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

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Summary

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

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

Findings 22 730 men were included in the analyses. During the observation period, 11 351 chlamydia infections were diagnosed in 6630 (30·1%) of 22 034 men over 25 991·2 person-years of PrEP use (incidence rate 43·7 cases [95% CI 42·9–44·5] per 100 person-years). Chlamydia incidence decreased from 48·7 cases per 100 person-years in July–December, 2016, to 42·0 cases per 100 person-years in July–December, 2019 (IRR for estimated change per 6-month period 0·98 [95% CI 0·97–0·99]; p=0·0031). 9391 gonorrhoea infections were diagnosed in 5885 (26·9%) of 21 845 men over 24 858·7 person-years of PrEP use (incidence rate 37·8 cases [95% CI 37·0–38·5] per 100 person-years). Gonorrhoea incidence decreased from 45·5 cases per 100 person-years in July–December, 2016, to 37·2 cases per 100 person-years in July–December, 2019 (IRR 0·97 [95% CI 0·96–0·98]; p<0·0001). Declines in chlamydia and gonorrhoea incidence were most prominent in the first 18 months of observation and incidence was stable thereafter. 2062 syphilis infections were diagnosed in 1488 (7·7%) of 19 262 men over 21 978·9 person-years of PrEP use (incidence rate 9·4 cases [95% CI 9·0–9·8] per 100 person-years). Syphilis incidence increased from 6·2 cases per 100 person-years in July–December, 2016, to 9·8 cases per 100 person-years in July–December, 2019 (IRR 1·08 [95% CI 1·05–1·10]; p<0·0001).

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

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Introduction

Reductions in HIV diagnoses among populations of gay and bisexual men and other men who have sex with men have been observed following the implementation of HIV pre-exposure prophylaxis (PrEP) programmes in multiple countries, including Australia.[1] Implementation of PrEP has also led to considerable increases in testing for sexually transmissible infections (STIs) among gay

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See Online for appendix

Research in context

Evidence before this study

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

Added value of this study

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

Implications of all the available evidence

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

and bisexual men, because PrEP prescribing guidelines recommend comprehensive screening for STIs at PrEP prescribing visits. Guidelines generally recommend either 3-monthly or 6-monthly screening on the basis of people receiving PrEP having a high baseline risk for STIs and an increased likelihood of condomless sex.[2]

In Australia, PrEP was initially made available through large implementation studies, which collectively enrolled more than 20 000 participants from early 2016, most notably in the states of Victoria and New South Wales,[3] where an estimated 67% of Australia's population of gay and bisexual men reside.[4] Data from a large, linked sentinel surveillance system allowed for the direct measurement of STI incidence among participants in these implementation studies. A previous analysis of gay and bisexual men enrolled in the PrEPX study in Victoria found that, after controlling for increases in rates of testing, STI incidence increased by 21% (95% CI 6–39) following PrEP initiation compared with the incidence 12 months before PrEP initiation. A relatively small proportion of men using PrEP, who had repeat infections, accounted for more than three-quarters of the burden of STI diagnoses.[5] Another analysis of gay and bisexual men enrolled in the EPIC-NSW study in New South Wales found similarly high rates of STI incidence during PrEP use, but found some attenuation in the already increasing trends in incidence of some STIs observed before the implementation of PrEP.[3]

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

STI incidence outside of implementation and demonstration projects might help explain how PrEP uptake and the associated increase in STI testing is influencing trends in STI incidence.

PrEP was made widely available through primary care in Australia in April, 2018, at a highly subsidised price, via the Pharmaceutical Benefits Scheme, to be prescribed at visits once every 3 months alongside comprehensive HIV and STI testing. Previous modelling studies on the effect of high rates of STI screening with PrEP use on population-level gonorrhoea and chlamydia incidence among gay and bisexual men have shown varied findings,[6,7] with one study suggesting that 3-monthly STI testing among men using PrEP would not be enough to reduce gonorrhoea prevalence among gay and bisexual men.[7] However, an Australian modelling study suggested that increased PrEP coverage might result in declines in new syphilis cases through increased STI testing.[8]

Increasing notifications of STIs among gay and bisexual men in Australia and internationally, especially in the context of more widespread PrEP use, suggests increasing transmission of STIs. However, notification data are influenced by changes in testing rates and might miss some nuances only captured by incidence trend estimates. Furthermore, PrEP uptake in Australia has been gradual, and the changing composition of the population using PrEP over time, especially between those enrolled in early implementation studies and those who accessed PrEP when it was more widely available, might influence incidence trend estimates.

