.6%) had attained a University degree. This was a predominantly urban sample, as the majority of participants lived in Sydney's densely populated gay areas (89, 28.4%) or Metropolitan Sydney (219, 67.0%).

The median study follow-up time was 461 days (IQR 406–532 days) and cumulative follow-up was 144,581 days (395.8 years). Overall, participants attended a total of 2487 study visits. Retention was 92.0% at Month 6 and 81.0% at Month 12.

PrEP Adherence and Early Discontinuations

At baseline, male and transgender participants reported on how long they were willing to take PrEP continuously, and the majority (269, 82.3%) stated at least 12 months, 22 (6.7%)—6 to 12 months, and 23 (7.0%)—less than 6 months, while nine participants did not provide any information. However, all 45 participants who reported a willingness to stay on PrEP for less than 12 months ended up taking PrEP for more than 12 months.

Overall, 84 participants (25.7%) stopped taking PrEP early. Among self-reported reasons for stopping PrEP, the most common were: a participant's own decision to stop PrEP ($n=18$, 5.5%, no trend over time: $z=1.09$, $p\text{-trend}=0.275$) or no longer being at high HIV risk ($n=16$, 4.9%, no trend over time, $z=1.80$, $p\text{-trend}=0.072$). Other reasons included: adverse events ($n=8$, see section Adverse events for more details); moving away, overseas or to another Australian jurisdiction ($n=4$); pregnancy ($n=3$); "relationship issues" ($n=2$); being unable to maintain daily PrEP adherence ($n=2$), and switching to PEP ($n=1$), while 30 participants (9.2%)

