Syphilis testing, incidence, and reinfection among gay and bisexual men in Australia over a decade spanning HIV PrEP implementation: an analysis of surveillance data from 2012 to 2022

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Summary

Background Gay and bisexual men (GBM) remain overrepresented among syphilis diagnoses in Australia and globally. The extent to which changes in sexual networks associated with HIV pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) may have influenced syphilis transmission among GBM at the population-level is poorly understood. We describe trends in syphilis testing and incidence among GBM in Australia over eleven years spanning widespread uptake of HIV PrEP and TasP.

Methods We analysed linked clinical data from GBM aged 16 years or older across a sentinel surveillance network in Australia from January 1, 2012, to December 31, 2022. Individuals with at least two clinic visits and with at least two syphilis tests during the observations period were included in testing and incidence analyses, respectively. Annual rates of testing and infectious syphilis incidence from 2012 to 2022 were disaggregated by HIV status and PrEP use (record of PrEP prescription; retrospectively categorised as ever or never-PrEP user). Cox regression explored associations between demographics, PrEP use and history of bacterial sexually transmissible infections (STIs) and infectious syphilis diagnosis.

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Findings Among 129,278 GBM (mean age, 34.6 years [SD, 12.2]) included in testing rate analyses, 7.4% were living with HIV at entry and 31.1% were prescribed PrEP at least once during the study period. Overall syphilis testing rate was 114.0/100 person-years (py) and highest among GBM with HIV (168.4/100 py). Syphilis testing increased from 72.8/100 py to 151.8/100 py; driven largely by increases among ever-PrEP users. Among 94,710 GBM included in incidence analyses, there were 14,710 syphilis infections diagnosed over 451,560 person-years (incidence rate = 3.3/100 py). Syphilis incidence was highest among GBM with HIV (6.5/100 py), followed by ever-PrEP users (3.5/100 py) and never-PrEP users (1.4/100 py). From 2012 to 2022, syphilis incidence increased among ever-PrEP users from 1.3/100 py to 5.1/100 py, and fluctuated between 5.4/100 py and 6.6/100 py among GBM with HIV. In multivariable Cox regression, previous syphilis diagnosis (adjusted hazard ratio [aHR] = 1.98, 95% CI = 1.83–2.14), living with HIV (aHR = 1.83, 95% CI = 1.12–1.25) and recent (past 12 m) prescription of PrEP (aHR = 1.78, 95% CI = 1.61–1.97) were associated with syphilis diagnosis.

Interpretation Syphilis trends between GBM with HIV and GBM with evidence of PrEP use have converged over the past decade in Australia. Our findings recommend targeting emergent syphilis control strategies (e.g. doxycycline post-exposure prophylaxis) to GBM with prior syphilis diagnoses, using HIV PrEP or who are living with HIV.

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Keywords: Syphilis; Treponema pallidum; Gay and bisexual men; Men who have sex with men; MSM; HIV; Pre-exposure prophylaxis; PrEP; Treatment as prevention; Incidence; Surveillance

Introduction

Despite substantial declines in cases during the second half of the twentieth century with the introduction of penicillin,[1] infectious syphilis remains a sexually transmissible infection (STI) of public health importance.[2–4] Untreated syphilis can lead to serious complications, including cardiovascular and neurological disease.[5] Syphilis infection has also been shown to increase the risk of onward transmission of HIV by increasing viral load among people with HIV,[6] and increasing acquisition risk through immunological impairment and the epithelial compromise associated with lesions of primary and secondary syphilis.[7]

Similar to other high income countries, gay and bisexual men (GBM) have the highest rate of syphilis compared to other population groups in Australia, and represent the majority of cases reported among men.[8] The diagnosis rate of infectious syphilis among men in Australia has increased each year over the past decade, from 9.1 per 100,000 men in 2010 to 37.0 in 2021.[8,9] While syphilis incidence has historically been greater among GBM with HIV compared to GBM without HIV,[8,10] recent analysis of data from more than 22,000 GBM using HIV pre-exposure prophylaxis (PrEP) in Australia highlighted increasing syphilis incidence among this population from 2016 to 2019, despite relatively stable rates of chlamydia and gonorrhoea.[11] Drivers of increasing STI notifications among GBM over the past decade are likely multifactorial and may include increased detection through greater rates of screening,[12] or increased transmission associated with changes in the way people meet sexual partners (such as through geosocial networking apps).[13] Declines in condom use[14] have also occurred alongside changes in sexual networks and reductions in serosorting (choosing sexual partners with the same HIV status) driven by greater awareness of HIV treatment as prevention (TasP or U=U) and increased use of PrEP.[15,16] In Australia, PrEP has been widely available since 2016,[17,18] with the majority of PrEP users reporting daily use,[19] and substantial declines in the time between HIV diagnosis and viral suppression among GBM has been attributed in part to increased awareness of TasP.[20] From 2016, Australian clinical PrEP guidelines have recommended all PrEP users be screened for bacterial STIs every three months, and from 2019 this recommendation has been extended to all sexually active GBM.[21,22]

In Australia, surveillance data show increasing syphilis diagnoses among heterosexual people[23] and, after virtual elimination in the early 2000's, congenital syphilis has re-emerged.[8] The drivers of increased syphilis transmission among heterosexual populations are not well understood, and while genomic analysis of syphilis in Australia suggests the epidemic is driven by multiple lineages, rather than one distinct outbreak, GBM are present in all lineages, including those mostly associated with heterosexual people.[24] Similar trends have been shown for gonorrhoea.[25] These data suggest bisexual men and other men who have sex with men and women may serve as a bridging population between the two groups and that a public health response that reduces syphilis transmission among GBM may have wider impact among other populations.