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

Methods

Study design and participants

We analysed routinely collected surveillance data from a large network of sentinel clinics across Australia. 37 clinics (19 sexual health clinics [including multiclinic and outreach services] and 18 general practice clinics) participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS) system were included in the study. The ACCESS protocol has been previously published.[9] Briefly, retrospective patient data (demographics, pathology reports, and electronic prescriptions) were deidentified and extracted from patient management systems of participating services using the specialised data extraction software suite GHRANITE. Participants' data were linked within and across services using a highly sensitive linkage algorithm, which utilised probabilistic and deidentifying linkage keys generated from patient identifiers created before data were extracted.[10]

HIV-negative cisgender and transgender gay and bisexual men aged 16 years or older who had attended an ACCESS service and had been prescribed PrEP during the observation period from Jan 1, 2016, to Dec 31, 2019, were eligible for inclusion in the analyses. Patients were included if they had STI testing at least twice during the observation period, as we used repeat testing methods to estimate STI incidence.[11]

Ethics approval was provided by the human research ethics committees at Alfred Hospital (248/17), Central Australia (CA-19-3355), Northern Territory Department of Health and Menzies School of Health (08/47), University of Tasmania (H0016971), Aboriginal Health and Medical Research Council (1099/15), AIDS Council of New South Wales (2015/14), Victorian AIDS Council and Thorne Harbour Health (VAC REP 15/003), Western Australian Aboriginal Health Ethics Committee (885), and St Vincent's Hospital (08/051). As our study analysed deidentified data collected under the auspices of public health surveillance, individual patient consent was not required. Individuals were able to opt out of the surveillance system at will.

Procedures

Data were extracted up to June 30, 2021, to reduce the effects of right-censoring bias on inflating incidence estimates in the final 6 months of the observation period.[12] Our analysis was censored before 2020 because restrictions were implemented following the COVID-19 pandemic that greatly influenced PrEP use and sexual behaviour among Australian gay and bisexual men,[13,14] which made it difficult to compare trends during this period.

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

Statistical analysis

For all STI tests conducted among participants within the observation period, we calculated the median and 90th percentile number of days since the participant's

	Participants (n=22 730)
Age at PrEP initiation, years	
Mean (SD)	36·4 (11·0)
Median (IQR)	34 (28–43)
16–29	7155 (31·5%)
30–39	7923 (34·9%)
40–49	4494 (19·8%)
≥50	3158 (13·9%)
Year of PrEP initiation	
2016	6494 (28·6%)
2017	5789 (25·5%)
2018	6027 (26·5%)
2019	4420 (19·4%)
Clinic type at PrEP initiation	
General practice	13 601 (59·8%)
Sexual health clinic	9129 (40·2%)
Clinic state at PrEP initiation	
New South Wales	11 633 (51·2%)
Victoria	6701 (29·5%)
Queensland	1247 (5·5%)
South Australia	1245 (5·5%)
Australian Capital Territory	825 (3·6%)
Western Australia	805 (3·5%)
Tasmania	262 (1·2%)
Northern Territory	12 (0·1%)

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

Table 1: **Participant characteristics**

	Chlamydia	Gonorrhoea	Syphilis	Any STI*
Person-years at risk				
Total	25 991·2	24 858·7	21 978·9	23 399·8
Mean (SD)	1·17 (0·95)	1·14 (0·93)	1·14 (0·94)	1·27 (0·99)
Diagnoses				
Total diagnoses	11 351	9391	2062	20 116
Individuals included	22 034	21 845	19 262	18 483
Individuals diagnosed	6630 (30·1%)	5885 (26·9%)	1488 (7·7%)	8223 (44·5%)
Number of diagnoses among individuals with ≥1 STI, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	2 (1–3)

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

Table 2: **Follow-up time and number of STI diagnoses**

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

For trend analyses, incidence rates per 100 person-years were calculated and plotted for each half calendar year (6-month) period from July, 2016, to December, 2019, and were calculated as the number of incident infections divided by the total person-time accumulated. A series of negative binomial regression models (one for each respective STI outcome) with robust variance estimators clustered by individual were used to test for trends across the study period. In each model, time—a continuous variable representing half calendar years from July–December, 2016, to July–December, 2019—was included as the single independent variable. Incidence rate ratios (IRRs) represent the estimated change in incidence rate per each half calendar year (6 months) across the study period. Tests of non-linearity were performed for each trend analysis; where non-linearity was detected, piecewise negative binomial regression was used to examine trends in two periods, split at the median value of half calendar years (before January–June, 2018, *vs* from January–June, 2018, onwards; appendix p 3). Additional sensitivity analyses were performed—namely, including clinic as a random effect in mixed-effects negative binomial regression models (appendix p 18) and using 6 months (rather than 4 months) since previous PrEP prescription as the cutoff time for censorship (appendix p 16).

To describe STI risk among gay and bisexual men initiating PrEP in different years, we performed a secondary analysis of incidence trends, where time was measured in days since participants' PrEP initiation, rather than calendar time. We calculated incidence rates for each STI outcome in 6-monthly intervals of PrEP use since PrEP initiation, and overall incidence rates for each group by year of PrEP initiation (ie, participants initiating PrEP in 2016, 2017, 2018, and 2019). Multivariable negative binomial regression was used to compare STI incidence among participants initiating PrEP in different years, and to calculate the association between time on PrEP (per 6-month increase) and STI incidence, adjusted for year of PrEP initiation. In these models, independent covariates were time on PrEP (continuous, 6-month intervals) and year of PrEP initiation (categorical). Separate negative binomial regression models were used to test for associations between time on PrEP and STI incidence for each group by year of PrEP initiation (those initiating PrEP in 2019 were excluded as at least 12 months of follow-up were needed to test for trend). Additional information on statistical methodology is provided in the appendix (pp 2–3). All analyses were performed using Stata (version 15.1).