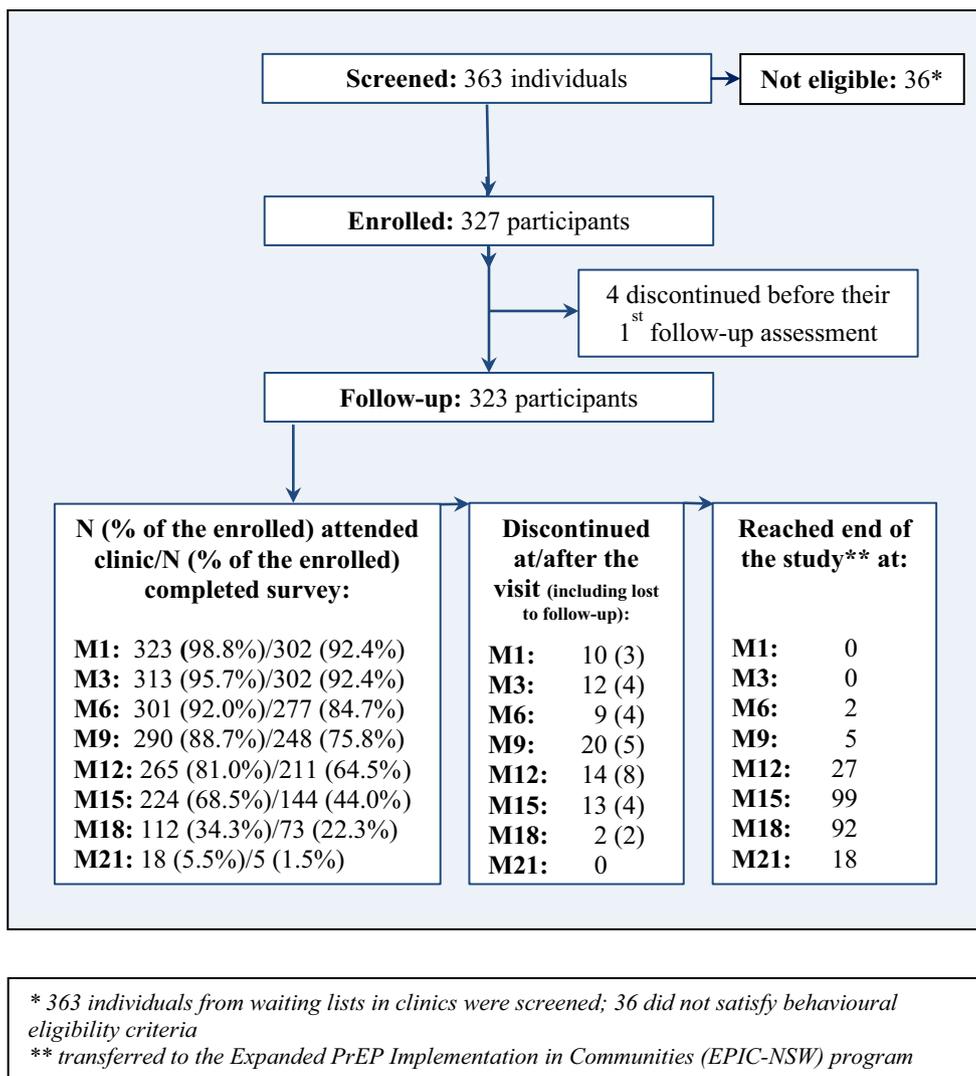


Fig. 1 Study flowchart

were lost to follow-up. As to the medication adherence, information about pill taking was available from 1798 (97.6%) out of 1843 scheduled follow-up visits. Participants reported taking all 7 pills/week on 1591 (88.5%) of 1798 follow-up visits, 4–6 pills/week on 153 (8.5%) visits and 0–3 pills/week on 54 (3.0%) visits. During the first 9 months of follow-up, the proportion of non-missing records when 7 pill/week were reported declined from 90.0% at Month 1 to 86.3% at Month 9, and the proportion when 0 pill/week were reported increased from 0.6 to 3.9% respectively, but these changes were not statistically significant (see Fig. 2).

As to the medication possession, only 9 individuals (2.8% of the sample) had MPR < 80%, 17 (5.3%) had MPR of 80 to 89% and 297 (91.9%) had MPR of 90% or more while being under follow-up.

Adverse Events

During follow-up, 243 participants (74.3%) reported at least one adverse event and 131 participants experienced multiple adverse events (median = 2, range = 2–12)—a total of 861 events. However, only 203 (23.6%) of all events reported by 120 individuals (36.7% of all participants) were categorised as related to the study medication (median = 1, IQR 1–8), and all of them were classified as Grade 1 (mild, n = 173) or Grade 2 (moderate, n = 30).

The most common events classified as drug-related (see Table 2) were diarrhoea (43, 12.2%), nausea (27, 8.3%) and fatigue (25, 7.6%). Abnormal renal and liver function tests were recorded in 7 (2.1%) and 14 (4.3%) of the participants, respectively. A total of 38 (18.7%) of the drug-related events were judged as not expected on the study drug, of which

Table 1 Socio-demographic characteristics of the study sample

Characteristic	N	%
Total	327	100%
Age: median and IQR	35	29–43
Age		
< 30	91	27.8%
30 to < 40	119	36.4%
40 to < 50	91	27.8%
≥ 50	26	8.0%
Ethnic background		
European	235	71.9%
Arab, Middle Eastern or Northern African	10	3.1%
Asian or Pacific Islander	38	11.6%
North or South American	20	6.1%
South or East African	4	1.2%
Missing	20	6.1%
Country of birth		
Australia	205	62.7%
New Zealand	12	3.7%
UK	21	6.4%
Elsewhere ^a	80	24.5%
Missing	9	2.8%
Arrived to Australia in the last 5 years ^b (n = 113)	22	19.5%
Employment		
Full or part-time	255	78.0%
Student	16	4.9%
Unemployed	26	8.0%
Other	22	6.7%
Missing	8	2.5%
Education		
Did not complete high school	16	4.9%
High school or TAFE	93	28.4%
Undergraduate University or higher	208	63.6%
Missing	10	3.1%
Place of residence ^c		
Densely populated gay areas ^d	89	27.2%
Metropolitan Sydney	219	67.0%
Regional/rural NSW	5	1.5%
Missing	14	4.3%
Gender		
Male	320	97.9%
Female	4	1.2%
Trans, male-to-female	1	0.3%
Trans, female-to-male	2	0.6%
Sexual self-identification		
Gay	290	88.7%
Bisexual	17	5.2%
Other	9	2.8%
Missing	11	3.4%

IQR interquartile range, TAFE technical and further education

^a32 other countries

^bParticipants who were born overseas

^cBased on postcode

^dDensely populated gay areas are four central Sydney postcodes with historically high proportion of males identifying as gay