To support the public health response to increasing rates of syphilis and help understand dynamic drivers of syphilis transmission among GBM in the HIV

Research in context

Evidence before this study

We searched PubMed for studies published in English between January 1, 2015, and June 30, 2023, using the terms "syphilis", "incidence", "pre-exposure prophylaxis", "men who have sex with men", "gay and bisexual men", and "HIV". Global meta-analyses on syphilis among gay and bisexual men (GBM) have focused mainly on point prevalence and incidence estimates, with meta-analyses of clinical trials and cohort studies reporting GBM living with HIV or using HIV pre-exposure prophylaxis (PrEP) experience high incidence rates of syphilis. Some studies have reported cohort-level increases in syphilis incidence among men after they initiated PrEP. Our previous population-level analysis of 20,000 PrEP users in Australia found that syphilis incidence increased over 24 months of PrEP use, while incidence of chlamydia and gonorrhea were stable. However, most studies exploring the impact of PrEP scale-up on syphilis incidence only report changes in PrEP users without consideration of the broader GBM population, including concurrent trends in syphilis incidence among those not using PrEP and those living with HIV. Reviews comparing annual trends in syphilis incidence between subgroups of GBM are restricted mostly to the pre-PrEP era. At the time of this study, no empirical data were available on population-level trends in syphilis incidence among both HIV-negative GBM and GBM with HIV in the context of substantial increases in country-level coverage of PrEP and TasP HIV prevention strategies.

Added value of this study

To our knowledge, this analysis represents the largest longitudinal cohort of syphilis incidence trends among GBM reported globally. This study also reports the only population-level analysis of syphilis incidence disaggregated by HIV status and PrEP use across a period of PrEP scale-up, and increases in TasP awareness and declines in population-level HIV viremia. 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 which includes high coverage of GBM using PrEP and engaged in HIV care in Australia. Among 94,710 GBM tested for syphilis at least twice across a total of 451,560 person-years of follow-up between January 1, 2012, and December 31, 2022, 10,480 (11%) were diagnosed with syphilis and more than 14,700 syphilis diagnoses were captured. Although syphilis incidence was highest and increased over the observation period among GBM with HIV, incidence converged between GBM with HIV and GBM prescribed PrEP towards the end of the study period. While syphilis incidence increased among GBM who had evidence of PrEP use, incidence in this group was already increasing prior to PrEP rollout in 2016. Reinfection was high, and past diagnosis of syphilis was the strongest predictor of future infection and remained so after adjusting for HIV status and PrEP use.

Implications of all the available evidence

Our analysis shows that over the past decade where highly subsidised and broad access to PrEP occurred in Australia alongside greater awareness of TasP, syphilis incidence rates among GBM with HIV and those using PrEP converged. These findings suggest that changes in sexual networks and increases in HIV serodiscordant sex in the biomedical prevention era has altered syphilis epidemiology among GBM in Australia. In the era of biomedical prevention for HIV, strategies to address increasing rates of syphilis, such as targeted screening and novel biomedical prevention strategies, should focus on interrupting transmission within sexual networks associated with higher rates of reinfection. Future guidelines for doxycycline post-exposure prophylaxis should include prior syphilis diagnosis as an indication for prescribing and consider prioritisation of prescribing for people using PrEP and living with HIV.

biomedical prevention era, we analysed a decade of sentinel surveillance data from a large network of general practice and sexual health clinics across Australia. We aimed to describe trends in syphilis testing and incidence among GBM with and without HIV in the years spanning nationwide PrEP implementation and greater awareness of TasP, and to explore demographic and clinical risk factors associated with infectious syphilis in the PrEP era.

Methods

Study design and participants

Data were extracted from a network of 27 clinical services (6 sexual health services [including multi-clinic and outreach services] and 21 general practice clinics) participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections and Blood Borne Viruses (ACCESS; www.accessproject.org.au). The ACCESS protocol has been previously published.[26] Briefly, retrospective patient data (demographics, pathology reports and electronic prescriptions) were de-identified and extracted from electronic medical records of participating services using specialised data extraction software called GHRANITE™. Individuals' data are linked within and across services using a highly sensitive linkage algorithm which utilises probabilistic and de-identifying linkage keys generated from patient identifiers created prior to data being extracted.[27]

For this analysis, GBM aged 16 years and over attending an ACCESS service during the observation

period were eligible for inclusion. The observation period for this study was 1st January 2012–31st December 2022, however data were extracted to 31st December 2023, with 2023 removed from trend analyses to reduce the effects of right-censoring on inflating incidence estimates in the final 12-month observation period. Gay or bisexual status was inferred from reported gender of sexual partners or from a previously validated algorithm based on history of a rectal swab for chlamydia or gonorrhoea.[28]

Statistical analyses

Rate analyses

We calculated annual rates of syphilis testing, syphilis incidence and repeat syphilis diagnosis per 100 person-years of follow-up from 2012 to 2022. For syphilis testing rate, individuals were included if they had at least two clinic visits at an ACCESS clinic during the study period, and were followed from their first visit until their last visit or 31st December 2022, whichever came first. Testing rate was defined as the number of syphilis test events divided by the total person-time of follow-up accrued in each year. All syphilis pathology results dated within seven days were considered part of the same test event.