Role of the funding source

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

	Individuals included	Person-years at risk	Diagnoses	Incidence rate per 100 person-years (95% CI)	IRR* (95% CI)	p value
Chlamydia						
Total	22 034	25 991·2	11 351	43·7 (42·9–44·5)	0·98 (0·97–0·99)†	0·0031
Rectal	21 121	25 251·0	8449	33·5 (32·8–34·2)	0·99 (0·98–0·99)†	0·049
Urogenital	21 001	25 064·9	3116	12·4 (12·0–12·9)	0·99 (0·97–1·01)	0·22
Pharyngeal	19 921	24 153·7	982	4·1 (3·8–4·3)	0·96 (0·93–1·00)	0·030
Age <35 years	12 103	12 753·0	6372	50·0 (48·8–51·2)	0·99 (0·98–1·01)†	0·44
Age ≥35 years	9931	13 238·2	4979	37·6 (36·6–38·7)	0·97 (0·96–0·99)	0·0003
Gonorrhoea						
Total	21 845	24 858·7	9391	37·8 (37·0–38·5)	0·97 (0·96–0·98)†	<0·0001
Rectal	20 984	24 184·2	5420	22·4 (21·8–23·0)	0·98 (0·96–0·99)†	0·0030
Urogenital	19 467	22 909·4	1569	6·8 (6·5–7·2)	0·97 (0·94–1·00)	0·079
Pharyngeal	21 261	24 399·7	5126	21·0 (20·4–21·6)	0·97 (0·96–0·99)†	0·0015
Age <35 years	11 958	12 305·8	5691	46·2 (45·1–47·5)	0·98 (0·97–1·00)†	0·045
Age ≥35 years	9887	12 552·9	3700	29·5 (28·5–30·4)	0·96 (0·94–0·98)	<0·0001
Syphilis						
Total	19 262	21 978·9	2062	9·4 (9·0–9·8)	1·08 (1·05–1·10)†	<0·0001
Age <35 years	10 544	10 897·1	1008	9·3 (8·7–9·8)	1·09 (1·05–1·13)†	<0·0001
Age ≥35 years	8718	11 081·8	1054	9·5 (9·0–10·1)	1·06 (1·03–1·10)†	0·0004
Any STI‡						
Total	18 483	23 399·8	20 116	86·0 (84·8–87·2)	0·99 (0·99–1·00)	0·17
Age <35 years	10 173	11 642·2	11 612	99·7 (97·9–101·6)	1·00 (0·99–1·01)	0·91
Age ≥35 years	8310	11 757·5	8504	72·3 (70·8–73·9)	0·99 (0·97–1·00)	0·036

Data are n unless otherwise stated. IRR=incidence rate ratio. STI=sexually transmissible infection. *Estimated change per half calendar year (6-month period) from July–December, 2016, to July–December, 2019; half calendar year included as continuous variable in negative binomial model. †Non-linearity detected, piecewise negative binomial regression performed (reported in appendix p 13). ‡Any STI analysis only includes participants who had at least two tests for each infection (chlamydia, gonorrhoea, and syphilis).

Table 3: **Incidence rates and trend estimates**

Results

22 730 men were included in the analyses (table 1). A total of 160 778 chlamydia tests, 155 861 gonorrhoea tests, and 120 875 syphilis tests were done during the observation period. The median time between tests was 84 days (IQR 55–104) for chlamydia tests, 84 days (54–104) for gonorrhoea tests, and 90 days (70–108) for syphilis tests (appendix pp 6–7).

During the observation period, 11 351 chlamydia infections were diagnosed in 6630 (30·1%) of 22 034 men over 25 991·2 person-years of PrEP use (table 2). The overall incidence rate of chlamydia was 43·7 cases (95% CI 42·9–44·5) per 100 person-years (table 3). 9391 gonorrhoea infections were diagnosed in 5885 (26·9%) of 21 845 men over 24 858·7 person-years of PrEP use (table 2). The overall incidence rate of gonorrhoea was 37·8 cases (95% CI 37·0–38·5) per 100 person-years (table 3). 2062 syphilis infections were diagnosed in 1488 (7·7%) of 19 262 men over 21 978·9 person-years of PrEP use (table 2). The overall incidence rate of syphilis was 9·4 cases (95% CI 9·0–9·8) per 100 person-years (table 3).