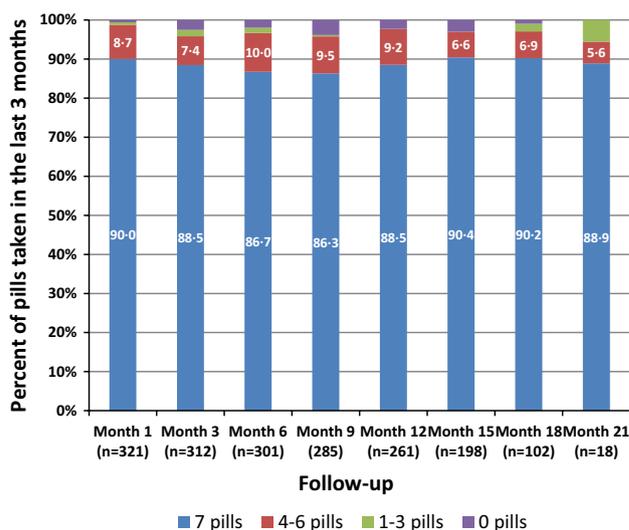


Fig. 2 Proportion of pills taken in the last 3 months (self-report to clinicians), by follow-up visit, among participants presenting for clinical follow-up. This figure includes only participants who presented for their follow-up visits

31 and 7 were Grade 1 and 2 events (mild and moderate, respectively).

Three individuals discontinued PrEP due to drug-related renal events (1 Grade 1 and 2 Grade 2 events), all three during their first month on PrEP, while other patients with abnormal liver or renal tests were able to continue on PrEP. There were also five patients who discontinued PrEP due to unrelated adverse events.

Figure 3 presents the probability of developing an adverse event while on PrEP and shows that most side effects occurred early. They were also short in duration (median = 11 days, IQR 6–48 days). The vast majority (92.7%) of drug-related events developed in the first 6 months (73.8% in the first month). About 68.4% of abnormal liver tests were recorded between Month 1 and 6, but 66.6% of abnormal renal tests were recorded between Months 6 and 12.

HIV Incidence

There were no HIV diagnoses recorded among the study participants during the follow-up time. HIV incidence was 0 [95% Confidence Interval 0–0.93 per 100 person-years (/100 PY)].

Sexually Transmitted Infections

At baseline STI screening, three of 323 men and transgender individuals were diagnosed with infectious syphilis (prevalence 0.9%, 95% CI 1.9–2.7%) and 20 with past infection (6.2%, 95% CI 3.8–9.4%); 34 were diagnosed with

Table 2 Drug-related adverse events

Diagnosis	Number of potentially drug-related adverse events	N (%) of participants reporting potentially drug-related adverse events
Total	203	120 (36.7%)
GI		
Abdominal discomfort	20	19 (0.8%)
Diarrhoea	43	40 (12.2%)
Nausea	27	27 (8.3%)
Subtotal	90	75 (22.9%)
Renal		
Decreased eGFR ^a	6	5 (1.5%)
Renal other	3	2 (0.6%)
Subtotal	9	7 (2.1%)
Hepatic		
Elevated LFTs ^b	16	14 (4.3%)
Subtotal	16	14 (4.3%)
Bone		
Decreased BMD ^c	2	2*
Subtotal	2	2 (0.6%)
Other		
Fatigue/lethargy/feeling sedated	25	25 (7.6%)
Headache	14	13 (4.0%)
Dizziness	6	6 (1.8%)
Insomnia/vivid dreams/nightmares	14	14 (4.3%)
Mood/depression	1	1 (0.3%)
Skin problems (rashes, dryness, etc.)	5	5 (1.5%)
Reduced libido	4	4 (1.2%)
Decreased concentration/forgetfulness	4	4 (1.2%)
Skeletomuscular pains/stiffness	4	4 (1.2%)
Loss of appetite/weight-loss	4	4 (1.2%)
Other	5	4 (1.2%)
Subtotal	86	60 (18.3%)

eGFR—estimated glomerular filtration rate. Normal renal function was defined as eGFR \geq 60 mL/min

Including elevated alanine aminotransferase (ALT) test results. Normal ALT test result was defined by the reference laboratory as $<$ 45 U/L

*Only one study clinic conducted bone densitometry (DXA) of spine and hips at 0 and 12 months on TDF. BMD loss was defined as $>$ 1% loss of BMD at any site over 1 year

chlamydia (10.5%, 95% CI 7.4–14.4%), including 23 anorectal, six urethral and eight pharyngeal infections, and 19 men and transgender participants were diagnosed with gonorrhoea (5.9%, 95% CI 3.6–9.0%), including nine anorectal, one urethral and 11 pharyngeal infections.

