

Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection

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IMPORTANCE Emerging evidence suggests that risk of bacterial sexually transmitted infections (STIs) increases among gay and bisexual men following initiation of HIV preexposure prophylaxis (PrEP).

OBJECTIVE To describe STI incidence and behavioral risk factors among a cohort of predominantly gay and bisexual men who use PrEP, and to explore changes in STI incidence following PrEP commencement.

DESIGN, SETTING, AND PARTICIPANTS The Pre-exposure Prophylaxis Expanded (PrEPX) Study, a multisite, open-label intervention study, was nested within the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) clinic network. A total of 4275 participants were enrolled (July 26, 2016–April 1, 2018) in Victoria, Australia. Of these, 2981 enrolled at 5 ACCESS clinics (3 primary care, 1 sexual health, and 1 community-based HIV rapid testing service), had at least 1 follow-up visit, and were monitored until April 30, 2018.

EXPOSURES Upon enrollment, participants received daily oral tenofovir disoproxil fumarate and emtricitabine for HIV PrEP, quarterly HIV and STI testing, and clinical monitoring.

MAIN OUTCOMES AND MEASURES The primary outcome was incidence of chlamydia, gonorrhea, or syphilis. Incidence rates and hazard ratios describing behavioral risk factors of STI diagnosis were calculated. Incidence rate ratios (IRRs), adjusted for change in testing frequency, described changes in STI incidence from 1-year preenrollment to study follow-up among participants with preenrollment testing data (n = 1378).

RESULTS Among the 2981 individuals (median age, 34 years [interquartile range, 28–42]), 98.5% identified as gay or bisexual males, 29% used PrEP prior to enrollment, 89 (3%) withdrew and were censored at date of withdrawal, leaving 2892 (97.0%) enrolled at final follow-up. During a mean follow-up of 1.1 years (3185.0 person-years), 2928 STIs were diagnosed among 1427 (48%) participants (1434 chlamydia, 1242 gonorrhea, 252 syphilis). STI incidence was 91.9 per 100 person-years, with 736 participants (25%) accounting for 2237 (76%) of all STIs. Among 2058 participants with complete data for multivariable analysis, younger age, greater partner number, and group sex were associated with greater STI risk, but condom use was not. Among 1378 participants with preenrollment testing data, STI incidence increased from 69.5 per 100 person-years prior to enrollment to 98.4 per 100 person-years during follow-up (IRR, 1.41 [95% CI, 1.29–1.56]). After adjusting for testing frequency, the increase in incidence from 1 year preenrollment to follow-up was significant for any STI (adjusted IRR, 1.12 [95% CI, 1.02–1.23]) and for chlamydia (adjusted IRR, 1.17 [95% CI, 1.04–1.33]).

CONCLUSIONS AND RELEVANCE Among gay and bisexual men using PrEP, STIs were highly concentrated among a subset, and receipt of PrEP after study enrollment was associated with an increased incidence of STIs compared with preenrollment. These findings highlight the importance of frequent STI testing among gay and bisexual men using PrEP.

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HIV preexposure prophylaxis (PrEP) is highly effective in reducing HIV acquisition risk among gay and bisexual men who have high medication adherence.¹⁻³ Following the regulatory approval of tenofovir/emtricitabine for daily use as PrEP in Australia in 2016,⁴ and prior to PrEP becoming subsidized through Australia's Pharmaceutical Benefits Scheme in April 2018, large implementation studies in several Australian jurisdictions, most notably in Melbourne and Sydney, experienced high rates of enrollment and provided more than 15 000 gay and bisexual men with access to PrEP.^{5,6} Despite the high efficacy of PrEP and emerging evidence of population-level decreases in incidence of newly acquired HIV following PrEP implementation,^{6,7} concerns remain that widespread PrEP uptake may result in behavioral change that leads to increases in bacterial sexually transmitted infections (STIs).⁸

Although early clinical trials reported no evidence of decreased condom use among PrEP users,^{1,3} a recent systematic review of 17 open-label PrEP studies found an increase in condomless anal sex and bacterial STIs, especially rectal infections, among gay and bisexual men following PrEP use.⁹ However, many studies have lacked comprehensive data for STI incidence prior to use of PrEP,⁹ and only a few^{10,11} have accounted for changes in population STI rates or for the confounding effect of increased STI testing, as recommended for PrEP users, on STI rates. As PrEP uptake among eligible populations increases, monitoring population changes in STI epidemiology and identifying individuals most at risk will become increasingly important for informing effective and focused STI prevention.

The Pre-exposure Prophylaxis Expanded (PrEPX) study was a multisite, open-label, population intervention study in Victoria, Australia. The primary study objective was to measure changes in population-level HIV incidence in Victoria following study rollout. This article reports findings addressing a key secondary study objective to assess the association of PrEP with STI risk by describing STI incidence among participants and exploring changes in STI risk following study enrollment.

Methods

Study Design and Data Collection

Ethics approval for the study and the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-Borne Viruses and Sexually Transmitted Infections (ACCESS) project were provided by the Alfred Hospital Human Research Ethics Committee (projects 100/16 and 248/17). All participants provided written consent. The study was undertaken during 2017 in the states of South Australia and Tasmania following funding from respective state governments, however the following analysis pertains only to the Victorian study, which was rolled out first, as per the study protocol. Study enrollment commenced on July 26, 2016, and 4275 people at risk of HIV were enrolled until April 1, 2018. Study methods have been published elsewhere,¹² and the study protocol is available online ([Supplement 1](#)). Individuals who met 1 or more prespecified eligibility criteria, based on self-reported HIV risk in the previous 3 months (eMethods in [Supplement 2](#)), and were

Key Points

Question Is the use of HIV preexposure prophylaxis (PrEP) associated with increased risk of sexually transmitted infections (STIs) among individuals at high risk of HIV infection?