Among the 18 483 individuals who contributed to the any STI outcome determination, there were 20 116 diagnoses of any STI over 23 399·8 person-years (mean follow-up 1·27 years [SD 0·99]; table 2); participants who initiated PrEP in 2016 were followed-up for a mean of 2·3 years (SD 1·2; median 2·4 years, IQR 1·0–3·2). 8223 (44·5%) of 18 483 men were diagnosed with any STI during the observation period; the median number of STI diagnoses per individual was two (IQR 1–3), and 1049 (5·7%) men were diagnosed with five or more STIs, which accounted for 7256 (36·1%) of 20 116 infections diagnosed (figure 1, appendix p 12).

Chlamydia incidence decreased from 48·7 cases per 100 person-years in July–December, 2016, to 42·0 cases per 100 person-years in July–December, 2019 (IRR 0·98, 95% CI 0·97–0·99; p=0·0031; figure 2, table 3). However, the decline was non-linear, with the greatest decline during the first 18 months of observation; chlamydia incidence reached 42·7 cases per 100 person-years in July–December, 2017, and remained relatively stable thereafter. Gonorrhoea incidence decreased from 45·5 cases per 100 person-years in July–December, 2016, to 37·2 cases per 100 person-years in July–December, 2019 (IRR 0·97, 95% CI 0·96–0·98; p<0·0001). Similar to chlamydia, the decline was non-linear, with the greatest decline during the first 18 months of observation; gonorrhoea incidence fell to 38·7 cases per 100 person-years in July–December, 2018, and remained relatively

stable thereafter. Infectious syphilis incidence increased during the observation period, from 6·2 cases per 100 person-years in July–December, 2016, to 9·8 cases per 100 person-years in July–December, 2019 (IRR 1·08, 95% CI 1·05–1·10; p<0·0001); the increase in syphilis incidence was greatest during the first 18 months of observation (1·25, 1·08–1·49; p<0·0001; figure 2, table 3).

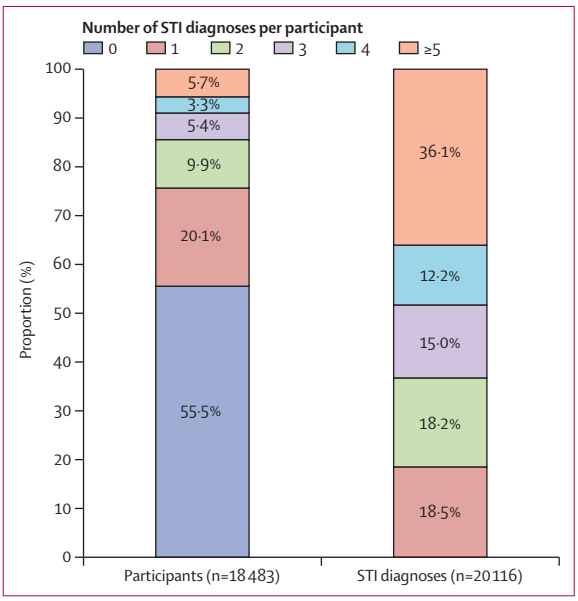

Figure 1: **Number of STI diagnoses per participant during PrEP use and distribution of all STI diagnoses**
PrEP=HIV pre-exposure prophylaxis. STI=sexually transmissible infection.

In secondary analysis of incidence trends measured in days since PrEP initiation, chlamydia incidence did not change with increased time on PrEP (IRR for estimated change per 6 months of PrEP use 1·01, 95% CI 1·00–1·02; p=0·098). After adjusting for year of PrEP initiation, time on PrEP was not associated with chlamydia incidence (adjusted IRR 0·99, 0·98–1·00; p=0·14; figure 3, table 4). Gonorrhoea incidence did not change with increased time on PrEP (IRR 1·00, 0·99–1·01; p=0·99). After adjusting for year of PrEP initiation, longer time on PrEP (each additional 6 months) was associated with a slight decrease in gonorrhoea incidence (adjusted IRR 0·98, 0·97–0·99; p=0·0016). Each additional 6 months of PrEP use was associated with a modest increase in syphilis incidence (IRR 1·08, 1·06–1·11; p<0·0001). After adjusting for year of PrEP initiation, longer time on PrEP was still associated with an increase in syphilis incidence (adjusted IRR 1·08, 1·05–1·11; p<0·0001; figure 3, table 4).

In the secondary analysis of incidence trends disaggregated by year of PrEP initiation, time on PrEP was only associated with a decrease in gonorrhoea incidence in participants who initiated PrEP in 2016, and an increase in syphilis incidence among those who initiated PrEP in 2016 and 2017 (appendix p 15). Extending the censorship cutoff for PrEP use to 6 months since the previous prescription led to slightly decreased