For syphilis incidence rate, individuals were included if they had at least two syphilis test events at an ACCESS clinic during the study period, and were followed from their first syphilis test event until their last test event or 31st December 2022, whichever came first. Incidence rate was defined as the number of new diagnoses of infectious syphilis divided by the total person-time of follow-up accrued in each year. To explore trends in repeated syphilis diagnosis, we explored a subgroup analysis restricted to individuals with a diagnosis of syphilis during the observation period and at least one subsequent syphilis test. In this analysis, individuals were followed from their first recorded syphilis diagnosis in ACCESS and until their last syphilis test event or 31st December 2022. Confidence intervals for incidence rates were calculated using the quadratic approximation to the Poisson log likelihood for the log–rate parameter.

New cases of infectious syphilis were defined using a previously validated algorithm of laboratory testing data (serological treponemal and non-treponemal tests, and syphilis PCR tests) which aligned with the national case definition for a new infectious syphilis (including primary, secondary, or early [<2 years] latent) diagnosis (Appendix 6). Date of infection was defined as the midpoint between date of positive test event and date of previous negative test. Syphilis diagnoses at individuals' first test event during the study period were excluded from the numerator of incidence rate calculations.

Subgroup analyses

Annual rates of syphilis testing, incidence and repeat diagnosis were disaggregated by age group, HIV status, and 'ever-PrEP' status. For trend analyses, HIV status was time-varying and individuals were classified as living with HIV from the date of their recorded HIV diagnosis or first evidence of HIV positivity. For PrEP user status, GBM without HIV were dichotomised into ever-PrEP users and never-PrEP users. Individuals with a PrEP prescription were prospectively and retrospectively categorised as ever-PrEP users for the entire period they were classified as HIV-negative, with people classified as never-PrEP users having no record of a PrEP prescription at an ACCESS clinic during the entire study period. This was to aid interpretation and comparison of trends between the two groups over the years of PrEP implementation and, without behavioural data, we could not reliably determine if individuals were taking PrEP as prescribed or when people ceased using PrEP.

Predictors of syphilis diagnosis

A secondary analysis was performed using Cox proportional hazards regression models to explore clinical and demographic factors associated with syphilis diagnosis during years of PrEP availability (2016–2022). In this survival analysis, the origin and date of entry were the date of individuals' first negative syphilis test from January 1st, 2016, and individuals were censored at their last syphilis test or December 31st, 2022 (whichever came first). We used the conditional risk set model to allow for multiple failures (syphilis diagnoses) per participant.[29] Aboriginal or Torres Strait Islander status, being born in Australia and age (in years) at cohort entry were included as time-fixed covariates. Time-varying covariates included HIV status; ever previously prescribed PrEP (at an ACCESS clinics since data availability); recently prescribed PrEP; ever previously diagnosed with syphilis; recently diagnosed with syphilis; ever previously diagnosed with chlamydia; recently diagnosed with chlamydia; ever previously diagnosed with gonorrhoea; recently diagnosed with gonorrhoea; ever previously diagnosed with rectal chlamydia and/or gonorrhoea; and recently diagnosed with rectal chlamydia/gonorrhoea. Recent PrEP or STI diagnosis exposures were for the previous 12 months and at an ACCESS clinic. In the conditional risk set model, time-varying covariates which were related to recent events (e.g. recent PrEP prescription, recent STI diagnosis) were coded as 1 from the date of the event to 12 months post-event, and as 0 from 12 months post-event onwards, or as 0 for all person-time for people who did not experience the event. We used a complete-case regression, with 38% of individuals who had at least one missing predictor dropped from the multivariable model (30% missing country of birth and 8% missing data on whether individuals were Aboriginal or Torres Straight Islander).

Covariates found to be associated with syphilis diagnosis ($p < 0.20$) in bivariable analyses were included

in an initial multivariable Cox model. We then used backward variable selection, by fitting the multivariable model and then removing the variable with the highest p-value until all variables in the model had a p-value below 0.05. The multivariable model was assessed for multi-collinearity by computing the tolerance for model covariates, with none showing evidence for multi-collinearity (cut-off tolerance for evidence of multi-collinearity <0.2; Appendix 7).[30] The proportional hazards assumption of the multivariable Cox model was tested first by using Schoenfeld residuals.[31] For variables which violated tests of the null hypothesis of proportional hazards at the $p < 0.05$ significance level, we plotted graphs of the log (-log (survival function)) by the log (survival time) and inspected the proportional hazards assumption visually (given the sensitivity of the Schoenfeld residuals test to large sample sizes). Only one variable violated the formal test ($p = 0.0133$), however the log–log graph showed no evidence of violation (Appendix 8).

The multivariable model was assessed for multi-collinearity by computing correlation coefficients and tolerance for model covariates, with evidence of multi-collinearity defined as bivariate Pearson correlation of >0.5 or tolerance of <0.2.[30] All analyses were performed using STATA (version 15.1).

Ethics

Ethics approval The human research ethics committees of the Alfred Hospital (248/17), the Northern Territory Department of Health and Menzies School of Health (08/47), the University of Tasmania (H0016971), the Aboriginal Health and Medical Research Council (NSW; 1099/15), and St. Vincent's Hospital (08/051) approved the study, as did the Central Australian Human Research Ethics Committee (19-3355), ACON (2015/14), the Victorian AIDS Council and Thorne Harbour Health (VAC REP 15/003), and the Western Australian Aboriginal Health Ethics Committee (885). Individual patient consent was not required for our analysis of de-identified data collected for public health surveillance.