Findings In this longitudinal study of 2981 mostly gay and bisexual men who received daily HIV preexposure prophylaxis, STI incidence was 91.9 per 100 person-years, with 736 participants (25%) accounting for 2237 (76%) of all STIs. Among 1378 participants with preenrollment STI testing data available, receipt of PrEP after study enrollment was associated with an increased incidence of STIs compared with preenrollment (adjusted incidence rate ratio, 1.12).

Meaning Findings suggest the importance of frequent testing for STIs among gay and bisexual men using PrEP.

predicted to have ongoing HIV risk in the next 3 months, were eligible to enroll. Participants who did not report the prespecified behavioral criteria were potentially eligible to enroll at the clinician's discretion. During screening for eligibility, clinicians asked potential study participants about their gender identity, their sex/gender assigned at birth, and their perceived sexuality, and responses were self-reported to clinicians. Potential participants were asked whether they identified as Aboriginal or Torres Strait Islander (ATSI) as the health status of indigenous Australians is a priority in Australia's National Strategies for HIV, STIs, and blood-borne viruses.¹³ Individuals could decline to answer the question about their ATSI status. Participants were also asked if they were currently using PrEP prior to enrolling into the study. At enrollment and quarterly study visits, participants received PrEP prescriptions, completed a self-reported electronic sexual behavioral survey regarding sexual partners and condom use, and underwent HIV and STI testing. Enrollment and behavioral survey data were collected and managed using REDCap electronic data capture tools hosted at the Burnet Institute.¹⁴ Comprehensive STI screening was undertaken in accordance with the Australian Sexually Transmitted Infection and HIV Testing guidelines,¹⁵ including nucleic acid amplification tests for pharyngeal, anorectal, and urethral chlamydia and gonorrhea; syphilis serology; and fourth-generation HIV testing. STI testing and self-reported behavioral data from visits at baseline and during study follow-up were extracted from participating study sites via the ACCESS project.¹⁶ ACCESS is a national STI and blood-borne virus sentinel surveillance system that routinely extracts deidentified patient data from clinical management systems at selected sexual health and general practice clinics. A number of study sites also participate in the ACCESS project, allowing for monitoring of STI outcomes among study participants. STI pathology results and patient demographic and behavioral data were extracted using specialized data extraction software, and patient records were linked across services using a matching algorithm.

Sample

Data were included from participants who were enrolled at any of the 5 study sites that participated in ACCESS: 3 high-caseload primary care settings, 1 sexual health clinic, and

1 community-based HIV rapid point-of-care testing service. All study participants who enrolled at one of the ACCESS clinics and underwent STI testing at their enrollment visit and at least 1 follow-up visit postenrollment were included in the analysis. To assess potential for selection bias, characteristics of participants included in the analysis were compared with those of participants not enrolled at ACCESS clinics and subsequently excluded from the analysis.

Outcomes

The primary outcome was the incidence of STIs, defined as a diagnosis of chlamydia, gonorrhea, or newly identified (primary, secondary, or early latent [<2 years]) syphilis. Positive results of the same infection at multiple anatomical sites from tests obtained on the same day (eg, pharyngeal gonorrhea and rectal gonorrhea) were considered a single infection, while concurrent diagnoses of different infections at the same or different anatomical sites were considered separate infections. Tests for chlamydia and gonorrhea within 30 days of a previous positive result at the same anatomical site were considered tests of cure and excluded from the analysis.¹⁷ Exploratory outcomes were behavioral risk factors associated with STI diagnosis, as well as changes in STI incidence from 1 year prior to enrollment to study follow-up. Changes in STI incidence were explored only among participants with preenrollment testing data. To determine the independent association of commencing PrEP on STI incidence, a post hoc disaggregation of results by whether participants reported no previous PrEP use (PrEP-naive) or were using PrEP at enrollment (PrEP-experienced) was performed.

Statistical Analyses

Cox proportional hazards regression was used to explore associations between behavioral and demographic characteristics and STI diagnosis by calculating hazard ratios with 95% CIs. The conditional risk set model proposed by Prentice, Williams, and Peterson was used to allow for multiple failures (STIs) per participant.¹⁸ In this Cox model, follow-up time commenced at enrollment visit and baseline STI test results were excluded. Participants were right-censored at time of last follow-up prior to April 30, 2018. Covariates found to be independently associated with STI diagnosis in bivariable analysis ($P < .10$) were included in a multivariable Cox model. Only participants with complete data for all included covariates were included in the multivariable Cox model. The multivariable model was assessed for multicollinearity by computing the tolerance for model covariates, with none showing evidence for multicollinearity (cutoff tolerance for evidence of multicollinearity <0.1).¹⁹ The proportional hazards assumption of the multivariable Cox model was tested using Schoenfeld residuals,²⁰ with individual covariate and global tests showing no evidence for rejection of the null hypothesis of proportional hazards at the P value of less than .05 significance level.

