CSIRO PUBLISHING
Sexual Health
https://doi.org/10.1071/SH18215

Estimating the syphilis epidemic among gay, bisexual and other men who have sex with men in Australia following changes in HIV care and prevention

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Abstract. ***Background*:** Syphilis control remains a challenge in many high-income countries, including Australia, where diagnoses are concentrated among gay, bisexual men and other men who have sex with men (GBM). The aim of this study is to project the syphilis epidemic among GBM under a range of scenarios. ***Methods*:** A dynamic coinfection model of HIV and syphilis transmission among GBM in Victoria, Australia, was parametrised to test data from clinics in Melbourne and syphilis case notifications in Victoria. Projected outcomes were new syphilis infections between 2018 and 2025 under seven testing and behaviour change scenarios. ***Results*:** Among HIV-negative GBM, the model estimated that increasing syphilis testing coverage (69% – 75%) and frequency (~8-monthly – 6-monthly) could prevent 5% and 13% of syphilis cases respectively between 2018 and 2025 compared to the status quo. Among HIV-positive GBM, less syphilis testing due to changes in HIV care increased syphilis cases by 29% between 2018 and 2025 compared to the status quo. Under a scenario of 20% HIV pre-exposure prophylaxis (PrEP) coverage among HIV-negative GBM (and associated increased serodiscordant sex, reduced condom use and increased syphilis testing), syphilis cases were estimated to decrease by 6% among HIV-negative GBM and by 3% among HIV-positive GBM compared to the status quo, driven by increased testing among PrEP users. ***Conclusion*:** The present study findings support syphilis control policies focusing on increased testing among GBM. Current Australian PrEP guidelines of quarterly syphilis testing are likely to negate any increases in syphilis due to risk compensation occurring with PrEP scale-up.

Additional keywords: Australasia, mathematical models, pre-exposure prophylaxis, testing.

Received 17 April 2018, accepted 7 February 2019, published online 30 May 2019

Introduction

Resurgence of syphilis, a sexually transmissible infection (STI) caused by *Treponema pallidum*, has been observed in Western Europe,[1,2] North America[3] and Australia.[4] Diagnoses of infectious syphilis in Australia have increased considerably (~200%) over the past decade, with ~3300 cases notified in 2016. In 2016, the majority (87%) of syphilis notifications were among men, with surveillance in sexual health clinics showing

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HIV-positive men had the highest incidence of infectious syphilis.[5] The public health importance of reducing syphilis transmission among gay, bisexual and other men who have sex with men (GBM), in particular, is highlighted by a study in Melbourne, Victoria, Australia; similar to evidence of an association between HIV and rectal chlamydia and gonorrhoea,[6] syphilis may increase the risk of HIV seroconversion among GBM.[7]

Sexual behaviour drives syphilis transmission and reducing risk practices remains a challenge; in Australia, gradual increases in the proportions of GBM reporting condomless anal sex with casual partners has been observed.[8] Although investment in condom promotion continues, the local responses have emphasised syphilis testing among GBM, including use of social marketing campaigns,[9] education of general practitioners and 'opt-out' syphilis testing among HIV-positive GBM (syphilis serology conjoined with HIV monitoring blood tests).[10,11] Testing-based syphilis prevention strategies, however, rely on high-frequency testing among high-risk individuals to reduce transmission; despite considerable efforts, only moderate increases in syphilis testing have been seen so far.[12,13] There are also concerns about scale-up of HIV pre-exposure prophylaxis (PrEP) among GBM and associated reductions in condom use; increases in other sexually transmissible infections (STIs) have been seen in trial settings[14,15] and evidence of increased STI incidence is emerging from Australian PrEP demonstration projects[16] and larger implementation trials.[17]

Mathematical modelling can offer insights into the syphilis epidemic dynamics and the effect of interventions within a population. Gray *et al.* previously modelled the syphilis epidemic among GBM in Victoria, Australia, using community-based surveys to estimate testing frequency and examined the prevention effect of increased testing coverage and frequency.[18–20] Here, we used clinic attendance and testing surveillance data to estimate the baseline testing frequency and coverage, and projected the effect of increased coverage and frequency of syphilis testing among GBM. We also projected new syphilis cases under scenarios not previously considered, specifically reduced frequency of syphilis testing among HIV-positive GBM likely to result from reduced frequency of HIV monitoring and potential changes to sexual behaviour and syphilis testing frequency associated with HIV PrEP scale-up. We focussed on modelling policy relevant scenarios and aim to somewhat address the dearth of evidence and subsequent uncertainty about how to respond to syphilis in Australia.

Methods

Setting

Data on syphilis testing were from the Victorian Primary Care Network for Sentinel Surveillance (VPCNSS), which collates data from two high caseload metropolitan general practices that specialise in gay men's health and one major metropolitan sexual health centre in Victoria, Australia.[21] These sites diagnose ~65% of syphilis cases among GBM in Victoria[22] and see approximately one-third of GBM living with HIV who are engaged in care (Victorian Department of Health and Human Services and Burnet Institute, 2015, unpubl. data). Syphilis tests among GBM aged ≥16 years attending these VPCNSS sites between 1 January 2007 and 31 December 2014 were included.

Detailed methods of the VPCNSS have been described previously.[21] Briefly, the VPCNSS collated laboratory data, including syphilis test date, test outcome (negative, not active, new infection, positive unknown and indeterminate), date of birth, sex and HIV status (negative, positive or unknown). Within the VPCNSS dataset, syphilis test events were one test per person within a 30-day period; any additional tests within 30 days were excluded to distinguish follow-up screens from new test events. Indeterminate syphilis test results were also excluded. Tests among men with no HIV testing history, no HIV test at the time of syphilis testing or no subsequent HIV-negative test within VPCNSS were classified as HIV unknown and were excluded from analyses used to derive parameters. Remaining testing data between 1 January 2007 and 31 December 2014 were described by HIV status and the overall median days between the two most recent syphilis tests (among men with ≥2 tests) for HIV-negative and HIV-positive GBM were used as the rates of diagnoses in the syphilis model.

Estimates of syphilis testing coverage were obtained from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of blood borne viruses and sexually transmitted infections (ACCESS), a 2014 expansion and refinement of the VPCNSS that also captured consultation and additional clinical data (i.e. HIV viral load tests).[23] The proportion of GBM tested for syphilis at each clinic visit was used to estimate testing coverage, provided within routine reports to the state government from ACCESS (Burnet Institute 2015, unpubl. data). The VPCNSS has ethics approval from the Victorian Department of Health and Human Services (Project Number: 52/05) and Alfred Health (Project Number: 21/05). ACCESS has ethics approval from Alfred Health (Project Number: 248/17).