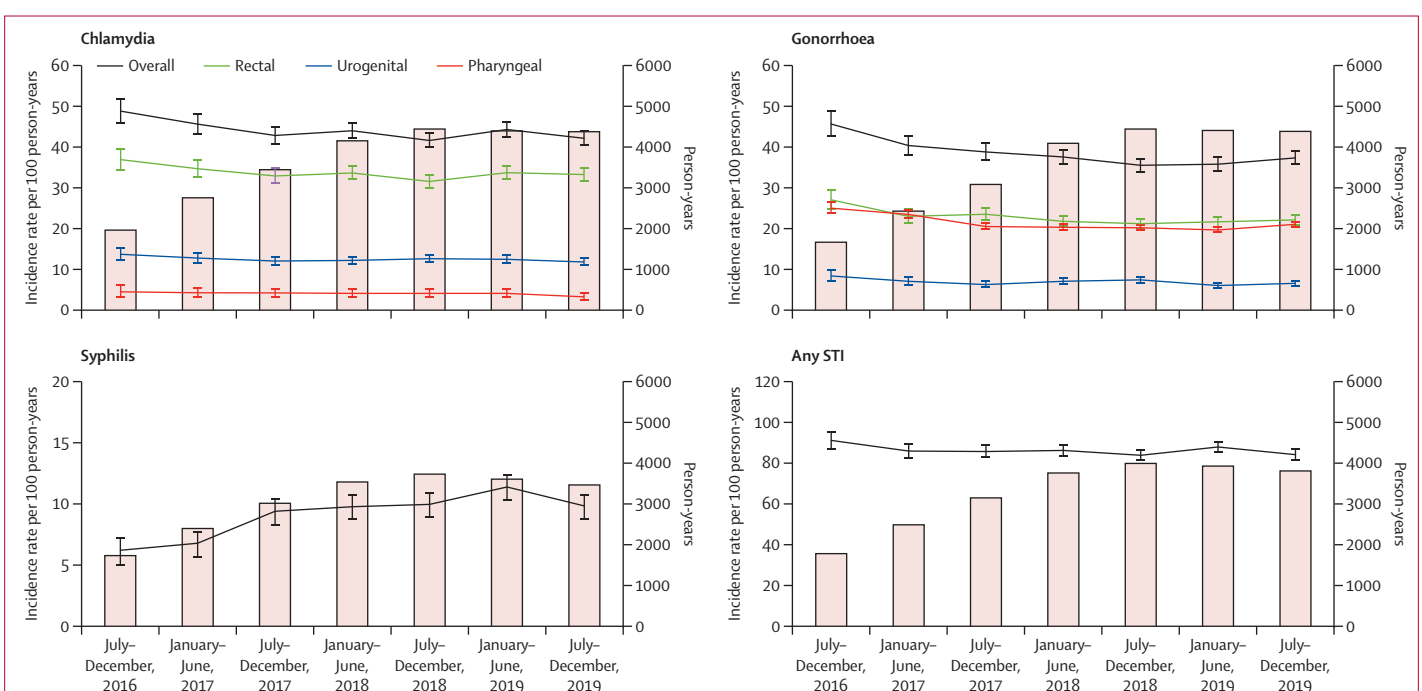

Figure 2: **STI incidence rates by calendar half year, from July–December, 2016, to July–December, 2019**
Error bars represent 95% CIs. Bars represent person-years of follow-up accrued in each period (right axis). Trends disaggregated by age group are shown in the appendix (p 10). STI=sexually transmissible infection.