During follow-up, 186 participants (57.6%) were diagnosed with at least one of the above three STIs. Infectious syphilis was diagnosed and treated in 28 individuals (8.7% of men and transgender participants), and six of these 28 (21.4%) had syphilis reinfection. There were 149 incident cases of gonorrhoea among 118 individuals (46.1% of men and transgender participants), including 40 (12.4%) who were diagnosed with gonorrhoea on 2–4 occasions. There were also 167 incident cases of chlamydia in 140 individuals

(43.3%), including 51 (15.8%) male/transgender participants diagnosed with chlamydia on 2–4 occasions). Eight of 23 (24.2%) diagnoses of incident syphilis, 23 of 167 (13.8%) diagnoses of incident chlamydia and 23 of 149 (15.4%) diagnoses of incident gonorrhoea were diagnosed during unscheduled visits.

The incidence of chlamydia (Fig. 4) was 82.6/100 PY (95% CI 65.0–105.0/100 PY) in the first 3 months on PrEP, with no statistically significant change over the study period. The incidence of gonorrhoea was 75.2/100 PY in the first 3 months; it increased non-significantly to 100.0/100 PY by 6 months, then declined significantly to 25.8/100 PY at 15 months of follow-up (Wald $\chi^2 = 22.32$, $p < 0.001$). The incidence of infectious syphilis was 7.4/100 PY in the first

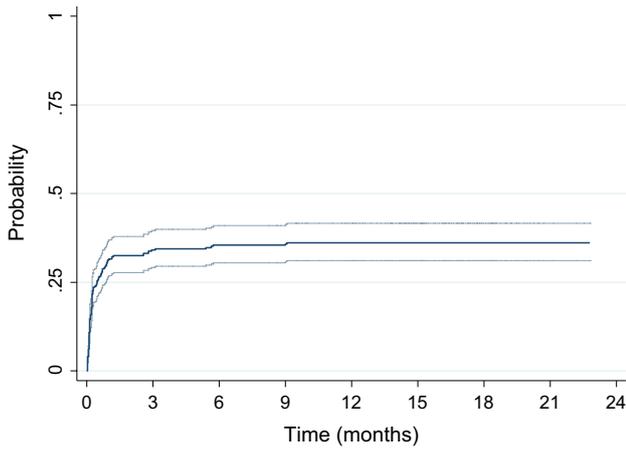


Fig. 3 Cumulative probability of developing an adverse event while on PrEP, with 95% confidence limits

3 months, and increased non-significantly to 13.8/100 PY at 15 months of follow-up.

Sexual Practices

With Main Regular Partners

Among the 323 men and transgender individuals, 126 (39.0%) reported having a main regular partner at baseline. Of these, 42 (33.3%) reported that their partner was HIV-positive, with undetectable viral load in 89.0% of cases. There was no significant change over time in the proportion of respondents with regular partners. About one-third (31.5%) reported having CLAI with these regular partners, and this did not change over time.

With Other Regular Sex Partners

At baseline, 238 of 323 male/transgender respondents (72.8%) reported having other regular sex partners (no change over time). In the preceding 3 months, the mean (SD) number of other regular partners whose HIV status was positive, negative or unknown, was 3.3 (4.3), 8.5 (15.1) and 9.9 (17.3), respectively. Overall, the mean number of such HIV-negative or unknown status partners did not change over time, while there was a significant increase in the mean number of HIV-positive partners (Wald $z=2.53$, $p=0.011$). At enrolment, 23.8, 58.1 and 41.3% of respondents reported having had CLAI in the preceding 3 months with other regular partners of HIV-positive, negative and unknown HIV status, respectively. At Month 3, these proportions were lower (18.2, 33.8 and 22.6%, respectively). Subsequently, the levels of CLAI increased again with HIV-positive and negative other regular sex partners (p -trend: 0.007 and 0.008, respectively), but not with those of unknown HIV status.