Model description

We used a dynamic co-infection model of HIV and syphilis among GBM in Victoria, Australia (Fig. 1).

HIV model

People in the model were classified as HIV negative or HIV positive. The HIV-negative population was stratified by HIV PrEP status (using PrEP or not using PrEP), and the HIV-positive population was stratified by stage in the care cascade (undiagnosed, diagnosed but not on treatment, on HIV treatment or on HIV treatment and virally supressed).

At each time step (representing 1 month in the model), HIV-negative individuals could become infected with HIV with a probability that depended on: their condom use; their PrEP status; the dynamic prevalence of HIV in the model (weighted to account for a reduction in infectiousness among HIV-positive people who were virally supressed); and a proportionality constant that was calibrated to fit the observed HIV prevalence over time in Victoria.

HIV-positive individuals were able to progress through the cascade of care at each time step. The rate of progression from

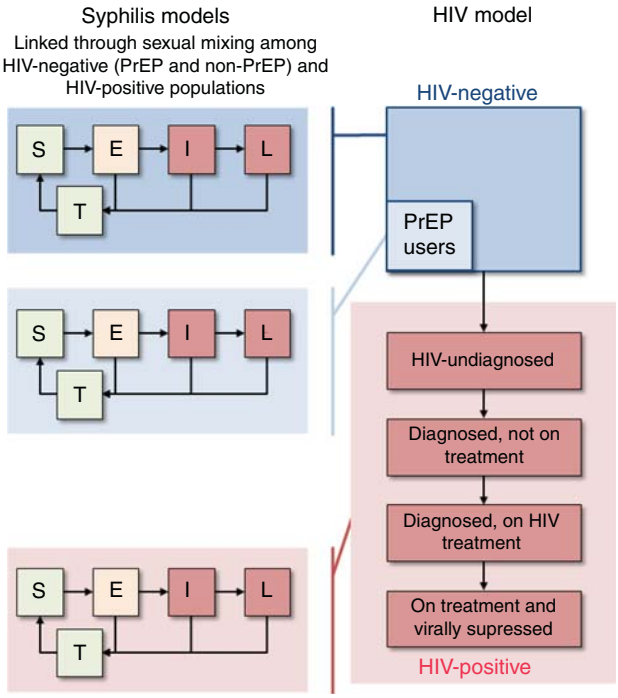

Fig. 1. Model schematic. A HIV transmission and care cascade progression model was coupled with a syphilis model for three subpopulations of gay and bisexual men (GBM): HIV-positive, HIV-negative not using pre-exposure prophylaxis (PrEP) and HIV-negative using PrEP. The syphilis models are linked through sexual mixing among the three subpopulations. Syphilis model compartments represent susceptible (S), exposed (E), infectious (I), late syphilis (L) and treatment (T). The three GBM population groups were further stratified so that a fraction were at higher risk of syphilis (not shown).

HIV undiagnosed to HIV diagnosed in the model was calibrated to fit Victorian HIV notification time series data.[5] Among people diagnosed with HIV, the fraction who were on treatment and the fraction who were virally supressed was fitted to estimates of the Australian HIV cascade of care and treatment.[5] For all forward projections, the HIV care cascade was modelled to continue to follow Australian trends towards achieving '95–95' (95% of people diagnosed started on treatment and 95% of people on treatment virally supressed) by 2030 (Figure S1, available as Supplementary Material to this paper).

Syphilis model

A syphilis model was included for HIV-negative individuals not on PrEP, HIV-negative individuals on PrEP and HIV-positive individuals. The syphilis models classified individuals as being susceptible (S; uninfected), exposed (E; infected but not infectious), infectious (I), in the late syphilis disease stage (L) or being treated (T).

At each time step, susceptible individuals could become infected with syphilis at a rate that depended on: their condom use; the dynamic syphilis prevalence in the model among the GBM they were assumed to mix with sexually; and a proportionality constant that was calibrated to fit the observed syphilis notifications among HIV-negative (PrEP and non-PrEP combined) and HIV-positive GBM over time in Victoria. In the base scenario, sexual mixing between HIV-negative and HIV-positive subpopulations was assumed to be mostly (95%) seroconcordant,[24] while HIV-negative PrEP and non-PrEP users were assumed to mix proportionally (i.e. at random).

Individuals who became infected, unless tested, were moved to the exposed compartment, and after an incubatory period of 3 weeks,[25,26] exposed individuals were moved to the infectious compartment (comprising of primary, secondary and early latent syphilis) where they spent an average of 2 years before entering the late latent syphilis stage.[26] A median time between tests was applied to the HIV-negative PrEP, HIV-negative non-PrEP and HIV-positive groups, and at any stage of syphilis infection if an individual was tested, they were assumed to be treated[25] and returned to the susceptible compartment.

Each subpopulation (HIV-negative PrEP, HIV-negative non-PrEP, HIV-positive) was further stratified by syphilis infection risk (high or low — PrEP trial data in Australia found that 18% of participants accounted for 68% of STI infections),[17] with the high-risk subgroup having 9.68-fold the force of infection as the low-risk group (Table S1, available as Supplementary Material to this paper).

Model population and calibration

The total model population varied over time based on the assumption that there were ~42 000 GBM in Victoria in 2006,[27] and that this number of GBM was assumed to grow by 5% per annum.

A two-step process was used to calibrate the model. First, the force of infection constant for HIV and the diagnosis rate for HIV were calibrated to best fit annual data for the estimated number of HIV-positive GBM in Victoria and Victorian HIV notifications. Once this was done, the force of infection constant for syphilis among HIV-negative GBM and the force of infection constant for syphilis among HIV-positive GBM were calibrated to best fit annual data for syphilis notifications among HIV-negative and HIV-positive GBM (enhanced surveillance provides proportion of notifications among GBM by HIV status).

Model parameters are provided in Table S1, and model population sizes and calibration data are provided in Table S2.

Dynamic transmission model outputs

Once calibrated, we used the model to estimate and project the number of new syphilis cases (as opposed to notifications) among Victorian HIV-negative and HIV-positive GBM between 2018 and 2025 for each scenario in Table 1.