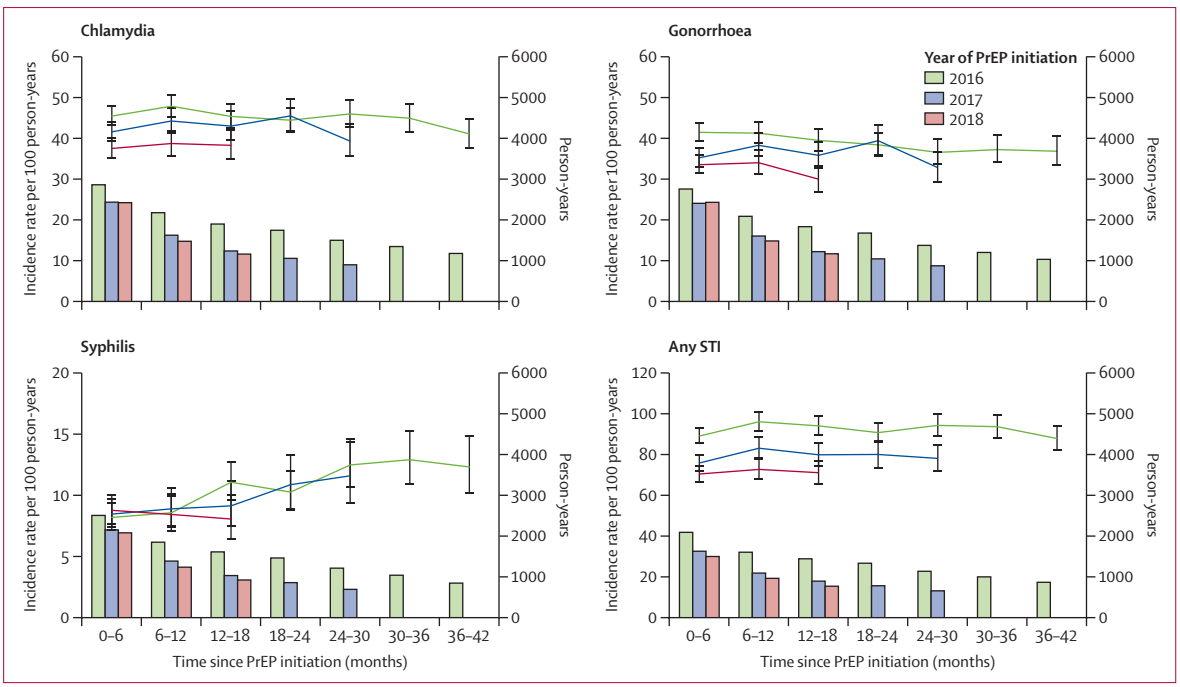

Figure 3: **6-monthly STI incidence rates, by time since PrEP initiation and by year of PrEP initiation**
Error bars represent 95% CIs. Bars represent person-years of follow-up accrued in each period (right axis). Incidence trends aggregated for all gay and bisexual men using PrEP are shown in the appendix (p 11). STI=sexually transmissible infection. PrEP=HIV pre-exposure prophylaxis.

overall incidence rate estimates for each outcome (appendix pp 16–17); however, the trends were similar to those in the primary analysis.

Discussion

To our knowledge, this is the largest cohort of gay and bisexual men using PrEP in which STI incidence rate estimates have been reported internationally. The large sample size in this study provided high precision in our estimates and statistical power to detect relatively small changes over time; significant trends should be interpreted with this in mind. Our analysis suggests that chlamydia and gonorrhoea incidence were high among gay and bisexual men using PrEP, particularly in the early months of nationwide PrEP implementation. Chlamydia and gonorrhoea incidence slightly declined in the years following broad access to PrEP in Australia, and seemed to stabilise later on in the study period. By contrast with chlamydia and gonorrhoea, syphilis incidence continued to increase among gay and bisexual men using PrEP during the study period. Approximately half (8223 [44·5%] of 18 483) of all participants using PrEP were diagnosed with any STI during the study period, and 5·7% of participants were diagnosed with five or more STIs, which accounted for more than one-third of all infections diagnosed. These data represent real-world, population-level incidence estimates of bacterial STIs following high and prolonged uptake of PrEP among gay and bisexual men and reinforce that gay and bisexual men using PrEP are a priority population for bacterial STIs.

There are several possible reasons for the observed trends showing a decline then stabilisation in the incidence of chlamydia and gonorrhoea. Changes in the cohort population over time, driven by the observed lower prospective STI risk of people initiating PrEP in later years, are likely to have influenced the incidence trends. The criteria for prescribing PrEP evolved during our observation period, with early PrEP demonstration studies requiring specific risk-based criteria to be met for enrolment, and less stringent criteria used for prescribing following the listing of PrEP on the Pharmaceutical Benefits Scheme in 2018. It is also possible that the high testing frequency among people using PrEP in Australia is affecting STI transmission through greater detection and shorter infection duration. The median time between tests for all STIs in our cohort closely reflected the recommended 3-monthly interval for STI testing among people using PrEP,[15] with 90% of all chlamydia and gonorrhoea tests occurring within 162 days of the previous test and 90% of all syphilis tests occurring within 174 days of the previous test. However, the effects of maintaining high STI testing rates on the incidence of STIs among people using PrEP are complex and multifaceted. Increased screening for STIs leads to greater likelihood of detecting an infection earlier, and therefore increases the rate of diagnosis and treatment of asymptomatic STIs among people using PrEP. More timely detection and treatment of bacterial STIs shortens the duration of infection, reducing the number of onward transmissions. However, shorter duration of infection, in