Time-fixed covariates in the multivariable Cox model included participant age; ATSI status; region of birth (Australia vs outside of Australia); previous use of PrEP; previous use of post-exposure prophylaxis; having ever exchanged sex for money; and self-reporting diagnosis of rectal chlamydia, rectal gonorrhea, or syphilis in the 3 months prior to enrollment. Time-

varying covariates included reporting of having a regular partner, number of casual oral sex partners (1-5, 6-10, 11-20, 21-50, >50), number of casual anal sex partners (1-5, 6-10, 11-20, 21-50, >50), participation in group sex (none, once or a few times, \geq monthly, \geq weekly), condom use with casual partners (always, usually [$>50\%$], sometimes [$\leq 50\%$], never), condom use with regular partners (always, usually [$>50\%$], sometimes [$\leq 50\%$], never), recreational drug use during sex, injection drug use, and self-reported PrEP adherence (daily, 4-6 days per week, 1-3 days per week, intermittent). Recall period for time-varying covariates was past 6 months, and responses were updated at each scheduled study visit.

To explore changes in STI risk following study enrollment, STI incidence was compared before and after enrollment among participants with at least 1 STI test in the ACCESS system longer than 6 months prior to enrollment (≥ 6 months of preenrollment person-time). Incidence rate ratios (IRRs) with 95% CIs comparing incidence 1 year before enrollment with incidence during study follow-up were calculated for each infection and anatomical site. In this before-and-after analysis, participants were considered at risk and contributed person-time from their earliest negative test for the respective infection and anatomical site in the ACCESS system, or from exactly 1 year prior to enrollment (whichever came later), and STIs diagnosed at the study enrollment visit were counted in the before-enrollment period. The overall change in testing rate across periods was also calculated by visit (number of visits when a test was performed divided by total person-time) and accounting for multiple infections tested for during the same visit (number of tests divided by total person-time).

Negative binomial regression (chosen over a Poisson model to account for overdispersion within the data; likelihood ratio test of $\alpha = 0$, $\chi^2 < 0.001$) was used to calculate adjusted incidence rate ratios (AIRRs) by including period (1 year preenrollment vs during study follow-up) in the model as an independent covariate. To control for the differential frequency in STI testing between before-enrollment and after-enrollment periods, the individual rate of testing (number of tests divided by person time of follow-up) in each period per participant was included in the model as a continuous variable. For the "any STI" model output, a test performed for each infection (chlamydia, gonorrhea, or syphilis) contributed to the sum of tests used to calculate the testing rate variable. Outcome of the model was number of STI diagnoses per participant in each period with log of individual follow-up time per period as an offset. Robust standard error calculations clustered by participant were used to account for within-participant dependency of number of STI diagnoses between periods. Despite a high proportion of participants experiencing no STIs, a standard negative binomial regression model was chosen over a zero-inflated negative binomial regression model because all participants were considered at risk of STI diagnosis, given the risk-based eligibility criteria for enrollment in the study and the fact that all participants in this analysis had at least 1 test in each period.

Because of the potential for type I error due to multiple comparisons, findings for secondary analyses should be interpreted as exploratory. P values were 2-sided with $\alpha = .05$ and $P < .05$

considered statistically significant. All statistical analyses were conducted using Stata version 14.2 for Windows (StataCorp).

Results

Participant Characteristics

Of the 4275 participants enrolled in the study in Victoria, 2981 were enrolled at ACCESS sites, had at least 1 postenrollment visit, and were included in the analysis (participant characteristics are shown in **Table 1**). Compared with participants not included in the analysis, included participants were more likely to have used methamphetamines in the 3 months prior to enrollment (13.8% vs 7.8%; $P < .001$), however were not significantly different across other self-reported sexual risk behaviors at enrollment (see eTable 2 in **Supplement 2** for comparison of included vs excluded participants). Included participants were aged 16 to 72 years at enrollment (median, 34 [interquartile range {IQR}, 28-42]) and 98.5% (n=2936) identified as gay or bisexual men (see eTable 1 in **Supplement 2** for breakdown of self-reported gender and sexuality). Previous use of antiretrovirals for reducing HIV-acquisition risk was common; 28.5% of participants (n=849) reported PrEP use before enrollment and 40.7% (n=1212) reported ever taking postexposure prophylaxis. The most common risk-based study eligibility criteria reported (in the previous 3 months) were condomless receptive anal intercourse with a partner with HIV or of unknown HIV status (48.1%; n=1435) or having more than 1 episode of condomless insertive anal intercourse with a partner of unknown HIV status or a partner with HIV not on antiretroviral treatment (35.1%; n=1046). Four-hundred and eighty-four (16.2%) participants self-reported a diagnosis of rectal chlamydia, rectal gonorrhea, or syphilis in the 3 months prior to enrollment, and 407 (13.7%) were diagnosed with an STI at their enrollment visit.

Primary Outcome

Of the 2981 participants included in the analysis, 89 (3%) formally withdrew from the study and were censored at date of withdrawal, leaving 2892 (97.0%) participants still enrolled at the time of final follow-up. Participants were monitored for a total of 3185.0 person-years after enrollment (median follow-up, 1.19 years [IQR, 0.71-1.48]). During this time, a total of 2928 STI diagnoses were made among 1427 (48%) participants. The number of STIs diagnosed during follow-up per participant ranged from 0 to 12 (median, 0). The **Figure** shows the proportion of participants diagnosed with 0, 1, or multiple STIs during follow-up and the corresponding proportion of all STIs diagnosed (eTable 3 in **Supplement 2** reports the number of STIs diagnosed per person). Multiple infections were observed in 736 (25%) participants, with infections among these participants accounting for 76% of all infections during follow-up. Seven hundred and eighty-eight concurrent infections (different STIs diagnosed during the same visit) occurred at 387 follow-up visits and accounted for 27% of all diagnoses.