Sensitivity analysis

A sensitivity analysis was conducted to test the influence of the various assumptions around increasing PrEP use. Scenarios were tested where PrEP uptake was either 10% or 30% of HIV-negative GBM compared with 20%; condom use was reduced by 25% or 75% among men on PrEP compared with being reduced by 50%; the amount of HIV serodiscordant mixing either did not change for men on PrEP or increased from 5% to 15% compared with increasing from 5% to 10%; and there was no increased testing as part of accessing PrEP

Table 1. Description of the intervention scenarios examined by the dynamic transmission model
GBM, gay, bisexual and other men who have sex with men; PrEP, HIV pre-exposure prophylaxis

Intervention	Description and model implementation
HIV-negative GBM: increase testing coverage.	a. Increasing the proportion of HIV-negative GBM testing at a median time of 224 days[A] from 69%[B] to 75%.
HIV-negative GBM: increase testing frequency.	b. Decrease the median time between syphilis tests from 224[A] to 180 days.
HIV-negative GBM: increase testing coverage and frequency.	c. Combine scenarios *a* and *b* among HIV-negative GBM.
HIV-positive GBM: decrease frequency of HIV care.	d. HIV-positive GBM who are engaged in care increase their time between tests (conjoined syphilis and HIV viral load) from a median of 133 days[A] to 180 days.[C,28]
Increasing PrEP coverage to 20% of GBM.	e. Increasing the proportion of serodiscordant anal sex acts from 5%[24] to 10% among the additional 20% of HIV-negative GBM on PrEP.
	f. Increase the proportion of serodiscordant anal sex acts from 5%[24] to 10%, and reduce condom use by 50%[16] among the additional 20% of HIV-negative GBM on PrEP.
	g. Increase the proportion of serodiscordant acts from 5%[24] to 10% and decrease time between syphilis tests from a median of 224 days[A] to 90 days[29] for the 20% of HIV-negative GBM on PrEP.
	h. Increase the proportion of serodiscordant acts from 5%[24] to 10%, reduce condom use by 50%[16] and decrease time between syphilis tests from a median of 224 days[A] to 90 days[29] for the additional 20% of HIV-negative GBM on PrEP.

[A]Victoria Primary Care Network for Sentinel Surveillance (VPCNSS) 2007–14, time between two most recent tests among GBM with multiple tests in this period.
[B]Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of blood borne viruses and sexually transmitted infections (ACCESS) 2015, unpubl. data.
[C]In 2014, 85% of HIV viral load tests were accompanied by syphilis serology among HIV-positive men attending VPCNSS clinics (unpubl. data, Burnet Institute 2015).

compared with men having a syphilis test every 90 days alongside their visits for supply of PrEP medication.

Results

Surveillance data

VPCNSS collated 102 041 syphilis tests conducted among GBM at the three VPCNSS clinics between 2007 and 2014. Analysis excluded 2930 tests because of indeterminate results ($n = 119$) and repeat tests within 30 days for the same individual ($n = 2811$). Of the remaining 99 111 syphilis tests, 3.7% ($n = 3668$) were among 2719 GBM with unknown HIV status, and therefore were excluded. A median time between individuals' two most recent syphilis tests of 224 days was used to approximate baseline testing frequency among HIV-negative GBM, and a median time of 133 days was used to approximate baseline testing frequency among HIV-positive GBM.

Syphilis testing coverage or frequency

The data showed rapidly increasing numbers of syphilis notifications for both HIV-negative and HIV-positive GBM between 2010 and 2015 (Fig. 2) and the model was calibrated to fit this trend. The model outputs for scenarios a–d, including the baseline scenario of status quo, are shown in Figure 3 and Table 2. The model estimated that among Victorian GBM, a cumulative 11 353 syphilis cases would occur between 2018 and 2025 under the status quo. Among HIV-negative GBM, increasing syphilis testing coverage from 69% to 75% was projected to avert 5% of syphilis cases compared to the status quo, while increasing syphilis testing frequency from approximately every 8 months to every 6 months averted 13% of syphilis cases compared to the status quo. Additional gains were achieved when syphilis testing coverage and frequency were increased together, with scenario (c) projected to avert 29% of cumulative syphilis cases in HIV-negative GBM between 2018 and 2025 compared to the status quo.

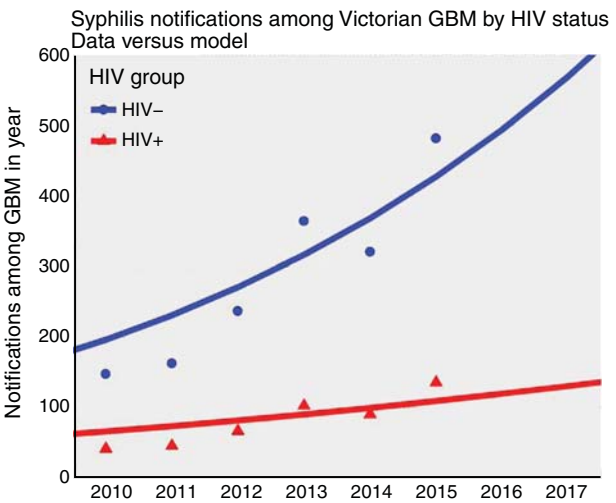

Fig. 2. Model calibration results. Annual notifications of syphilis 2010–15 (unpubl. data, Burnet Institute, provided by Victorian Department of Health and Human Services) among HIV-negative and HIV-positive gay and bisexual men (GBM) in Victoria, compared with the model fit.

Despite the intervention population for scenarios a–c being HIV negative GBM, benefits were also observed for HIV-positive GBM due to HIV serodiscordant sex (assumed 5%; Fig. 3 and Table 2).