	Diagnoses	Person-years at risk	Incidence rate per 100 person-years (95% CI)	Unadjusted IRR (95% CI)	Unadjusted p value	Adjusted IRR (95% CI)	Adjusted p value
Chlamydia							
Year							
2016	5749	12 688·9	45·3 (44·2–46·5)	1 (ref)	..	1 (ref)	..
2017	3089	7236·0	42·7 (41·2–44·2)	0·94 (0·89–0·99)	0·031	0·93 (0·88–0·99)	0·016
2018	1921	5052·7	38·0 (36·4–39·8)	0·84 (0·79–0·89)	<0·0001	0·83 (0·78–0·88)	<0·0001
2019	652	1693·8	38·5 (35·6–41·6)	0·85 (0·78–0·93)	0·0002	0·83 (0·76–0·91)	<0·0001
Time on PrEP*	..	..	..	1·01 (1·00–1·02)	0·098	0·99 (0·98–1·00)	0·14
Gonorrhoea							
Year							
2016	4693	11 942·3	39·3 (38·2–40·4)	1 (ref)	..	1 (ref)	..
2017	2592	7138·5	36·3 (34·9–37·7)	0·92 (0·86–0·98)	0·011	0·90 (0·85–0·96)	0·0020
2018	1667	5076·2	32·8 (31·3–34·5)	0·83 (0·78–0·89)	<0·0001	0·80 (0·75–0·86)	<0·0001
2019	562	1692·6	33·2 (30·6–36·1)	0·84 (0·77–0·93)	0·0052	0·80 (0·72–0·89)	<0·0001
Time on PrEP*	..	..	..	1·00 (0·99–1·01)	0·99	0·98 (0·97–0·99)	0·0016
Syphilis							
Year							
2016	1080	10 514·2	10·3 (9·7–10·9)	1 (ref)	..	1 (ref)	..
2017	572	6110·7	9·4 (8·6–10·2)	0·91 (0·78–1·06)	0·23	0·98 (0·84–1·14)	0·80
2018	360	4230·6	8·5 (7·7–9·4)	0·83 (0·71–0·97)	0·016	0·94 (0·81–1·11)	0·48
2019	104	1312·9	7·9 (6·5–9·6)	0·77 (0·62–0·96)	0·020	0·93 (0·74–1·17)	0·53
Time on PrEP*	..	..	..	1·08 (1·06–1·11)	<0·0001	1·08 (1·05–1·11)	<0·0001
Any STI†							
Year							
2016	8722	9459·5	92·2 (90·3–94·2)	1 (ref)	..	1 (ref)	..
2017	4087	5041·3	81·1 (78·6–83·6)	0·88 (0·83–0·93)	<0·0001	0·88 (0·83–0·93)	<0·0001
2018	2345	3224·3	72·7 (69·8–75·7)	0·79 (0·74–0·84)	<0·0001	0·80 (0·75–0·85)	<0·0001
2019	708	975·3	72·6 (67·4–78·1)	0·79 (0·72–0·86)	<0·0001	0·80 (0·73–0·87)	<0·0001
Time on PrEP*	..	..	..	1·03 (1·02–1·04)	<0·0001	1·00 (0·99–1·02)	0·34

Data are n unless otherwise stated. For individuals initiating PrEP in 2016, 2017, 2018, and 2019, analyses included 42 months, 30 months, 18 months, and 6 months of PrEP use, respectively. No non-linearity in IRRs was detected (appendix pp 13–14). STI=sexually transmissible infection. PrEP=HIV pre-exposure prophylaxis. IRR=incidence rate ratio. *Estimated change per 6 months of PrEP use, included as continuous variable in negative binomial model. †Any STI analysis only includes participants who had at least two tests for each infection (chlamydia, gonorrhoea, and syphilis).

Table 4: **Negative binomial regression models for STI incidence by year of PrEP initiation and time on PrEP**

turn, means individuals become susceptible to new infections faster.

In addition to the effects of increased testing, PrEP roll-out is likely to have contributed to substantial changes in both the size and constituents of sexual networks among gay and bisexual men. Data suggest that gay and bisexual men using PrEP are more likely to have condomless sex with other people using PrEP compared with gay and bisexual men not using PrEP.[16] Given the relatively small number of people using PrEP in Australia in 2016, high rates of chlamydia and gonorrhoea in the first year of PrEP roll-out might reflect a high rate of homogenous mixing within relatively small sexual networks of early adopters of PrEP who had a high baseline risk for STIs. As PrEP use expanded in 2017 and 2018, sexual networks are likely to have also expanded, leading to more disassortative mixing between early adopters of PrEP with higher risk and individuals with lower risk who initiated PrEP in later years, leading to a diffusion of STIs among a wider network. This heterogeneous mixing between early adopters and later adopters of PrEP might partly explain the observed chlamydia and gonorrhoea incidence declines in gay and bisexual men using PrEP, and the declines in gonorrhoea incidence among participants who initiated PrEP in 2016 in our subgroup analysis by time on PrEP.

The divergent steady increase in syphilis incidence might also have emerged as a result of changing sexual networks, in this case due to the increasing likelihood of HIV serodiscordant sex. Routinely collected bio-behavioural data from gay and bisexual men in Australia show decreases in serosorting among both HIV-negative gay and bisexual men and gay and bisexual men living with HIV during our study period.[17] Increases in serodiscordant sex might have had a greater effect on syphilis transmission, given that syphilis diagnoses in Australia were much higher among gay and bisexual men living with HIV than among HIV-negative gay and

bisexual men during our study period.[18] An Australian survey conducted in 2018 showed that 48% of gay and bisexual men using PrEP reported being comfortable having condomless sex with gay and bisexual men living with HIV who had an undetectable viral load, compared with only 6% of gay and bisexual men not using PrEP. However, 78% of gay and bisexual men using PrEP reported being comfortable having condomless sex with other people using PrEP.[16] These data suggest that, among gay and bisexual men using PrEP, comfort in having condomless sex with gay and bisexual men living with HIV might have evolved slower than comfort in having condomless sex with other gay and bisexual men using PrEP, potentially explaining the gradual increase in syphilis incidence among gay and bisexual men using PrEP in the years after PrEP implementation, compared with relatively stable trends in chlamydia and gonorrhoea incidence. Separate analysis of data from the ACCESS network suggests that there has been an increase in syphilis incidence among gay and bisexual men living with HIV from 2017 onwards.[19]