With Casual Partners

At baseline, 287 (88.9%) of male/transgender respondents reported the numbers of casual sex partners over previous 3 months: the means (SD) of HIV-positive, negative and unknown-serostatus casual partners were 3.9 (5.4), 11.2 (23.1) and 12.2 (16.8), respectively. The mean number of HIV-positive casual partners increased over time (Wald $z=13.41$, $p<0.001$), while the mean number of HIV-negative or unknown status casual partners did not change. At baseline, 79.2, 78.9 and 78.9% of the male/transgender participants who had HIV-positive, negative and unknown serostatus casual partners reported having had CLAI with these partners in the previous 3 months. These proportions

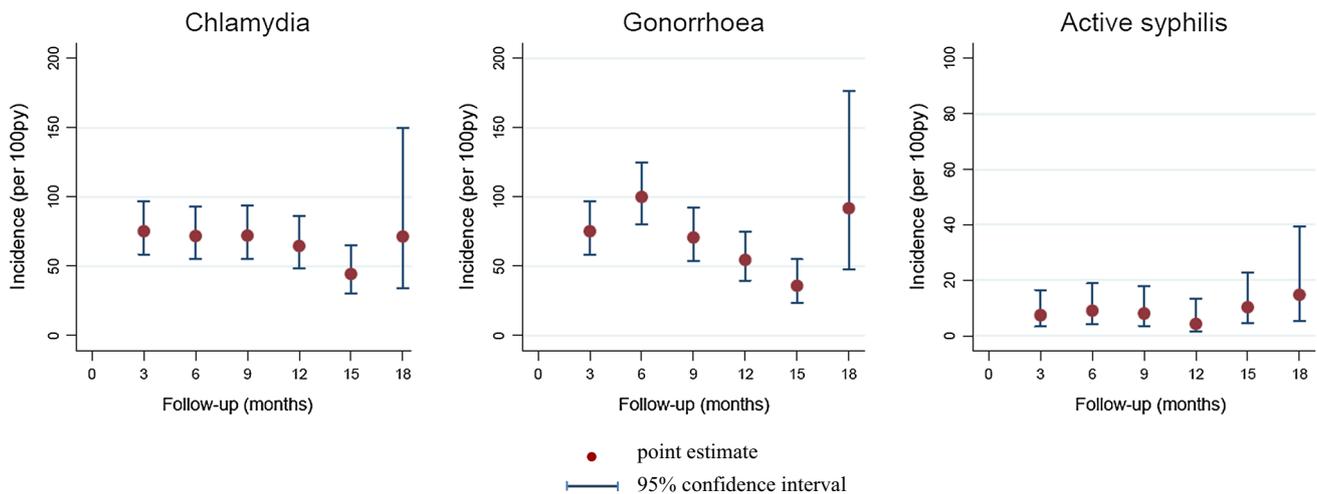


Fig. 4 Incidence/100 PY of gonorrhoea, chlamydia and syphilis infections among 323 participants in the PrELUDE study

significantly increased over time, regardless of the HIV status of casual partners (Fig. 5).

Discussion

The PrELUDE findings confirmed that PrEP implementation among MSM in Australia was very feasible. Enrolment and retention of men on PrEP was high, as was adherence to the medication. MSM and transgender individuals, who took PrEP through the PrELUDE study, were at high risk of acquiring HIV at baseline, and risk behaviour significantly increased over 18 months of follow-up (particularly, the number of HIV-positive partners and practice of CLAI). However, there were no HIV infections recorded during the follow-up. Adverse events related to PrEP had an early onset but were mild and transient. STI incidence was very high and changed little over the study period; infections of gonorrhoea increased, though insignificantly, in the first six months, followed by a significant decline.

Retention and adherence to PrEP remain key issues in PrEP implementation. In our study, the retention rates at 6 and 12 months were high—92.0 and 81.2%, respectively. Among those still under follow-up at 12 months, the MPR was also very high: only 2.8% had MPR < 80% while 91.9% had MPR of at least 90%. In our study, the retention of participants was higher than in the US multi-city Demo Project cohort (2012–2014) [15], in other demonstration and implementation studies [16, 17] and in the routine clinical practice cohort (e.g., Howard Brown Health patients (2012–2017) [18]). A likely explanation is that, because these participants were some of the first men on PrEP in Australia, they had been on waiting lists for some time and were very motivated to get access to it.