Role of the funding source

The funders of the study had no role in the design or conduct of the study, including data collection, management, analysis, or interpretation of the results; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Results

Syphilis testing rate

Among 129,278 GBM included in testing rate analyses, the mean age was 39.9 years (SD, 12.1), 13,519 (10.5%) were living with HIV at the end of the study period, and 40,194 (31.1%) were prescribed PrEP at least once during the study period (Table 1). There were 746,120 syphilis test events over 654,579 person-years (py) of follow-up (median 4.7 years, IQR = 1.3–10.5). The overall syphilis testing rate during the study period was 114.0/100 person-years (Table 2). Testing increased from 72.8/100 py in 2012 to 151.8/100 py in 2022, with a

	Included in testing analyses (had at least 2 clinic visits) N = 129,278 n (%)	Included in incidence analyses (had at least 2 syphilis tests) N = 94,710 n (%)
Age at cohort entry, years, mean (SD)	34.6 (12.2)	35.0 (12.0)
Age group at cohort entry, years		
16–29	55,992 (43.3)	39,315 (41.5)
30–39	34,719 (26.9)	26,460 (27.9)
40–49	21,178 (16.4)	15,905 (16.8)
≥50	17,389 (13.5)	13,030 (13.8)
HIV status as cohort entry		
HIV-positive	9525 (7.4)	9915 (10.5)
HIV-negative	119,753 (92.6)	84,795 (89.5)
Aboriginal or Torres strait islander		
Yes	2682 (2.1)	1802 (1.9)
No	112,171 (86.8)	83,577 (88.2)
Not stated/missing	14,425 (11.2)	9331 (9.9)
Region of birth		
Australia	65,495 (50.3)	49,634 (52.4)
Oceania (excluding Australia)	3781 (2.9)	2929 (3.1)
North-West Europe	10,587 (61.4)	7624 (8.0)
Southern and Eastern Europe	2603 (63.4)	1929 (2.0)
North Africa and Middle East	1688 (64.7)	1294 (1.4)
South-East Asia	9628 (72.1)	7656 (8.1)
North-East Asia	7116 (77.6)	5467 (5.8)
Southern and Central Asia	2833 (79.7)	2211 (2.3)
Americas	7702 (85.7)	5853 (6.2)
Sub-Saharan Africa	1572 (86.9)	1251 (1.3)
Not stated/missing	17,109 (13.2)	8862 (9.4)
Prescribed PrEP during observation period		
Yes	40,194 (31.1)	36,317 (38.4)
No	89,084 (68.9)	58,393 (61.7)
Clinic type at cohort entry		
Sexual Health Clinic	75,068 (58.1)	51,723 (54.6)
General Practice	54,210 (41.9)	42,987 (45.4)
Year of entry (first visit or first syphilis test)		
2012	52,713 (40.8)	31,433 (33.2)
2013	7758 (6.0)	5601 (5.9)
2014	8912 (6.9)	6642 (7.0)
2015	9275 (7.2)	7277 (7.7)
2016	9739 (7.5)	8528 (9.0)
2017	9642 (7.5)	9349 (9.9)
2018	8888 (6.9)	8156 (8.6)
2019	8053 (6.2)	6819 (7.2)
2020	5134 (4.0)	4121 (4.4)
2021	4475 (3.5)	3584 (3.8)
2022	4689 (3.6)	3200 (3.4)

Table 1: **Characteristics of gay and bisexual men included in syphilis testing and incidence rate analyses at cohort entry.**

	Entire observation period (2012–2022)				
	N included in analysis	Person-years of follow-up	Number of outcome (tests or diagnoses)	N (%) of GBM who experienced the outcome (test of diagnosis)	Overall rate/100 person-years (95% CI)
Syphilis testing *(GBM with at least 2 clinic visits at ACCESS clinics from 2012 to 2022)*					
All GBM	129,278	654,579	746,120	103,708 (80.2)	114.0 (113.7–114.2)
Never PrEP users	79,559	314,468	196,710	57,585 (72.4)	62.6 (62.3–62.8)
Ever PrEP users	40,194	241,895	384,064	36,802 (91.6)	158.8 (158.3–159.3)
GBM with HIV	13,519	98,216	165,346	12,109 (89.6)	168.4 (167.5–169.2)
Syphilis incidence *(GBM with at least 2 syphilis test events at ACCESS clinics from 2012 to 2022)*					
All GBM	94,710	451,560	14,710	10,480 (11.1)	3.3 (3.2–3.3)
Never PrEP users	48,478	174,847	2490	2177 (4.5)	1.4 (1.7–1.5)
Ever PrEP users	36,317	193,241	6825	5179 (14.3)	3.5 (3.4–3.6)
GBM with HIV	11,980	83,471	5395	3264 (27.2)	6.5 (6.3–6.6)
Repeated Syphilis diagnosis *(GBM with a positive syphilis results and at least 1 subsequent syphilis test event at ACCESS clinics from 2012 to 2022)*					
All GBM	11,612	44,382	5709	3606 (31.1)	12.9 (12.5–13.2)
Never PrEP users	2948	7894	748	599 (20.3)	9.5 (8.8–10.2)
Ever PrEP users	5067	16,340	2103	1421 (28)	12.9 (12.3–13.4)
GBM with HIV	3934	20,148	2858	1624 (41.3)	14.2 (13.674–14.7)

See Appendix 1 for additional data on average length of person-time of follow-up and average number of tests and diagnoses per person.

Table 2: **Person-years of follow-up and rates of syphilis testing and diagnosis during the study period.**

drop in 2020 (115.5/100 py) (Fig. 1). The median time between syphilis test events in the incidence analysis was 119 days (IQR 83–215), and decreased from 140 in 2012 to 109 in 2019, then increased to 126 in 2022.