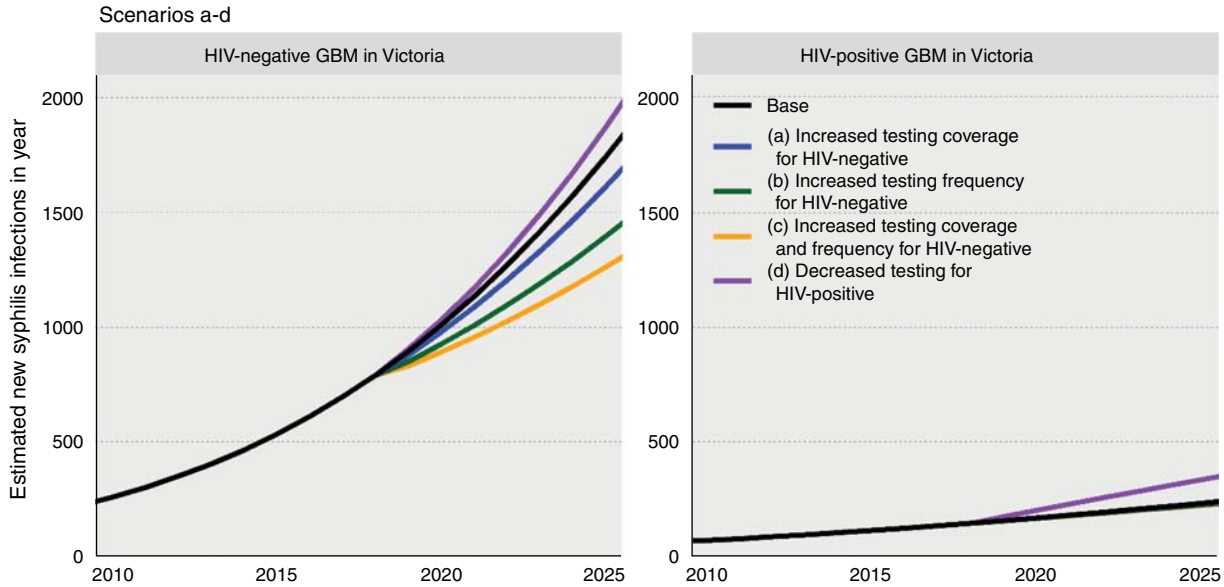

Fig. 3. Model projections for changes in testing coverage and frequency. Estimated annual number of new syphilis infections among HIV-negative gay and bisexual men (GBM) (left) and HIV-positive GBM (right) when: (a) the proportion of HIV-negative GBM testing frequently was increased from 69% to 75%; (b) the median time between syphilis tests for HIV-negative GBM was reduced from 224 days to 180 days; (c) scenarios (a) and (b) together; and (d) 90% of HIV-positive GBM increased their time between tests from the median of 133 days to every 180 days.

Table 2. Projected syphilis cases among Victorian GBM by HIV status after implementing scenarios (a) to (h) in the model. Estimates for the cumulative number of cases (*n*) and percentage difference (%) comparing the base scenario of status quo and the intervention scenario, between 2018 and 2025

GBM, gay, bisexual and other men who have sex with men; PrEP, HIV pre-exposure prophylaxis

Time	HIV-negative cumulative cases 2018–25	HIV-positive cumulative cases 2018–25	Total cumulative cases 2018–25
Cumulative syphilis cases under status quo	9837	1516	11 353
Scenarios			
a. HIV-negative GBM: increase testing coverage	9353 (–5%)	1508 (–1%)	10 861 (–4%)
b. HIV-negative GBM: increase testing frequency	8539 (–13%)	1494 (–1%)	10 032 (–12%)
c. Scenarios *a* and *b* combined	8024 (–18%)	1485 (–2%)	9508 (–16%)
d. HIV-positive GBM: decrease frequency of HIV care	10269 (4%)	1956 (29%)	12 225 (8%)
Introduction of pre-exposure prophylaxis:			
e. Increasing the proportion of serodiscordant sex acts from 5 to 10%	9933 (1%)	1482 (–2%)	11 415 (1%)
f. Increase serodiscordant sex and reduce condom use by 50% among the 20% of HIV-negative GBM using PrEP	10 668 (8%)	1493 (–2%)	12 161 (7%)
g. Increase serodiscordant sex and increase testing frequency to 90 days for the 20% of HIV-negative GBM using PrEP	8684 (–12%)	1466 (–3%)	10 149 (–11%)
h. Increase serodiscordant sex, reduce condom use and increase testing frequency for the 20% of HIV-negative GBM using PrEP	9256 (–6%)	1474 (–3%)	10 730 (–5%)

Decreasing testing frequency for HIV-positive GBM

Reducing the frequency of syphilis testing among HIV-positive GBM from ~4-monthly to every 6 months resulted in a 29% increase in syphilis cases among HIV-positive GBM between 2018 and 2025 compared to the status quo. This scenario also resulted in a 4% increase in syphilis cases among HIV-negative GBM between 2018 and 2025 due to HIV serodiscordant sex.

Introduction of HIV pre-exposure prophylaxis

The scale-up of HIV PrEP coverage from a baseline scenario of no HIV PrEP to 20% of HIV-negative GBM accessing PrEP was estimated to result in a 6% reduction in syphilis cases among HIV-negative GBM between 2018 and 2025 compared to the status quo [Fig. 4 and Table 2 (scenario h)]. The observed reduction was because the negative effects of reduced condom use and increased mixing with a higher syphilis prevalence group (HIV-positive GBM) were outweighed by the benefits of an increased testing frequency for GBM on PrEP (Table 2, scenarios e–g).

PrEP scale-up among HIV-negative GBM was also projected to decrease syphilis cases among HIV-positive GBM by 3% between 2018 and 2025 (scenario h), due largely to the increased serodiscordant sex with the lower syphilis prevalent

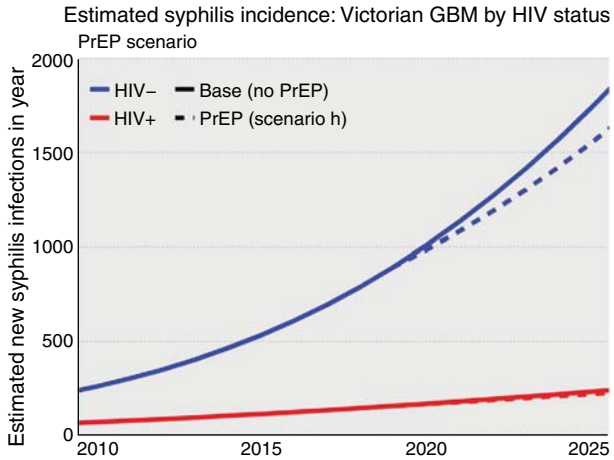

Fig. 4. Model projections for increased pre-exposure prophylaxis (PrEP) uptake. Estimated annual number of new syphilis infections among HIV-negative and HIV-positive gay and bisexual men (GBM) for an estimated 20% increase in HIV-negative GBM on PrEP. For men on PrEP, the proportion of serodiscordant acts was increased from 5% to 10%, condom use was reduced by 50% and syphilis testing was increased from a median of 224 days to 90 days (scenario (h) in Table 3).

HIV-negative GBM population. Among all GBM, PrEP scale-up was projected to result in a 5% decrease in syphilis cases between 2018 and 2025 compared to the status quo (Table 2, scenario h).