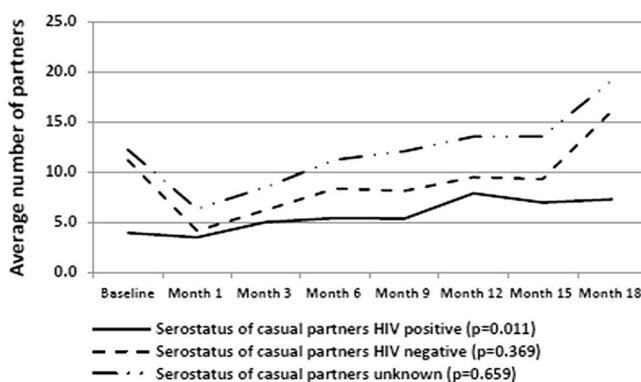
Our findings are in agreement with previous reports that most attracted to PrEP and motivated to use it are people

at highest risk of HIV infection [19]. Due to this motivation, they are most likely to use PrEP appropriately [20, 21]. Our PrEP dispensing data show similar medication possession levels as in the PROUD study (2014–2015) [6]. Following the release of the results from two landmark studies, IPERGAY (France and Canada) and PROUD (the UK), which both reported 86% efficacy of PrEP among very high-risk MSM [6, 7], concerns that high and ongoing levels of PrEP adherence were unachievable were alleviated [24]. Clinicians' confidence in prescribing PrEP has increased, and so has adherence to PrEP among MSM [17, 22, 23, 25]. Indeed, this adherence to the medication among high-risk MSM has swayed the roll-out of PrEP in the US [26] and France [27], and also in Australia [28].

The zero HIV infections in the PrELUDE cohort during follow-up, despite high levels of risk behaviour and STI diagnoses, further confirms the appropriate use of PrEP by the PrELUDE participants. They followed the recommended schedule closely, and only two discontinued PrEP stating a difficulty maintaining adherence to daily dosing. Most participants stayed on PrEP for the whole duration of the study. While 84 (25.7%) discontinued PrEP at different times and for varying reasons, these men may recommence PrEP later, as they go through further periods of risk exposure, or 'seasons of risk'.

Our adverse events data are in agreement with the reports from clinical trials on TDF/FTC safety [29]. Most of the observed adverse events occurred early and did not affect PrEP adherence. Seven PrELUDE participants (2.1%) had abnormal renal tests (mainly between months 6 and 12 on PrEP). Further investigation of renal issues among long-term PrEP users and research on alternative PrEP options, such as intermittent dosing or other antiretroviral drugs, may find options for people with a propensity to develop renal abnormalities.

(a) Average number of casual sex partners



(b) Condomless anal intercourse with casual partners (among men who had such partners)

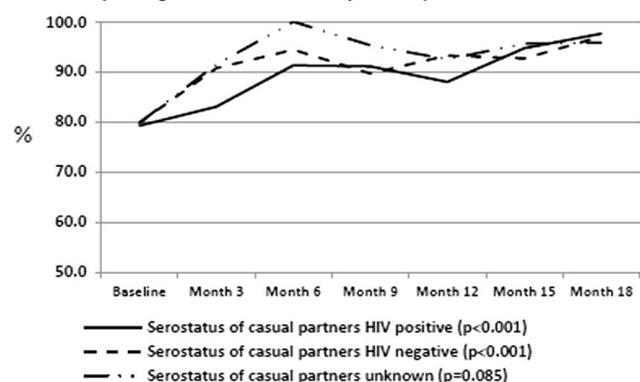


Fig. 5 Sexual practices among participants of the PrELUDE study

For participants who discontinued PrEP, we did not have information about HIV serostatus after follow-up ceased. However, any HIV infections acquired during the study follow-up are highly unlikely: most participants who discontinued for unknown reasons ($n=30$) had been well adherent to PrEP prior to leaving the study (23 of them reported taking all or most pills). On the other hand, there is less evidence about risk behaviour and HIV risk after discontinuing PrEP. Individuals who were previously classified as being at high risk for HIV and stopped taking PrEP, permanently or temporarily, may continue being exposed to HIV. Their behaviour, risk reduction strategies and risk of acquiring HIV in post-PrEP (or not-on-PrEP) period are less well understood. Follow-up of the participants after PrEP discontinuation was beyond the scope of the PrELUDE study, but it will be investigated in the subsequent EPIC-NSW study.