Syphilis testing rate was highest for GBM with HIV (168.4/100 py), followed by HIV-negative ever-PrEP users (158.8/100 py), and HIV-negative never-PrEP users (62.6/100 py). From 2012 to 2022, syphilis testing rate increased among never-PrEP users from 46.3/100 py to 86.9/100 py, and decreased among GBM with HIV from 183.2/100 py to 154.3/100 py. Syphilis testing rate among ever-PrEP users increased prior to PrEP introduction in 2016 (from 70.3/100 py in 2012 to 104.6/100 py in 2015), then increased to 201.1/100 py by 2019 (Fig. 1).

Syphilis testing rate increased over the study period across all age groups and was highest among age groups 30–39 and 40–49 years. Testing rate decreased with

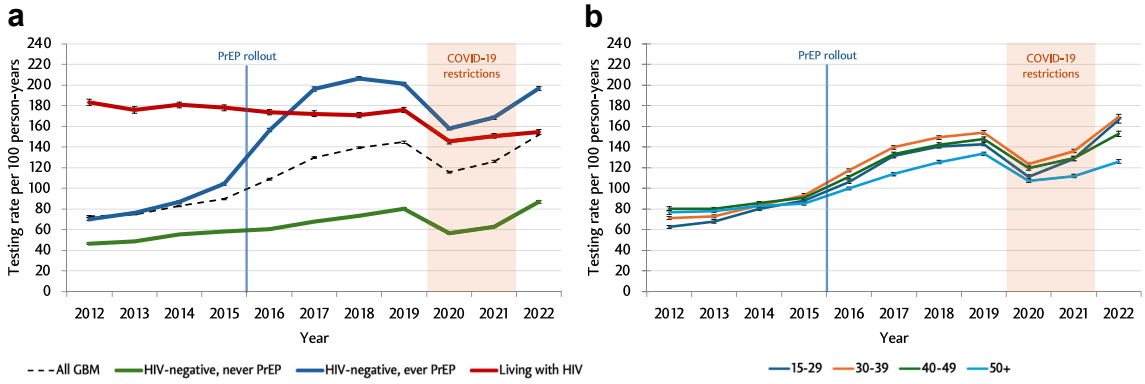

Fig. 1: **Annual syphilis testing rate per 100 person-years among GBM attending ACCESS clinics from 2012 to 2022, by (a) HIV status and ever-PrEP use status and (b) age group.** Appendix 2 contains numerical values for testing rates. Vertical bars represent 95% confidence intervals. PrEP was scaled up from early 2016 through large demonstration studies. COVID-19 lockdown restrictions occurred throughout 2020 and 2021.

greater age among GBM with HIV and never-PrEP users, and increased with greater age among ever-PrEP users (Appendix 4).

Syphilis incidence rate

Among 94,710 individuals included in incidence rate analyses, the mean age was 35.5 years (SD, 12.1), 11,980 (12.6%) were living with HIV at the end of the study period and 36,317 (38.3%) were prescribed PrEP at least once during the study period (Table 1). There were 14,710 syphilis diagnoses over 451,560 person-years (median follow-up = 4.4 years, IQR = 1.6–8.4). The overall syphilis incidence rate during the study period was 3.3/100 py, with incidence increasing from 2.2/100 py in 2012 to 4.6/100 py in 2022 (Table 2). Syphilis incidence rate was highest among GBM with HIV (6.5/100 py), followed by HIV negative ever-PrEP users (3.5/100 py) and HIV-negative never-PrEP users (1.4/100 py). From 2012 to 2022, among GBM with HIV, syphilis incidence fluctuated between 5.4/100 py and 7.6/100 py. Syphilis incidence increased among ever-PrEP users, from 1.3/100 py to 5.1/100 py, and among never-PrEP users, from 1.3/100 py in 2012 to 1.9/100 py in 2022 (Fig. 2).

Syphilis incidence rate increased over the study period across all age groups, and was highest among age groups 30–39 and 40–49 years. Among never-PrEP users and GBM with HIV, incidence rate decreased with increasing age, however among ever-PrEP users, incidence was greatest among those aged 30–39 and 40–49 years (Appendix 5).

Repeated syphilis diagnosis rate

Among 11,612 GBM included in the subgroup analysis of repeated syphilis diagnosis, there were a total of 5709 subsequent syphilis diagnoses following individuals' first-recorded syphilis diagnosis over 44,382 person-years. The overall rate of repeated syphilis diagnosis was 12.9/100 py (Table 2). Rate of repeated syphilis diagnosis was highest among GBM with HIV (14.2/100 py) and HIV-negative ever-PrEP users (12.9/100 py), with the rates between the two groups comparable between 2016 and 2022 (Fig. 2), and was 9.5/100 among never-PrEP users (Fig. 2).

Appendix 1 contains additional data for testing and incidence rate analyses, including mean and median follow-up time and number of syphilis tests and diagnoses.

Risk factors for syphilis infection post-PrEP availability

In the secondary analyses of predictors of syphilis diagnosis restricted to 2016–2022 (post-widespread PrEP availability), a total of 85,716 GBM were included.