Incidence of any STI diagnosis during study follow-up was 91.9 per 100 person-years, with incidences of 45.0 per 100 person-years for chlamydia, 39.0 per 100 person-years for

Table 1. Characteristics of Participants at Enrollment (N = 2981)^a

	No. (%) ^b
Age, median (interquartile range), y	34 (28-42)
Gender identity ^c	
Male (cisgender ^d or transgender)	2958 (99.2)
Female (cisgender ^d or transgender)	10 (0.3)
Nonbinary/gender fluid	13 (0.4)
Trans or gender diverse ^c	37 (1.2)
Sexuality	
Gay/homosexual	2817 (94.5)
Bisexual	125 (4.2)
Heterosexual	9 (0.3)
Not specified	30 (1.0)
Born in Australia (n = 2187)	1557 (71.2)
Aboriginal or Torres Strait Islander (n = 2204)	65 (2.9)
Use of injection drugs (n = 2241)	
Ever	270 (12.0)
Recently (past 12 mo)	190 (8.5)
Ever accessed postexposure prophylaxis	1212 (40.7)
Currently using PrEP at enrollment	849 (28.5)
Regular partner at enrollment visit (n = 2083)	1047 (50.3)
HIV status of regular partner (n = 1047)	
Positive	179 (17.1)
Negative	786 (75.1)
Unknown	82 (7.8)
If HIV-positive, viral load of partner (n = 179)	
Undetectable	156 (87.2)
Detectable	8 (4.5)
Unknown	15 (8.4)
Diagnosed at enrollment visit	
Any sexually transmitted infection	407 (13.7)
Chlamydia	246 (8.3)
Rectal	185 (6.2)
Urethral	65 (2.2)
Pharyngeal	16 (0.5)
Gonorrhea	194 (6.5)
Rectal	100 (3.4)
Urethral	17 (0.6)
Pharyngeal	111 (3.7)
Syphilis	34 (1.1)
In the 3 mo Prior to Enrollment Visit	
Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status	1435 (48.1)
>1 Episode of condomless insertive anal intercourse with a casual male partner with HIV or of unknown HIV status	1046 (35.1)
>1 Episode of anal intercourse without correct and consistent condom use (eg, condom slipped off or broke)	918 (30.8)
Used methamphetamines	412 (13.8)
Self-reported diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis	484 (16.2)

Abbreviation: PrEP, preexposure prophylaxis.

^a For excluded participants' comparison, see eTable 2 in Supplement 2.

^b Indicates percentage with nonmissing responses (N=2981) unless otherwise stated.

^c Gender identity and trans and gender diverse experience data are based on participants' self-reported gender and self-reported sex assigned at birth (eTable 1 in Supplement 2 for breakdown).

^d Indicates a person whose gender identity corresponds with the sex the person had or was identified as having at birth.

gonorrhea, and 8.0 per 100 person-years for syphilis. Rectal infections were most common for both chlamydia and gonorrhea, and the incidence of any STI was greatest among those aged 25 to 34 years (Table 2).

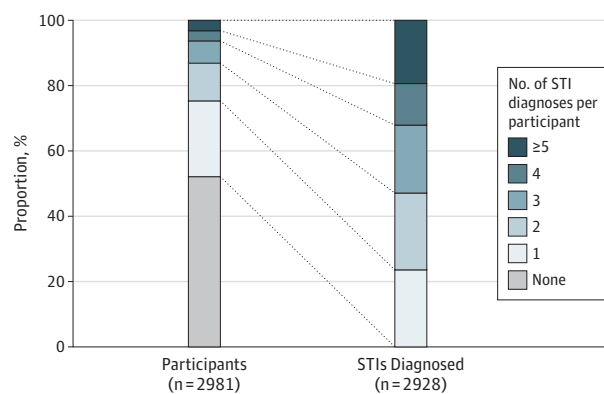
Exploratory Outcomes

Table 3 shows unadjusted and adjusted hazard ratios for factors associated with STI diagnosis during study follow-up. In bivariable Cox regression analyses, characteristics associated with greater STI risk included younger age; use of PrEP and postexposure prophylaxis prior to enrollment; diagnosis of rectal gonorrhea, rectal chlamydia or syphilis prior to enrollment; greater

numbers of oral sex partners; greater numbers of anal sex partners; inconsistent or no condom use with casual partners; and participation in group sex. A total of 2058 (69%) participants had complete data for all behavioral responses included in the multivariable model and contributed to the multivariable analysis. In the multivariable model, younger age; diagnosis of rectal gonorrhea, rectal chlamydia or syphilis prior to enrollment; a greater number of anal sex partners; and participation in group sex remained significantly associated with greater STI risk, however inconsistent or no condom use with casual partners was not significantly associated with STI risk.

There were 1378 participants who had at least 1 prestudy STI test and were included in the before-and-after analysis, contributing 1347.5 person-years preenrollment and 1563.4 person-years postenrollment. Compared with the 1603 participants who were not included in the before-and-after analysis, included participants were older (mean age, 39.0 years vs 33.8 years; $P < .001$) and less likely to report injection drug use at enrollment (3.7% vs 6.5%; $P < .001$). Additionally, these same participants were more likely to report using methamphetamines (16.4% vs 11.6%; $P < .001$) and report more than 1 episode of insertive condomless anal intercourse with a partner of unknown HIV status (40.1% vs 30.8%; $P < .001$) in the 3 months prior to enrollment (see eTable 4 in Supplement 2 for comparison of participants included vs excluded in the before-and-after analysis). Among the 1378 participants included the before-and-after analysis, incidence of any STI increased from 69.5 per 100 person-years in the year prior to enrollment to 98.4 per 100 person-years during study follow-up (IRR, 1.41 [95% CI, 1.29-1.56]; incidence rate difference [IRD], 28.9/100 person-years [95% CI, 22.3-35.5]).