One of the strengths of our study was the high level of detail about participants' risk practices and very high survey participation rates. We found that, from the outset, this cohort was at very high risk of HIV infection [30]. We observed significant increases in practices commonly associated with HIV exposure, such as high numbers of sex partners of HIV-positive and unknown status and condomless anal intercourse. However, these increases in risk practices were offset by the adequate levels of coverage with PrEP and therefore had no impact on HIV diagnoses.

STI transmission among PrEP users is one of the key challenges in PrEP roll-out [31]. Despite the ongoing increases in STI diagnoses in Australia prior to our study [32] and the observed increases in risky behaviour in the cohort, there were no significant increases in STI diagnoses (indeed, the incidence of gonorrhoea declined after 6 months). This is in agreement with previous observations in Australia and internationally [31, 33] and modelling projections [34]. This can be explained by already high levels risk behaviour and STI diagnoses at the start and frequent STI testing and management in the study.

Nevertheless, two lessons emerge from our STI findings: STI increases are likely to be observed in the early stages of PrEP use, and, despite three-monthly STI testing, at least 15% of STI diagnoses were made between regular follow-ups. This indicates a need for continued frequent STI testing of PrEP users. With a growing number of MSM taking PrEP, new models of STI testing services will be required.

PrELUDE had several limitations. As a one-arm open-label demonstration study, it did not have a control group to assess the true medication-related adverse events and the magnitude of the effects of PrEP on behaviour and STI diagnoses. The study had a modest sample size and its follow-up was affected by the expanded implementation of PrEP in NSW and more broadly in Australia, which limited our analyses of longer term follow-up on PrEP. This sample included a limited number of transgender individuals and women,

which precluded analyses of PrEP use in these groups. We also acknowledge the self-reported nature of our indicators of behaviour and medication adherence, which are prone to misreporting.

Despite these limitations, the demonstration study PrELUDE contributed to the development and piloted the newly developed PrEP eligibility criteria which were subsequently adopted by PrEP guidelines nationally [13]. Internationally, completeness and detail of data from the PrELUDE behavioural follow-up provide important insights into changes in behaviour among MSM on PrEP.

Acknowledgements **PRELUDE Study Team:** Mark Bloch, Andrew Carr, Ching (Yvonne) Cheung (study clinical coordinator), Rosalind Foster, Chris Gianacas (clinical data manager), Andrew Grulich, Rebecca Guy, Martin Holt, John Kaldor, Brent Mackie, Kenneth Mayer, John McAllister, Anna McNulty, Dean Murphy, Catriona Ooi, Catherine Pell, Isobel Mary Poynten, Garrett Prestage, Nathan Ryder, David Templeton, Stefanie Vaccher (behavioural data manager), John de Wit, Edwina Wright, and Iryna Zablotska (chief investigator and protocol chair). **Participating clinics:** Clinic 16 at Royal North Shore Hospital, Holdsworth House Medical Practice, Newcastle Sexual Health Service, RPA Sexual Health, St Vincent's Hospital HIV Immunology and Infectious Diseases Unit, Sydney Sexual Health Centre, Taylor Square Private Clinic, and Western Sydney Sexual Health Centre. **Community partner organisations:** ACON (formerly AIDS Council of NSW) and Positive Life NSW.

Author Contributions IBZ, AEG, RG, IMP and GP were involved in the conception and design of the study. IBZ was the Protocol Chair. SJV, MB, AC, RF, AM, CO, CP, NR and DT oversaw participant recruitment and data collection. IBZ and SJV conducted the analysis. IBZ wrote the manuscript with input from all co-authors. All authors met the International Committee of Medical Journal Editors criteria for authorship, and read and approved the final manuscript.

Funding The study was funded by the NSW Ministry of Health. Gilead Sciences provided the study medication, Truvada®. The views expressed in this publication do not necessarily represent the position of these organisations.

Compliance with Ethical Standards

Ethical Approval The study protocol was reviewed and approved by the St Vincent's Hospital Human Research Ethics Committee (HREC) in Sydney, NSW (Protocol #HEPP 1403; identification #HREC/14/SVH/130) and was registered at ClinicalTrials.gov (identifying #NCT02206555).

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