Sensitivity analysis

Figure 5 shows model sensitivity to the four key assumptions around PrEP uptake: coverage, condom use, serodiscordant sex and testing frequency. Model outcomes were most sensitive to changes in syphilis testing behaviour for GBM on PrEP. If 90-day syphilis testing among men on PrEP did not occur, that is, testing remained every ~200 days because men declined testing or testing was not offered at every 3-monthly PrEP care visit, then the model estimated there to be a 10% increase in syphilis cases between 2018 and 2025 compared to the status quo. Possible decreases in condom use associated with PrEP uptake also had an influence on epidemiological outcomes in the model (Fig. 5 top right and Table 3). For example, decreases in condom use of 25, 50 or 75% among GBM when on PrEP were projected to lead to 8%, 5% or 3% decreases in estimated syphilis cases between 2018 and 2025 respectively.

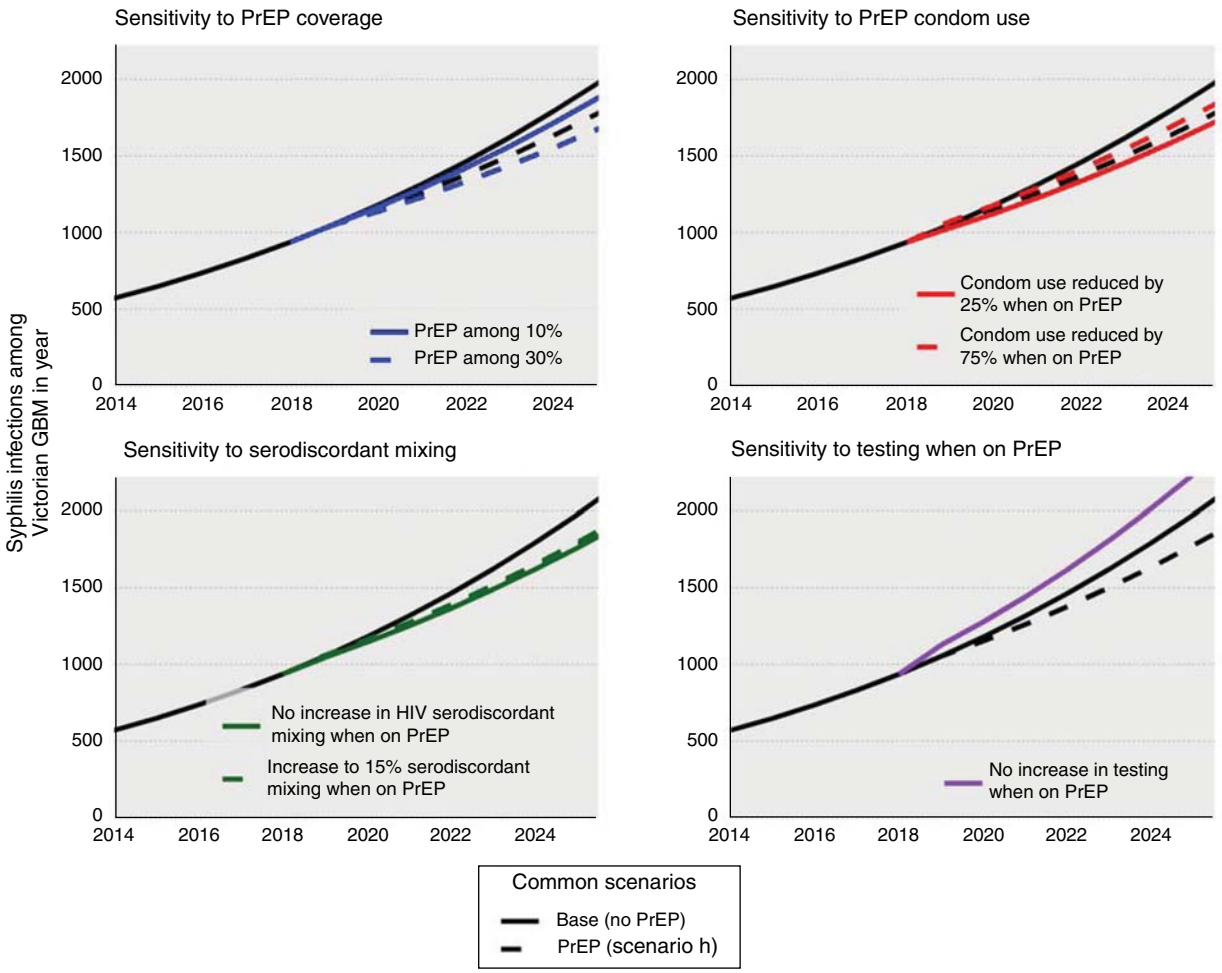

Fig. 5. Model sensitivity to assumptions around pre-exposure prophylaxis (PrEP) uptake. Estimated annual number of new syphilis infections among all gay and bisexual men (GBM) in Victoria when: PrEP uptake was either 10% or 30% of HIV-negative GBM compared with 20% (top left); condom use was reduced by 25% or 75% among men on PrEP compared with being reduced by 50% (top right); the amount of HIV serodiscordant mixing either did not change for men on PrEP or increased from 5% to 15% compared with increasing from 5% to 10% (bottom left); and there was no increased testing as part of enrolment in PrEP compared with a 90-day requirement (bottom right).

Table 3. Changes in the number of projected syphilis cases when altering single, specific parameters around PrEP uptake within scenario (h)

PrEP scenario (h) was: increase the proportion of serodiscordant acts from 5% to 10%, reduce condom use by 50% and decrease time between syphilis tests from a median of 224 days to 90 days for the additional 20% of HIV-negative GBM on PrEP. PrEP, HIV pre-exposure prophylaxis

Scenario	Estimated cumulative number of new syphilis infections 2018–30	Percentage change from scenario with no PrEP
Base (no PrEP)	11 353	N/A
PrEP (scenario h)	10 730	–6
PrEP, among 10% of men only	11 047	–3
PrEP, among 30% of men only	10 404	–8
PrEP, with condom use reduced by 25%	10 439	–8
PrEP, with condom use reduced by 75%	11 023	–3
PrEP, with no increase in HIV serodiscordant mixing	10 641	–6
PrEP, with 15% increase in HIV serodiscordant mixing	10 817	–5
PrEP, with no increase in syphilis testing frequency	12 535	+10

Discussion

We used local surveillance data to establish pre-existing syphilis testing trends among GBM and used a mathematical model to project the effect that changes in syphilis testing could have on syphilis incidence in the context of modern HIV prevention and care. Consistent with other studies,[18,30] the model projected that reducing new syphilis cases is dependent on increasing testing coverage and frequency, and that relatively modest improvements in routine testing could substantially effect local syphilis epidemiology. The model projected that overall syphilis incidence may decrease as a result of PrEP scale-up among GBM, as a result of more regular testing associated with 3-monthly PrEP clinic visits; however, reduced syphilis testing associated with a reduced frequency of HIV clinical care visits could lead to an increase in syphilis transmissions. Our findings provide important practical and pragmatic guidance for syphilis prevention interventions among GBM.