Figure. Distribution of Participants and STI Diagnoses by Number of Infections per Participant During Follow-up



See eTable 3 for corresponding data.

Table 2. Incidence of Sexually Transmitted Infections During Follow-up Among Included Participants (N = 2981)

	No. of Infections	Person-Years of Follow-up (n = 3185.0) ^a	Incidence Rate per 100 Person-Years (95% CI)
All STIs	2928		91.9 (88.7-95.3)
Chlamydia	1434		45.0 (42.7-47.4)
Rectal ^b	1091		34.3 (32.3-36.3)
Urethral ^b	381		12.0 (10.8-13.2)
Pharyngeal ^b	127		4.0 (3.3-4.7)
Gonorrhea	1242		39.0 (36.9-41.2)
Rectal ^b	719		22.6 (21.0-24.3)
Urethral ^b	233		7.3 (6.4-8.3)
Pharyngeal ^b	629		19.7 (18.3-21.3)
Syphilis	252	3140.8	8.0 (7.1-9.0)
Site ^b			
Rectal infections	1810		56.8 (53.4-60.4)
Urethral infections	614		19.3 (17.4-21.3)
Pharyngeal infections	756		23.7 (22.0-25.6)
Age group, y ^c			
18-24 (n = 307)	161	186.1	86.5 (74.6-101.5)
25-29 (n = 634)	554	536.3	103.3 (94.9-112.1)
30-34 (n = 620)	733	684.4	107.1 (99.8-115.3)
35-39 (n = 482)	495	593.2	83.4 (76.4-91.2)
40-44 (n = 356)	354	432.2	81.9 (73.8-90.9)
45-49 (n = 437)	486	548.0	88.7 (81.2-97.1)
≥50 (n = 145)	145	204.7	70.8 (60.2-83.4)

Abbreviation: STI, sexually transmitted infection.

^a Number of person-years indicated unless otherwise stated.

^b Sum is greater than all STIs total as concurrent diagnosis of same infection at multiple anatomic sites was considered a single infection in the all STIs total.

^c Subgroup analysis indicates all STIs.

Table 3. Unadjusted and Adjusted Hazard Ratios for Factors Associated With Sexually Transmitted Infection Diagnosis Among Participants During Follow-up^a

Characteristic	Bivariable Analysis		Multivariable Analysis (n = 2058)	
	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Age (5-y increase)	0.95 (0.93-0.98)	<.001	0.94 (0.90-0.97)	<.001
Aboriginal or Torres Strait Islander	0.92 (0.64-1.33)	.68		
Born outside of Australia	1.06 (0.95-1.18)	.28		
Ever used PrEP before enrollment	1.11 (1.00-1.22)	.04	1.10 (0.96-1.27)	.16
Ever used postexposure prophylaxis before enrollment	1.29 (1.18-1.42)	<.001	1.09 (0.96-1.25)	.20
Exchanged sex for money in past 12 mo	1.21 (0.92-1.59)	.18		
Use of injection drugs				
Ever	1.42 (1.24-1.64)	<.001	0.90 (0.64-1.26)	.54
Recently (past 12 mo)	1.53 (1.31-1.81)	<.001	1.30 (0.90-1.86)	.16
Enrollment risk criteria (≤3 mo prior to enrollment)				
Self-reported diagnosis of rectal gonorrhea, rectal chlamydia, or syphilis	1.66 (1.49-1.85)	<.001	1.23 (1.05-1.45)	.01
Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status	1.28 (1.17-1.41)	<.001	1.17 (1.02-1.34)	.03
Used methamphetamines	1.45 (1.29-1.63)	<.001	0.90 (0.73-1.11)	.32
>1 Episode of anal intercourse without proper condom use	1.13 (1.03-1.25)	.01	1.11 (0.97-1.28)	.11
Regular partner during the last 6 mo	0.96 (0.84-1.10)	.55		
Self-reported PrEP adherence (%) ^b				
Taking PrEP daily (95.5)	1 [Reference]			
Taking PrEP 4-6 d per wk (3.4)	1.18 (0.81-1.55)	.24		
Taking PrEP 1-3 d per wk (0.4)	0.81 (0.42-1.56)	.52		
Intermittent use of PrEP (0.8)	0.67 (0.37-1.21)	.19		
No. of oral sex partners in last 6 mo (%) ^b				
1-5 (36.6)	1 [Reference]		1 [Reference]	
6-10 (26.9)	1.64 (1.38-1.95)	<.001	1.17 (0.94-1.45)	.16
11-20 (19.9)	1.97 (1.64-2.35)	<.001	0.95 (0.74-1.22)	.69
21-50 (12.8)	2.31 (1.90-2.82)	<.001	0.86 (0.63-1.17)	.33
>50 (3.9)	2.05 (1.49-2.81)	<.001	0.78 (0.30-1.87)	.59
No. of anal sex partners in last 6 mo (%) ^b				
1-5 (45.3)	1 [Reference]		1 [Reference]	
6-10 (25.3)	1.54 (1.31-1.82)	<.001	1.30 (1.06-1.59)	.01
11-20 (17.6)	2.19 (1.85-2.58)	<.001	1.91 (1.48-2.46)	<.001
21-50 (9.5)	2.32 (1.88-2.86)	<.001	2.17 (1.57-3.00)	<.001
>50 (2.4)	2.47 (1.72-3.55)	<.001	2.53 (1.58-4.03)	<.001
Condom use with regular partner in last 6 mo (%) ^b				
Always (7.3)	1 [Reference]		1 [Reference]	
Usually (>50% of the time) (19.7)	2.08 (1.37-3.15)	.001	1.27 (0.81-2.00)	.30
Sometimes (≤50% of the time) (25.5)	2.42 (1.62-3.62)	<.001	1.27 (0.82-1.98)	.29
Never (47.5)	1.84 (1.23-2.74)	.003	1.06 (0.36-1.29)	.24
Condom use with casual partners in last 6 mo (%) ^b				
Always (14.0)	1 [Reference]		1 [Reference]	
Usually (>50% of the time) (29.2)	1.82 (1.41-2.36)	<.001	1.38 (0.96-1.97)	.08
Sometimes (≤50% of the time) (38.4)	2.13 (1.67-2.71)	<.001	1.38 (0.96-1.99)	.08
Never (18.5)	1.94 (1.48-2.54)	<.001	1.31 (0.88-1.97)	.18
Group sex in last 6 mo (%) ^b				
None (40.0)	1 [Reference]		1 [Reference]	
Once or a few times (47.9)	1.89 (1.64-2.19)	<.001	1.28 (1.09-1.49)	.002
≥Monthly (10.8)	2.70 (2.22-3.29)	<.001	1.45 (1.15-1.83)	.002
≥Weekly (1.4)	3.17 (2.14-4.71)	<.001	1.67 (1.16-2.40)	.006