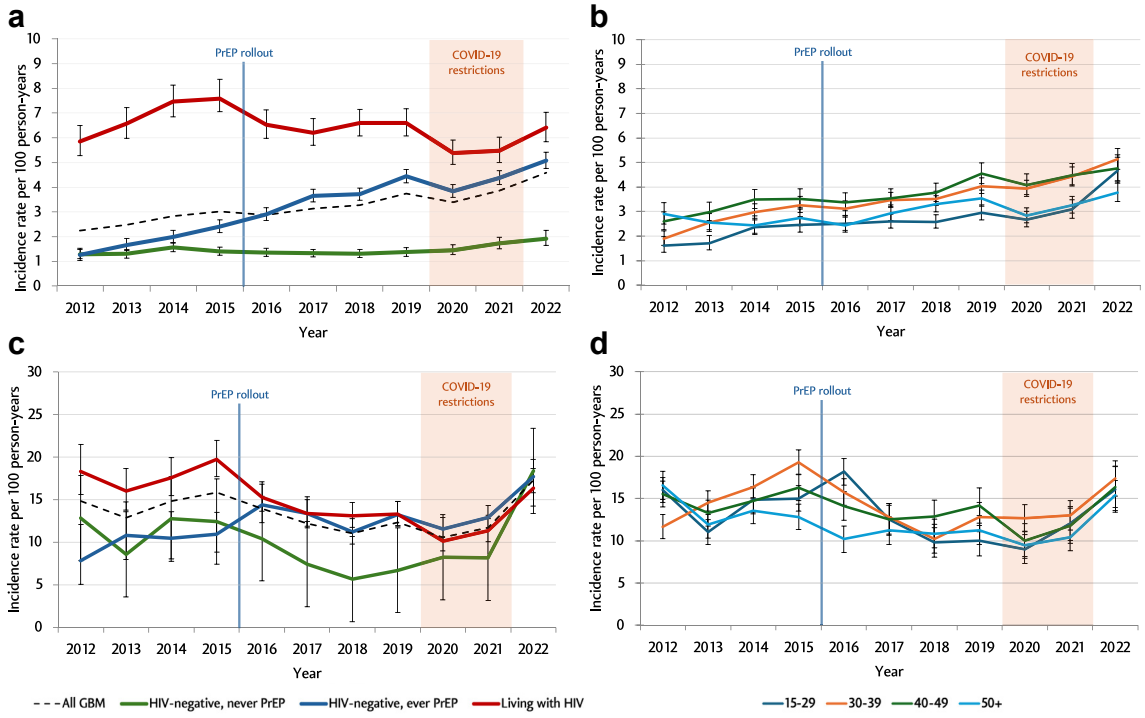

Fig. 2: **(a and b) Annual rate of syphilis incidence per 100 person-years by (a) HIV status and PrEP use and (b) age group, and (c and d) repeated syphilis diagnosis rate per 100 person-years by (c) HIV status and PrEP use and (d) age group, among GBM tested for syphilis at ACCESS clinics from 2012 to 2022.** Appendix 3 contains numerical values for testing rates. Vertical bars represent 95% confidence intervals. PrEP was scaled up from early 2016 through large demonstration studies. COVID-19 lockdown restrictions occurred throughout 2020 and 2021.

Unadjusted and adjusted hazard ratios are presented in Table 3. In univariable analyses, the strongest predictors of syphilis diagnosis were being recently or ever diagnosed with bacterial STIs previously. Recent PrEP use, living with HIV and being born outside of Australia were also associated with syphilis diagnosis.

In the final multivariable model, ever being previously diagnosed with syphilis (HR = 1.98, 95% CI = 1.83–2.14) was the strongest predictor of syphilis diagnosis, followed by living with HIV (HR = 1.83, 95% CI = 1.70–1.98) and recently prescribed PrEP (HR = 1.78, 95% CI = 1.61–1.97). Associations with other STI diagnosis and syphilis infection were attenuated in multivariable analysis (Table 3).

Discussion

To our knowledge, this analysis represents the largest longitudinal cohort of syphilis incidence trends among GBM reported globally, and the only population-level analysis of syphilis incidence among GBM with and without HIV with follow-up prior to and after widespread availability of PrEP. Across our national network of sentinel clinics, we observed increasing rates of syphilis infection among both HIV-negative GBM and GBM with HIV, with the most notable increase among GBM with evidence of PrEP use. Increases in syphilis incidence were observed alongside modest increases in overall syphilis testing but a steadily decline in testing among GBM with HIV, which fell below the rate of testing among PrEP users from 2017 onwards. Among those with a recorded syphilis diagnosis across the network, the rate of repeated syphilis diagnosis was almost four times greater than the overall syphilis incidence rate, and was comparable between GBM with and without HIV. The historically high rates of syphilis infection among GBM with HIV has previously been attributed to repeat infections in relatively closed sexual network. Our findings suggest diversifying sexual networks, including changing trends in serosorting influenced by PrEP use, and possibly a greater awareness of TasP, which is impacting syphilis infection rates among GBM without HIV.

Increasing rates of syphilis transmission among GBM without HIV have been reported internationally.[32,33] A European study based on over 270,000 GBM across 31 countries found that the proportion of participants diagnosed with syphilis in the past 12 months increased from 2.3% in 2010 to 4.5% in 2017, with similar concentration of cases among GBM using HIV PrEP and living with HIV.[34] Our analysis shows most of the increase in syphilis diagnoses among GBM in Australia is occurring among a subgroup of GBM who have ever used PrEP. While syphilis in the ever-PrEP group did not surpass the incidence of GBM with HIV, the inclusion in the ever PrEP group of GBM who may have ceased PrEP use during the observation period may be underestimating syphilis incidence associated with PrEP. Our previous analysis of HIV-negative GBM with continuous PrEP use (i.e. individuals were censored after four months since their last PrEP prescription) in Australia found a syphilis incidence rate of 9.4/100 py (CI: 9.0–9.8),[11] above the incidence rate of GBM with HIV in every year in this analysis. In addition, after multivariable adjustment, risk associated with recent PrEP use (HR = 1.78) and living with HIV (HR = 1.83) were comparable. Of note, Syphilis incidence among GBM