We show that combined modest increases in syphilis testing frequency and coverage among HIV-negative GBM could have a considerable effect on the syphilis epidemic. However, even increasing syphilis testing frequency modestly among GBM may prove challenging. Despite significant investment in strategies to enhance HIV testing among GBM in Australia,[31,32] only small improvements in testing frequency have been seen.[12,33] While structural barriers associated with clinic-based laboratory HIV testing identified by GBM locally[34,35] could be addressed through point-of-care[36] and self-testing models,[37] such adaptive models are not possible in high syphilis incidence settings without a reliable non-*Treponema pallidum* syphilis point-of-care test.[38]

Maintaining conjoined syphilis testing for HIV-positive GBM as part of routine HIV monitoring[10,11,39] also appears critical. Any further gains in increasing HIV testing in clinics would therefore benefit syphilis control, and interventions that increase in syphilis testing could enhance HIV testing.[40] However, following recent changes in HIV care guidelines,[41] evidence of less frequent HIV monitoring at Australian sexual health clinics is emerging.[13] Our findings suggest this change in practice may undermine syphilis prevention and highlights an urgent need to develop new strategies to facilitate HIV-positive GBM screening for syphilis and other STIs outside routine HIV care appointments.

Our model suggests an overall positive effect of PrEP scale-up on syphilis transmissions among GBM compared to the status quo. Despite enhanced syphilis transmission risk associated with increased HIV serodiscordant sex and reduced condom use among HIV-negative GBM using PrEP, this was more than offset by 3-monthly syphilis tests occurring during PrEP clinic visits. These findings have implications for syphilis prevention in settings where PrEP can be accessed without opportunities for STI testing, such as through self-importation, or where guidelines recommend less than 3-monthly STI testing. Jenness *et al*. modelled the current US recommendation of biannual STI testing among PrEP users and showed that considerable reductions in incident gonorrhoea and chlamydia infections occurred, but further reductions would be possible with quarterly testing.[42] Initial data from Melbourne's only PrEP implementation trial showed an increased incidence of STIs following initiation of PrEP. However, STI testing increased substantially, particular among naïve PrEP users (48% increase in clinic visits compared with the 12 months before starting PrEP), which therefore increased the detection of infections.[17]

The model projected the effect of scenarios that are plausible and policy-relevant and accounted for differences in testing and treatment per syphilis disease stage and HIV status; however, there were limitations. Parameters were derived from data collected at high caseload clinics participating in sentinel surveillance. The model assumed that only a proportion of GBM accessed testing services, and the testing frequency of these GBM was based on clinics in the VPCNSS data. GBM self-refer to these clinics (including HIV-positive men) and their testing frequency may not be completely representative of all GBM. Our base scenario estimate of risk compensation for GBM taking PrEP was derived from a local demonstration project with a short follow up and potential selection bias (i.e. early adopters, high-risk men) and may under or over state population-level reductions of condom use. However, this represents the best

available local evidence and we tested the sensitivity of the condom use parameter. Measuring changes in condom use associated with PrEP uptake should be a focus of future studies to ensure reliable understandings of the effect PrEP scale-up will have for STI transmission. There were also limitations to the modelling methodology. For example, our syphilis infectious compartment covers both primary, secondary syphilis and early latent syphilis. Individuals may be more infectious in the primary and secondary stages, but because robust estimates of the relative increase in infectiousness are largely unavailable, a single compartment was used to represent a combined average. If the majority of onward transmission occurs within primary and secondary stages (i.e. within 3–6 months of exposure) due to elevated infectiousness, then high-frequency testing strategies would be even more critical and more effective than we have estimated. We also assumed that PrEP use was static because data on individuals cycling on and off PrEP was not available at the time of the study, and we also did not model lost-to-follow-up in the HIV care cascade; however, this is unlikely to influence results, as our aims relate primarily to the syphilis component of the model.

Syphilis control among GBM remains a challenge in many settings. While based on local data, our study provides valuable learnings to inform planning and advocate for investment in targeted interventions in other settings where syphilis transmission is concentrated among GBM. Mitigating the potential for increased syphilis transmission among GBM due to innovations in biomedical HIV prevention is needed. Fewer opportunities for STI testing in the context of less frequent visits for HIV care are likely to increase syphilis transmission. Alongside an ongoing role for condom distribution and education programs, our findings emphasise the need for frequent syphilis testing as a part of PrEP access programs and for seeking opportunities for syphilis testing between clinic visits for PrEP and HIV care.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

This work was supported by The Victorian Department of Health and Human Services through support for surveillance projects within the Burnet Institute. The National Health and Medical Research Council provide funding to Margaret Hellard as a Principal Research Fellow (1112297) and Mark Stoové as a Career Development Fellow (1090445). Dr Nick Scott is supported by funding through the Margaret and Jim Beaver Fellowship. This work was supported by the Victorian Operational Infrastructure Support Program. The authors acknowledge the clinics and laboratories that contribute surveillance data and their patients. The data that support the findings of this study are available from ACCESS and the Victorian Department of Health and Human Services, but restrictions apply to the availability of these data and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of ACCESS or Victorian Department of Health and Human Services.