(continued)

Table 3. Unadjusted and Adjusted Hazard Ratios for Factors Associated With Sexually Transmitted Infection Diagnosis Among Participants During Follow-up^a (continued)

Characteristic	Bivariable Analysis		Multivariable Analysis (n = 2058)	
	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
Substance use before or during sex in the last 6 mo (%) ^b				
Alcohol (49.0)	1.28 (1.13-1.46)	<.001	0.91 (0.79-1.06)	.24
Amyl nitrite (poppers) (45.8)	1.55 (1.37-1.76)	<.001	1.08 (0.94-1.26)	.26
Methylenedioxyamphetamine (ecstasy) (16.2)	1.38 (1.18-1.62)	<.001	0.92 (0.76-1.10)	.35
Methamphetamines (13.9)	1.87 (1.62-2.16)	<.001	1.25 (0.99-1.57)	.06
Gamma hydroxybutyrate (GHB) (11.5)	1.92 (1.64-2.24)	<.001	1.25 (1.03-1.52)	.03
Cocaine (8.9)	1.49 (1.24-1.78)	<.001	1.13 (0.92-1.40)	.25

Abbreviation: PrEP, preexposure prophylaxis.

^a There were 2058 participants with complete data for all responses who were included in the multivariable analysis. All 2981 participants provided data for at least 1 measurement in bivariable analyses.^b For repeated behavioral measures, % is the proportion of all nonmissing responses during follow-up, noting that participants completed different numbers of surveys.

Post Hoc Analyses

Of the 1378 participants with preenrollment testing data, 541 reported PrEP use prior to enrolling in the study, leaving 837 PrEP-naïve participants. Compared with PrEP-naïve participants, PrEP-experienced participants were more likely to meet the risk-based behavioral criteria at enrollment (see eTable 5 in Supplement 2 for comparison of PrEP-experienced vs PrEP-naïve participants). Post hoc disaggregation of results by preenrollment PrEP use showed that STI incidence in the year prior to enrollment was significantly greater among PrEP-experienced participants (92.4/100 person-years) than PrEP-naïve participants (55.1/100 person-years) (IRR, 1.68 [95% CI, 1.47-1.91]; IRD, 37.3/100 person-years [95% CI, 27.7-47.0]) (Table 4). Among PrEP-naïve participants, incidence of any STI increased significantly to 94.2 per 100 person-years (IRR, 1.71 [95% CI, 1.49-1.96]; IRD, 39.1/100 person-years [95% CI, 31.0-47.2]) during follow-up, whereas the change in incidence among PrEP-experienced participants to 104.1/100 person-years during follow-up was not significant (IRR, 1.13, 95% CI, 0.99-1.28; IRD, 11.7/100 person-years [95% CI, -0.3 to 23.5]) (Table 4). Among PrEP-naïve participants, incidence significantly increased for chlamydia (IRR, 1.84, 95% CI, 1.55-2.20; IRD, 21.3/100 person-years [95% CI, 15.5-27.1]) and gonorrhea (IRR, 1.69, 95% CI, 1.42-2.01; IRD, 16.9/100 person-years [95% CI, 11.4-22.4]) overall and at each anatomical site (Table 4) from before enrollment to during PrEP use. No significant change was observed for syphilis between preenrollment and postenrollment periods in either the PrEP-experienced (IRR, 1.32, 95% CI, 0.89-1.95; IRD, 2.4/100 person-years [95% CI, -1.1 to 5.7]) or PrEP-naïve (IRR, 1.24, 95% CI, 0.87-1.78; IRD, 1.5/100 person-years [95% CI, -1.0 to 4.1]) group.