Covariate	HR	p-value	aHR	p-value
Age at cohort entry (per 5 year increase)	0.93 (0.93–0.94)	<0.001	[a]	
Aboriginal or Torres Strait Islander	1.13 (0.97–1.31)	0.115	[a]	
Born outside Australia	1.33 (1.25–1.41)	<0.001	1.18 (1.12–1.25)	<0.001
Living with HIV	1.46 (1.38–1.54)	<0.001	1.83 (1.70–1.98)	<0.001
Previously prescribed PrEP (ever)[a]	1.62 (1.54–1.70)	<0.001	1.14 (1.03–1.26)	0.013
Recently prescribed PrEP (12 months)	1.88 (1.79–1.97)	<0.001	1.78 (1.61–1.97)	<0.001
Previous Syphilis diagnosis (ever)	3.06 (2.92–3.21)	<0.001	1.98 (1.83–2.14)	<0.001
Recent syphilis diagnosis (12 months)[a]	3.95 (3.71–4.21)	<0.001	1.64 (1.49–1.81)	<0.001
Previous CT diagnosis (ever)[a]	2.71 (2.58–2.84)	<0.001	1.32 (1.21–1.44)	<0.001
Recent CT diagnosis (12 months)[a]	3.40 (3.25–3.55)	<0.001	1.53 (1.39–1.68)	<0.001
Previous NG diagnosis (ever)	2.71 (2.59–2.84)	<0.001	1.39 (1.29–1.50)	<0.001
Recent NG diagnosis (12 months)	3.43 (3.28–3.59)	<0.001	1.58 (1.46–1.70)	<0.001
Previous rectal STI diagnosis (ever)	2.95 (2.82–3.09)	<0.001	1.18 (1.07–1.30)	0.001
Recent rectal STI diagnosis (12 months)	3.61 (3.46–3.77)	<0.001	1.21 (1.09–1.35)	<0.001

Observation for risk-factor analysis was restricted to 2016–2019 to include years where PrEP was available and prior to the impact of COVID-19. STI, sexually transmitted infection; CT, Chlamydia trachomatis; NG, Neisseria gonorrhoea. [a]Variables omitted during backward variable selection as variables deemed non-informative in multivariable model. In initial multivariable model with all covariates, p-values were Age (p = 0.929) and Aboriginal or Torres Strait Islander (p = 0.798).

Table 3: **Unadjusted and adjusted hazard ratios for factors associated with syphilis infection among GBM attending ACCESS clinics between 2016 and 2022.**

with HIV peaked in 2015, then declined when PrEP was rolled out from 2016. Taken together, these data show a convergence of syphilis risk among GBM with HIV and PrEP users.

Syphilis incidence was increasing among GBM classified as ever-PrEP users prior to PrEP availability in 2016. With retrospective classification of individuals as ever-PrEP users, higher and increasing incidence in this group likely reflects both pre-existing behaviours (e.g. early phases of PrEP roll-out in Australia through implementation studies included risk-based eligibility criteria, including recent condomless sex and prior STI diagnosis[35,36]) and the impact of initiating PrEP. However, previous analyses of GBM enrolled in two large PrEP implementation studies in Australia found no significant change in syphilis incidence immediately following PrEP initiation and no change in the rate of change of syphilis positivity following PrEP initiation, respectively.[17,37] The increasing rates of syphilis in the more prolonged observation period in this study suggest an acceleration of pre-existing trends caused by progressive changes in sexual networks which have been driven by increasing adoption of biomedical HIV risk reduction practices. Serial cross-sectional surveys from Melbourne show serosorting with casual partners declined from 67.5% in 2012 to 32.2% in 2021 among GBM with HIV.[19,38] Similarly, the number of GBM disclosing their HIV status to casual partners has declined,[19] and more GBM report comfort relying on PrEP for condomless sex.[15]

While the overall rate of repeated infection was stable over the observation period, previous diagnosis of syphilis was the strongest predictor of a future diagnosis and repeated syphilis incidence was higher than overall incidence. This included higher reinfection incidence among GBM with no evidence of PrEP, where repeated syphilis incidence was almost 7-fold greater than overall incidence, and across the entire observation period, not just in the period of widespread PrEP availability. However, testing and reinfection rates declined among GBM with HIV, likely due to less frequent HIV monitoring testing over time, as guidelines on how often GBM with HIV should have viral load/CD4 tests changed during the observation period. Taken together, these findings support the hypothesis that sexual networks play a key role in driving syphilis transmission, and that while these networks may be associated with serosorting among GBM with HIV in earlier years, and with reduced serosorting among PrEP users and GBM with HIV in the era of PrEP and U=U, networks likely also include HIV-negative GBM not using PrEP. Fully understanding the impact of sexual networks on syphilis transmission is made difficult by a lack of individual-level data on sexual mixing for detailed sexual network analysis.