References

1 Jebbari H, Simms I, Conti S, Marongui A, Hughes G, Ward H, Powers C, Thomas DR, Evans B. Variations in the epidemiology of primary, secondary and early latent syphilis, England and Wales: 1999 to 2008. *Sex Transm Infect* 2011; 87(3): 191–8. doi:10.1136/sti.2009.040139

2 Simms I, Wallace L, Thomas DR, Emmett L, Shankar AG, Vinson M, Padfield S, Andrady U, Whiteside C, Williams CJ, Midgley C, Johnman C, McLellan A, Curri A, Logan J, Leslie K, Hughes G. Recent outbreaks of infectious syphilis, United Kingdom, January 2012 to April 2014. *Euro Surveill* 2014; 19(24): pii=20833. doi:10.2807/1560-7917.ES2014.19.24.20833

3 Bernstein KT, Stephens SC, Strona FV, Kohn RP, Philip SS. Epidemiologic characteristics of an ongoing syphilis epidemic among men who have sex with men, San Francisco. *Sex Transm Dis* 2013; 40(1): 11–7. doi:10.1097/OLQ.0b013e31827763ea

4 Guy RJ, Leslie DE, Simpson K, Hatch B, Leydon J, Hellard ME, Kelly HA. Sustained increase in infectious syphilis notifications in Victoria. *Med J Aust* 2005; 183(4): 218.

5 Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2017. Sydney: Kirby Institute, UNSW Sydney; 2017.

6 Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. *J Acquir Immune Defic Syndr* 2010; 53(4): 537–43. doi:10.1097/QAI.0b013e3181c3ef29

7 Guy RJ, Spelman T, Stoove M, El-Hayek C, Goller J, Fairley CK, Leslie D, Tee BK, Roth N, Grulich AE, Hellard ME. Risk factors for HIV seroconversion in men who have sex with men in Victoria, Australia: results from a sentinel surveillance system. *Sex Health* 2011; 8(3): 319–29. doi:10.1071/SH10095

8 Mao L, Kippax SC, Holt M, Prestage GP, Zablotska IB, de Wit JB. Rates of condom and non-condom-based anal intercourse practices among homosexually active men in Australia: deliberate HIV risk reduction? *Sex Transm Infect* 2011; 87(6): 489–93. doi:10.1136/sextrans-2011-050041

9 Pedrana A, Hellard M, Guy R, El-Hayek C, Gouillou M, Asselin J, Batrouney C, Nguyen P, Stoové M. Stop the drama Downunder: a social marketing campaign increases HIV/sexually transmitted infection knowledge and testing in Australian gay men. *Sex Transm Dis* 2012; 39(8): 651–8. doi:10.1097/OLQ.0b013e318255df06

10 Callander D, Baker D, Chen M, Guy R. Including syphilis testing as part of standard HIV management checks and improved syphilis screening in primary care. *Sex Transm Dis* 2013; 40(4): 338–40. doi:10.1097/OLQ.0b013e31828052c5

11 Guy R, El-Hayek C, Fairley CK, Wand H, Carr A, McNulty A, Hoy J, Bourne C, McAllister J, Tee BK, Baker D, Roth N, Stoové M, Chen M. Opt-out and opt-in testing increases syphilis screening of HIV-positive men who have sex with men in Australia. *PLoS One* 2013; 8(8): e71436. doi:10.1371/journal.pone.0071436

12 Wilkinson AL, El-Hayek C, Spelman T, Fairley C, Leslie D, McBryde E, Hellard M, Stoové M. "Seek, test, treat" lessons from Australia: a study of HIV testing patterns from a cohort of men who have sex with men. *J Acquir Immune Defic Syndr* 2015; 69(4): 460–5. doi:10.1097/QAI.0000000000000613

13 Chow EPF, Callander D, Fairley CK, Zhang L, Donovan B, Guy R, Lew DA, Hellard M, Read P, Ward A, Chen MY. Increased syphilis testing of men who have sex with men: greater detection of asymptomatic early syphilis and relative reduction in secondary syphilis. *Clin Infect Dis* 2017; 65(3): 389–95. doi:10.1093/cid/cix326

14 Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrota M, Hosek S, Mosquera C, Casapia M, Motoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, *et al*. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014; 14(9): 820–9. doi:10.1016/S1473-3099(14)70847-3

15 Beymer MR, DeVost MA, Weiss RE, Dierst-Davies R, Shover CL, Landovitz RJ, Beniasians C, Talan AJ, Flynn RP, Krysiak R, McLaughlin K, Bolan RK. Does HIV pre-exposure prophylaxis use lead to a higher incidence of sexually transmitted infections? A case-crossover study of men who have sex with men in Los Angeles, California. *Sex Transm Infect* 2018; 94(6): 457–62. doi:10.1136/sextrans-2017-053377

16 Lal L, Audsley J, Murphy D, Fairley CK, Stoové M, Roth N, Moore R, Tee BK, Puratmaja N, Anderson PL, Leslie D, Grant RM, de Wit J, Wright E. Medication adherence, condom use and sexually transmitted infections in Australian PrEP users: interim results from the Victorian PrEP Demonstration Project. *AIDS* 2017; 31 (12): 1709–14. doi:10.1097/QAD.0000000000001519

17 Traeger M, Asselin J, Price B, Cornelisse V, Roth N, Wilcox J, Tee BK, Fairley C, Chang C, Armishaw J, Vujovic O, Penn M, Cundill P, Forgan-Smith G, Gall J, Lal L, Mak A, Spelman T; PrEPX Study Team. Changes, patterns and predictors of sexually transmitted infections in gay and bisexual men using PrEP; interim analysis form the PrEPX demonstration study. Presented at the 22nd International AIDS Conference; 23–27 July 2018; Amsterdam, The Netherlands. Available online at: http://programme.aids2018.org/Programme/Session/1457 [verified 22 May 2019].

18 Gray RT, Hoare A, Prestage GP, Donovan B, Kaldor JM, Wilson DP. Frequent testing of highly sexually active gay men is required to control syphilis. *Sex Transm Dis* 2010; 37(5): 298–305.

19 Down I, Wilson DP, McCann PD, Gray R, Hoare A, Bradley J, Donovan B, Prestage G. Increasing gay men's testing rates and enhancing partner notification can reduce the incidence of syphilis. *Sex Health* 2012; 9(5): 472–80. doi:10.1071/SH12023

20 Wilson DP, Prestage GP, Gray RT, Hoare A, McCann P, Down I, Guy RJ, Drummond F, Klausner JD, Donovan B, Kaldor JM. Chemoprophylaxis is likely to be acceptable and could mitigate syphilis epidemics among populations of gay men. *Sex Transm Dis* 2011; 38(7): 573–9. doi:10.1097/OLQ.0b013e31820e64fd

21 Goller JL, Guy RJ, Gold J, Lim MS, El-Hayek C, Stoové MA, Bergeri I, Fairley CK, Leslie DE, Clift P, White B, Hellard ME. Establishing a linked sentinel surveillance system for blood-borne viruses and sexually transmissible infections: methods, system attributes and early findings. *Sex Health* 2010; 7(4): 425–33. doi:10.1071/SH09116

22 Victorian Department of Health and Human Services. Victorian Infectious Disease Bulletin Vol 17 Issue 1 March 2014. In Infectious disease surveillance in Victoria. Communicable Disease Prevention and Control. Melbourne: Department of Health and Human Services; 2014. Available online at: https://www2.health.vic.gov.au [verified 15 January 2017].