In addition to high-frequency STI testing, other interventions are required to drive down gonorrhoea and chlamydia incidence and to curtail the rise in syphilis incidence among gay and bisexual men using PrEP. As with previously reported data from gay and bisexual men using PrEP in Victoria, Australia,[5] our data suggest that STI diagnoses remain highly skewed, with about 6% of individuals accounting for more than one-third (36%) of all STIs diagnoses. Gay and bisexual men who have repeat and concurrent STIs might be prime candidates for novel biomedical prevention strategies. There is growing interest in Australia in the use of doxycycline prophylaxis for the prevention of STIs, with a study published in 2019 showing that 9·9% (95% CI 8·1–11·8) of people using PrEP attending a large sexual health centre in Melbourne reported using doxycycline prophylaxis in the previous month.[20] Daily and event-driven doxycycline use have been shown to reduce rates of chlamydia and syphilis incidence,[21,22] and although it is not currently approved or recommended for STI prophylaxis in Australia, doctors can prescribe doxycycline off-label. A large study of doxycycline for the prevention of syphilis is ongoing in Australia.[23] In addition, there are future prospects for vaccines for bacterial STIs, including an ongoing randomised controlled trial of a meningococcal B vaccine (Bexsero) for gonorrhoea prevention.[24] In addition to novel biomedical prevention strategies, new models of partner notification (including community-led or peer-led models) and testing (self-testing or home-based testing) might be highly acceptable among people using PrEP and be effective in reducing STI transmission.

Our findings have implications for other countries currently implementing or planning to implement PrEP programmes at scale. These data show that incorporating a PrEP programme into existing clinical services and achieving high (3-monthly) STI testing rates can be accomplished. In this context, PrEP implementation reduces HIV diagnoses,[1] leading to cost-benefits in the long-term, and our analyses suggest that concerns around exponentially increasing rates of STI transmission following wide-scale PrEP implementation have not materialised in gay and bisexual men in Australia. Instances of stigma and hesitancy among practitioners to prescribe PrEP to individuals due to fear of increased STI acquisition risk, especially in the USA,[25] are likely to have hindered progress towards achieving optimal PrEP coverage. Our analysis adds to the body of evidence showing that comprehensive and frequent STI screening of gay and bisexual men using PrEP might have benefits for STI transmission at the population level. Other benefits of PrEP use, including reduced HIV-related anxiety and increased pleasure,[26] should also be considered.

Our analysis has a number of notable strengths, including the high PrEP coverage and large national cohort size. We estimate that our analyses captured approximately 70% of the 32 831 people dispensed publicly funded PrEP in Australia between 2016 and 2019.[27] Other strengths of this study include long periods of follow-up with frequent testing, and data linkage between ACCESS clinics, which allowed us to follow individuals who transferred care between clinics involved in ACCESS and reduced loss to follow-up.

Several limitations of our analysis should be noted. First, individuals attending the ACCESS network might not be representative of all gay and bisexual men using PrEP across Australia. However, the included clinical services specialise in the care of gay and bisexual men and are responsible for a large share of HIV treatment,[28] and we captured a large proportion of gay and bisexual men using PrEP in Australia. Second, individuals might have accessed PrEP or STI testing, and therefore been diagnosed with an STI, at a service outside of the ACCESS network. However, given the short intervals between the tests included in this analysis (median 84–90 days), the effect of external testing is likely to have been minimal; individuals were censored from this analysis if they did not return for PrEP within 4 months of the previous prescription. Third, for individuals attending general practice clinics, we relied on an algorithm of rectal swab testing among male patients to infer status of gay and bisexual men, which might have misclassified some patients. Fourth, we were not able to definitively define periods of PrEP use, but rather inferred PrEP use on the basis of the date of the most recent prescription. It is possible that some gay and bisexual men received their PrEP prescription but did not initiate PrEP, or were using PrEP intermittently. By including participants in our analyses until 4 months after their previous PrEP prescription, we believe we have captured a period of follow-up that is likely to reflect STI risk during PrEP use. Routinely collected

biobehavioural surveillance data suggest that event-driven PrEP use was low among Australian gay and bisexual men during our study period, with less than 10% of men using PrEP reporting non-daily use in 2019 and even fewer in earlier years.[29] Fifth, as the majority of these data were extracted from general practice clinics providing routine PrEP care, and as behavioural data are not routinely collected at these clinics, we were not able to include individual-level behavioural data or data on symptoms in our analyses. Finally, as only clinical testing data were extracted, and not data on STI treatments prescribed to participants, it could not be ensured that every STI was treated effectively and that all positive diagnoses were incident infections. However, the clinics included in this study are highly experienced in managing STIs and followed standard STI treatment guidelines. Australian STI testing guidelines for gay and bisexual men using PrEP did not change during the study period.

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

Contributors

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

Declaration of interests

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

Data sharing

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

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