The mean number of clinic visits per year increased between preenrollment and postenrollment periods from 3.2 to 4.7 among PrEP-naïve participants (absolute difference, 1.5 [95% CI, 1.3-1.7]) and from 4.4 to 4.7 among PrEP-experienced participants (absolute difference, 0.3 [95% CI, 0.1-0.6]). The mean number of STI tests per year increased between preenrollment and postenrollment periods from 8.5 to 12.9 among PrEP-naïve participants (absolute difference, 4.4 [95% CI, 4.1-4.7]) and from 11.7 to 13.0 among PrEP-experienced participants (absolute differ-

ence, 1.3 [95% CI, 0.9-1.7]; see eTable 6 in Supplement 2 for number of tests performed before and after enrollment).

After adjusting for change in individual STI testing frequency between periods, a significant increase across periods was observed for any STI (adjusted IRR, 1.12 [95% CI, 1.02-1.23]) and for chlamydia (adjusted IRR, 1.17 [95% CI, 1.04-1.33]) for all participants (eTable 7 in Supplement 2) and for PrEP-naïve participants with any STI (adjusted IRR, 1.21 [95% CI 1.06-1.39]) and with chlamydia (adjusted IRR, 1.38 [95% CI 1.13-1.66]) (Table 4). However, after adjusting for testing frequency, the change in incidence of any STI from preenrollment to postenrollment among PrEP-experienced participants was not significant (adjusted IRR, 1.05 [95% CI 0.92-1.19]), and no significant change was observed in either group of participants for gonorrhea or syphilis (Table 4).

Discussion

This cohort of predominantly gay and bisexual men who accessed PrEP through a PrEP intervention study in Victoria experienced high rates of bacterial STIs, with STI diagnoses highly concentrated among a subgroup of participants during follow-up. STI diagnosis during follow-up was associated with reporting higher numbers of anal sex partners and participation in group sex; however, in the multivariable analysis, there was no independent association with reported levels of condom use, a factor historically strongly associated with STI risk. STI incidence increased from before to after commencing PrEP with the increase greatest for chlamydia infection. Although the incidence of bacterial STIs increased from the period before PrEP use to during PrEP use among participants commencing PrEP for the first time, the study design did not include a control group that did not receive PrEP and could not directly imply that PrEP initiation per se caused the observed increase in STI risk. The lack of association with condoms and clustering of STIs in a small group of participants suggested that commencing PrEP may be associated with unknown or unmeasured factors that drive STI risk, such as changes in the size and constituents of sexual networks or other unmeasured sexual behaviors.

Table 4. Incidence of Sexually Transmitted Infections Before and After Enrollment (n = 1378)^a

Outcome (No. of Participants) ^b	PrEP-Experienced Participants (n = 541)				PrEP-Naive Participants (n = 837)							
	IR 1 Year Before Enrollment ^c	IR During Follow-up ^c	IRR (95% CI)	P Value	Adjusted IRR (95% CI) ^d	P Value	IR 1 Year Before Enrollment ^c	IR During Follow-up ^c	IRR (95% CI)	P Value	Adjusted IRR (95% CI) ^d	P Value
All STIs	92.4	104.1	1.13 (0.99-1.28)	.07	1.05 (0.92-1.19)	.49	55.1	94.2	1.71 (1.49-1.96)	<.001	1.21 (1.06-1.39)	.006
Chlamydia (n = 1318)	45.8	52.4	1.14 (0.97-1.35)	.12	1.04 (0.88-1.23)	.66	25.2	46.5	1.84 (1.55-2.20)	<.001	1.38 (1.13-1.66)	.001
Rectal (n = 1240)	36.3	40.5	1.12 (0.81-1.36)	.28	0.98 (0.81-1.18)	.83	19.4	34.4	1.78 (1.44-2.19)	<.001	1.20 (0.95-1.51)	.13
Urethral (n = 1304)	13.1	14.1	1.08 (0.78-1.49)	.65	0.96 (0.69-1.33)	.80	7.6	13.9	1.83 (1.30-2.56)	<.001	1.32 (0.91-1.90)	.14
Pharyngeal (n = 1061)	2.6	4.0	1.52 (0.73-3.18)	.26	1.40 (0.66-2.95)	.38	2.6	5.1	1.99 (1.10-3.62)	.02	1.64 (0.86-3.13)	.13
Gonorrhea (n = 1324)	40.1	43.4	1.08 (0.90-1.30)	.38	0.99 (0.83-1.17)	.87	24.6	41.5	1.69 (1.42-2.01)	<.001	1.11 (0.92-1.34)	.26
Rectal (n = 1241)	24.6	25.6	1.04 (0.82-1.33)	.75	0.93 (0.73-1.19)	.57	15.1	25.2	1.67 (1.33-2.09)	<.001	1.00 (0.78-1.28)	.99
Urethral (n = 1309)	7.4	9.5	1.28 (0.88-1.86)	.20	1.17 (0.80-1.70)	.42	3.6	7.5	2.06 (1.29-3.31)	.002	1.33 (0.84-2.09)	.23
Pharyngeal (n = 1274)	17.5	19.7	1.13 (0.86-1.47)	.38	1.03 (0.79-1.34)	.83	11.6	17.7	1.53 (1.17-1.99)	.002	1.04 (0.78-1.38)	.78
Syphilis (n = 1318)	7.4	9.8	1.32 (0.89-1.95)	.17	1.28 (0.87-1.90)	.21	6.4	7.9	1.24 (0.87-1.78)	.24	0.93 (0.62-1.40)	.74
Rectal infections (n = 1243)	60.9	66.0	1.08 (0.91-1.30)	.38	0.95 (0.79-1.13)	.54	34.7	59.6	1.72 (1.44-2.05)	<.001	1.10 (0.91-1.32)	.32
Urethral infections (n = 1310)	20.7	23.6	1.14 (0.89-1.45)	.29	1.01 (0.79-1.29)	.95	11.5	21.3	1.86 (1.40-2.48)	<.001	1.26 (0.94-1.70)	.13
Pharyngeal infections (n = 1276)	20.1	23.5	1.17 (0.91-1.51)	.23	1.03 (0.80-1.32)	.85	13.8	23.1	1.67 (1.31-2.14)	<.001	1.14 (0.88-1.47)	.34

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; PrEP, preexposure prophylaxis; STI, sexually transmitted infection.