23 Guy RJ, Kong F, Goller J, Franklin N, Bergeri I, Dimech W, Reilly N, Sullivan E, Ward J, Kaldor JM, Donovan B; the ACCESS Collaboration. A new national chlamydia sentinel surveillance system in Australia: evaluation of the first stage of implementation. *Commun Dis Intell Q Rep* 2010; 34(3): 319–28.

24 Lee E, Mao L, McKenzie T, Batrouney C, West M, Prestage G, Zablotska I, de Wit J, Holt M. Gay community periodic survey: Melbourne 2016. Sydney: Centre for Social Research in Health, UNSW Australia; 2016.

25 Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. *JAMA* 2014; 312(18): 1905–17. doi:10.1001/jama.2014.13259

26 French P. Syphilis. *BMJ* 2007; 334(7585): 143–7. doi:10.1136/bmj.39085.518148.BE

27 Prestage G, Ferris J, Grierson J, Thorpe R, Zablotska I, Imrie J, Smith A, Grulich AE. Homosexual men in Australia: population, distribution and HIV prevalence. *Sex Health* 2008; 5(2): 97–102. doi:10.1071/SH07080

28 Australian Society for HIV Medicine. Antiretroviral guidelines US DHHS guidelines with Australian commentary. Sydney: Australian Society for HIV Medicine; 2016. Available online at: http://arv.ashm.org.au/ [verified 4 September 2017].

29 Wright E, Grulich AE, Roy K, Boyd M, Cornelisse V, Russel D, O'Donnell D, Whittaker B, Crooks L, Zablotska I. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines. *J Virus Erad* 2017; 3(3): 168–84.

30 Tuite A, Fisman D. Go big or go home: impact of screening coverage on syphilis infection dynamics. *Sex Transm Infect* 2016; 92(1): 49–54. doi:10.1136/sextrans-2014-052001

31 Wilkinson AL, Pedrana AE, El-Hayek C, Vella AM, Asselin J, Batrouney C, Fairley CK, Read TR, Hellard M, Stoové M. The impact of a social marketing campaign on HIV and sexually transmissible infection testing among men who have sex with men in Australia. *Sex Transm Dis* 2016; 43(1): 49–56. doi:10.1097/OLQ.0000000000000380

32 Knight V, Wand H, Gray J, Keen P, McNulty A, Guy R. Implementation and operational research: convenient HIV testing service models are attracting previously untested gay and bisexual men: a cross-sectional study. *J Acquir Immune Defic Syndr* 2015; 69(5): e147–55. doi:10.1097/QAI.0000000000000688

33 Wilkinson AL, El-Hayek C, Spelman T, Fairley CK, Leslie D, McBryde ES, Hellard M, Stoové M. A 'test and treat' prevention strategy in Australia requires innovative HIV testing models: a cohort study of repeat testing among 'high-risk' men who have sex with men. *Sex Transm Infect* 2016; 92(6): 464–6. doi:10.1136/sextrans-2015-052421

34 Conway DP, Holt M, Couldwell DL, Smith DE, Davies SC, McNulty A, Keep P, Cunningham P, Guy R. Barriers to HIV testing and characteristics associated with never testing among gay and bisexual men attending sexual health clinics in Sydney. *J Int AIDS Soc* 2015; 18(1): 20221 doi:10.7448/IAS.18.1.20221

35 Prestage G, Brown G, Keen P. Barriers to HIV testing among Australian gay men. *Sex Health* 2012; 9(5): 453–8. doi:10.1071/SH12033

36 Leitinger D, Ryan KE, Brown G, Pedrana A, Wilkinson AL, Ryan C, Hellard M, Stoové M. Acceptability and HIV prevention benefits of a peer-based model of rapid point of care HIV Testing for Australian gay, bisexual and other men who have sex with men. *AIDS Behav* 2018; 22(1): 178–189.

37 Jamil MS, Prestage G, Fairley CK, Grulich AE, Smith KS, Chen M, Holt M, McNulty AM, Bavinton BR, Conway DP, Wand H, Keen P, Bradley J, Kolstee J, Batrouney C, Russell D, Law M, Kaldor JM, Guy RJ. Effect of availability of HIV self-testing on HIV testing frequency in gay and bisexual men at high risk of infection (FORTH): a waiting-list randomised controlled trial. *Lancet HIV* 2017; 4(6): e241–50. doi:10.1016/S2352-3018(17)30023-1

38 Causer LM, Kaldor JM, Fairley CK, Donovan B, Karapanagiotidis T, Leslie DE, Robertson PW, McNulty AM, Anderson D, Wand H, Conway DP, Denham I, Ryan C, Guy RJ. A laboratory-based evaluation of four rapid point-of-care tests for syphilis. *PLoS One* 2014; 9(3): e91504. doi:10.1371/journal.pone.0091504

39 Trubiano JA, Hoy JF. Taming the great: enhanced syphilis screening in HIV-positive men who have sex with men in a hospital clinic setting. *Sex Health* 2015; 12(2): 176–8. doi:10.1071/SH14164

40 Zou H, Fairley CK, Guy R, Chen MY. The efficacy of clinic-based interventions aimed at increasing screening for bacterial sexually transmitted infections among men who have sex with men: a systematic review. *Sex Transm Dis* 2012; 39(5): 382–7. doi:10.1097/OLQ.0b013e318248e3ff

41 Australasian Society for HIV Medicine. Australian Commentary. US public health service clinical practice guidelines on prescribing PrEP. Sydney: Australasian Society for HIV Medicine; 2015. Available online at: http://arv.ashm.org.au/images/Australian_National_PrEP_Guidelines.PDF [verified 19 June 2017].

42 Jenness SM, Weiss KM, Goodreau SM, Gift T, Chesson H, Hoover KW, Smith DK, Liu AY, Sullivan PS, Rosenberg ES. Incidence of gonorrhea and chlamydia following HIV preexposure prophylaxis among men who have sex with men: a modeling study. *Clin Infect Dis* 2017; 65(5): 712–8. doi:10.1093/cid/cix439