Networks of high rates of reinfection offer ideal opportunities to impact population-level incidence by interrupting transmission chains. While campaigns aimed at reducing risk behaviour or improving early symptom recognition have generally shown poor impact,[39] clinically-led prevention interventions to enhance testing, detection and treatment rates, as well as novel biomedical prevention strategies such as doxycycline post-exposure prophylaxis (doxyPEP), which interrupt chains of transmission, may deliver population-level benefits. Multiple trials have explored the efficacy of doxyPEP,[40,41] with a recent trial showing reductions in syphilis of 87–77% among PrEP users and GBM with HIV receiving doxyPEP.[41] When balancing the potential impact of doxycycline PEP with concerns around adverse effects on gut health and the potential for community-level antimicrobial resistance associated with widespread use,[42] it should be acknowledged that doxycycline as STI prophylaxis is acceptable to many GBM[43] and data from Melbourne show that some GBM are already using doxycycline prophylactically.[44] Our finding that prior syphilis infection is the strongest predictor of future infection aligns with findings from US modelling which found prescribing doxyPEP for 12 months to GBM diagnosed with recent STIs, regardless of PrEP use or HIV status, would be an efficient strategy for reducing the number needed to treat to prevent a syphilis diagnosis.[45] Future guidelines for doxyPEP prescribing should include prior diagnosis as an indication for doxycycline prescribing, and not be limited to GBM using PrEP or living with HIV, as recommended in a recent Australian consensus statement on doxyPEP.[46]

Our data show that frequency of syphilis testing among all groups of GBM is well below the currently recommended three-monthly STI (syphilis, chlamydia and gonorrhea) screening for all sexually active GBM.[22] An Australian modelling study found that higher frequency of testing associated with wider PrEP uptake in isolation would likely not be enough to curtail the growing syphilis epidemic among the wider GBM population.[47] This model suggested that increasing testing frequency among those already being tested would have a greater impact on syphilis transmission than increasing testing coverage, a finding that has been echoed in modelling studies from North America.[48,49] In the context of limited resources and clinic capacity to increase testing, strategies that prioritise increased screening among people with a previous diagnosis may provide the greatest yield for diagnosing and interrupting transmission chains. Modelling highlights that strategies that increase screening among GBM with a prior syphilis infection are among the most efficient at reducing population-level syphilis.[50] New models of self-testing, including novel rapid point-of-care tests which detect acute syphilis infection[51,52] have great potential for enhancing overall rates of testing as well as supplementing clinic testing in specific subgroups who may benefit from more frequent screening.

Strengths and limitations

A number of limitations of our analysis should be noted. First, individuals might have been tested and diagnosed with syphilis at a clinic outside of the ACCESS network. However, given the short intervals between the tests included in this analysis (median 119 days), the effect of external testing is likely to have been minimal. Second, for individuals attending general practice clinics, in the absence of sexuality recorded on their electronic medical record, we relied on an algorithm of rectal swab testing among male patients to infer status of gay and bisexual men, which might have misclassified a small number of patients, although specificity for this algorithm was high (99%).[28] Third, 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. Fourth, we relied on electronic health record data for defining covariates in the Cox regression, and as such we were not able to adjust for unmeasured confounders, including behavioural and other sociodemographic factors associated with STI incidence. Further, hazard ratios have an inherent built-in selection bias as over time individuals in exposed and unexposed groups may not be interchangeable.[53] Finally, as missing data were likely missing due to system differences across clinics, and not missing at random, we were not able to impute missing data. Complete-case analysis may have introduced selection bias.

There are considerable strengths to this analysis. First, clinics participating in the ACCESS surveillance project have a significant coverage of GBM attending for STI testing in Australia. Although sexual orientation is not collected in national census data, a previous analysis which aimed to estimate the population of GBM in Australia by triangulating multiple data sources, including census data on same-gender-partnered households and six different surveys, estimated a population size of 130,000 GBM residing in Australia in 2016.[54] While our cohort reflects GBM attending over an 11-year period, approximating coverage using this population-size estimate, our syphilis incidence analysis captures in the order of 60–70% of all GBM residing in Australia. Second, the highly accurate data linkage between ACCESS clinics allowed us to longitudinally monitor individuals who transferred care between clinics participating in ACCESS and reduce loss to follow-up.

Conclusions

In this analysis of a large cohort of GBM accessing syphilis testing in Australia, we found that syphilis trends between GBM with HIV and those prescribed PrEP have converged over the past eleven years, and that rates of testing for syphilis continue to fall below recommended screening guidelines. While GBM with HIV and with a history of PrEP use were more likely to be diagnosed with syphilis, previous syphilis infection was the strongest predictor of subsequent infection, and rates of reinfection were high regardless of HIV status and PrEP use. In the era of HIV biomedical prevention, strategies to address increasing rates of syphilis, such as targeted screening and novel biomedical prevention strategies should focus on interrupting transmission within sexual networks associated with high rates of reinfection. Future guidelines for doxyPEP should include prior syphilis diagnosis as an indication for prescribing.

Contributors

MWT, RG, CT and MAS conceived the study.

MWT, RG, CT, VJC, EPFC, CKF, BD, MEH, MAS contributed substantially to interpretation of the data.

MWT undertook the formal data analysis.

MWT, JA and AC curated the data.

RG, JA, AC, BD, MEH and MAS coordinate the ACCESS study and were responsible for funding acquisition.

EPFC, MB, CKF, AM, PR, LO, NR, DJT 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.

MAS and MEH provided academic supervision.

MWT lead 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.

Data sharing statement

De-identified 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 de-identified data is available via the Burnet Institute 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.[26]

Declaration of interests

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M.E.H. reports investigator-initiated research grants from Gilead Sciences and Abbvie outside of the submitted work.

M.A.S. reports investigator-initiated research grants from Gilead Sciences and Abbvie and consulting fees from Gilead Sciences outside of the submitted work.

M.B. reports medical advisory boards and speakers' honoraria from Gilead Sciences and ViiV Healthcare, and funding to attend scientific meetings from Gilead Sciences, investigator-initiated research grants from ViiV Healthcare.

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VC received payment from Gilead Science for participation on advisory board.

DO is CEO of Health Equity Matters, Australia's peak community HIV organization, for part of the period during which the research was undertaken.

All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101175.

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