^a Analyses of change in incidence disaggregated by PrEP-experienced vs PrEP-naive participants were post hoc. Incidence rates, IRRs, and adjusted IRRs for all 1378 participants combined are shown in eTable 7 in Supplement 2.

^b The number of participants for each STI outcome category counts only those with a test result for that specific

^c Values are per 100 person-years.

^d Adjusted for change in individual testing frequency between before enrollment and during follow-up. Adjusted IRRs were calculated using negative binomial regression with robust standard errors clustered by participant.

STI and anatomical site in the year prior to enrollment and during follow-up. Participants could contribute multiple diagnoses in each period (before enrollment and during follow-up).

Rates of chlamydia and gonorrhea were high during study follow-up, but were comparable to rates among other cohorts of gay and bisexual men using PrEP reported internationally.^{10,11,21,22} Most STIs observed during study follow-up were diagnosed within a subgroup of participants who experienced high rates of reinfection. This finding highlights an opportunity to interrupt community-level STI transmission by offering frequent, easily accessible STI screening and other prevention strategies to PrEP users who are diagnosed with multiple STIs. A recent modeling study found that while PrEP use may lead to increased STI incidence following individual-level behavior change, the timely diagnosis and short duration of STIs among PrEP users due to high screening frequency may lead to an overall decrease in STI prevalence and incidence among the wider gay and bisexual male population.²³

After multivariable adjustment, reporting greater numbers of recent casual sex partners and participation in group sex remained principal indicators of STI risk, and a dose-response relationship was observed between STI risk and increased partner numbers and frequency of group sex. In contrast, in the adjusted model, there was no significant difference in STI risk between participants who used condoms usually (>50% of the time), sometimes (≤50% of the time), or never with casual partners compared with those who reported always using condoms. The observation that consistent condom use was not significantly associated with decreased STI risk may be due to low-levels of consistent condom use across the cohort and the partial efficacy of condoms to prevent bacterial STI transmission. Recent work has suggested that bacterial STIs, particularly gonorrhea, are readily transmitted during oro-penile and oro-anal sex, for which gay and bisexual men rarely use condoms, and perhaps during tongue kissing.²⁴ While condoms continue to play an important role in STI prevention, their use among Australian gay and bisexual men has been declining in recent years,²⁵ and in a recent review of PrEP studies, condom use was shown to decline following initiation of PrEP.⁹ Findings suggested that STI prevention campaigns should not focus solely on condom use but also on reducing the time to STI diagnosis and treatment by promoting easy access to frequent testing.

Limitations

This study has several limitations. First, early adopters of PrEP are typically individuals whose attendant STI risk is high,²¹ and those enrolling into PrEP studies may not be representative of the wider population of gay and bisexual men who will use PrEP outside of a study environment. Second, participants included

in the before-and-after analysis were those accessing STI screening at ACCESS clinics before enrollment, and comparative analysis found that included participants were more likely than excluded participants to report methamphetamine use and report having more than 1 episode of condomless insertive anal intercourse with a partner of unknown HIV status or a partner with HIV not taking antiretroviral treatment in the 3 months prior to enrollment. Hence, selection bias may be present in this analysis, and findings may not be generalizable to all gay and bisexual men. Third, behavioral responses relied on self-reporting, which may lead to recall or social desirability bias. However, computer-assisted self-interview methods, as used in this study, have been shown to reduce such biases in sexual behavior reporting.²⁶ Fourth, although participant movement between clinics participating in ACCESS was captured, it is possible that some participants sought medical treatment for STIs at nonparticipating clinics. However, given that participants were routinely attending clinics involved in the study prior to enrollment, this would have little effect on the before-and-after analysis. Fifth, as only clinical testing data were extracted, and not data on STI treatments prescribed to participants, it could not be ensured that every STI was treated effectively and that all positive diagnoses were incident infections. However, these clinics are highly experienced in managing STIs, and participating study clinics followed standard STI treatment guidelines.¹⁵ A conservative 30-day window was used to define new infections, so results were unlikely to be affected. Sixth, we did not report on the incidence of STIs in individuals who may have been using the study medication in an on-demand fashion. Study participants were advised to take PrEP on a daily basis, and use of on-demand preexposure prophylaxis was not collected systematically throughout the study. It will be important to evaluate the incidence of STIs among individuals using on-demand preexposure prophylaxis in future studies. Seventh, it is possible that participants who were lost to follow-up may have had differential STI risk compared with those not lost to follow-up, affecting the generalizability of our findings.

Conclusions

Among gay and bisexual men using PrEP, sexually transmitted infections were highly concentrated among a subset of study participants, and receipt of PrEP after study enrollment was associated with an increased incidence of STIs compared with preenrollment. These findings highlight the importance of frequent STI testing among gay and bisexual men using PrEP.

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