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# Incidence of syphilis among HIV-infected men in Singapore, 2006–2017: temporal trends and associated risk factors

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## ABSTRACT

**Objective** There have been recent reports globally on substantial increase in syphilis diagnoses particularly among high-risk men. The aim of this study was to assess temporal trends of incident syphilis and associated risk factors among HIV-infected men in Singapore.

**Methods** We conducted retrospective cohort analysis using the clinical database maintained by the Clinical HIV Programme at the National Centre for Infectious Diseases, Singapore. HIV-infected men with a negative syphilis result at baseline who had undergone at least one subsequent test in 2006–2017 were included. Factors associated with incident syphilis were investigated using Cox proportional hazards regression analyses.

**Results** A total of 1069 HIV-infected men were tested for syphilis at least once following their negative baseline test during the 12-year period, and they contributed 4284 person-years of follow-up (PYFU). There were 266 cases of incident syphilis, giving an overall incidence of 6.21 per 100 PYFU (95% CI 5.49–7.00). The incidence of syphilis per 100 PYFU increased from 1.21 (95% CI 0.33 to 3.10) in 2010 to 26.04 (95% CI 19.97 to 33.40) in 2017. In the multivariable model, risk factors for syphilis seroconversion were: age 15–24 years at HIV diagnosis (adjusted HR (aHR) 1.64, 95% CI 1.05 to 2.56) versus  $\geq 45$  years, being Chinese (aHR 1.82, 95% CI 1.01 to 3.29) versus Indian and other minority ethnic groups, men having sex with men (MSM) (aHR 3.29, 95% CI 2.22 to 4.87) versus heterosexuals, and HIV diagnosis in later periods of 2009–2011 (aHR 1.96, 95% CI 1.41 to 2.74), 2012–2014 (aHR 3.96, 95% CI 2.68 to 5.83) and 2015–2017 (aHR 7.94, 95% CI 4.52 to 13.95) versus 2006–2008.

**Conclusion** The annual incidence rate of syphilis in HIV-infected men was on the rise, and it was consistently higher among MSM than in heterosexual men. The findings supported regular screening for syphilis and enhanced behavioural interventions in Singapore.

## INTRODUCTION

Syphilis has re-emerged as a global public health concern with recent reports highlighting substantial increases in the diagnosis of infectious syphilis, particularly among high-risk groups such as gay, bisexual and other men who have sex with men (MSM).<sup>1,2</sup> Worldwide, MSM are also one of the key populations disproportionately affected by HIV infection.<sup>3</sup>

The interplay between HIV and syphilis infection has important implications for the prevention and treatment of HIV, as well as STI control via HIV-care based screening.<sup>4</sup> HIV and *Treponema pallidum*, the causative agent of syphilis, share similar routes of transmission. Syphilis coinfection has been shown to negatively impact HIV prognosis; syphilis infection was associated with increase in HIV viral load and decrease in CD4 cell count.<sup>5</sup> HIV may, in turn, adversely affect the clinical course of syphilis, such as conferring an increased risk of developing neurosyphilis, treatment failure and relapse of infection.<sup>6</sup> The diagnosis of syphilis in HIV-infected patients can be complicated as HIV infection can lead to much higher false-positive rates of serologic results for *T. pallidum*.<sup>7</sup> The rate of asymptomatic syphilis infection may be higher in HIV-infected patients, with studies reporting a range from 33% to 51%.<sup>8,9</sup> Hence, effective prevention, early diagnosis and prompt treatment of syphilis in HIV-infected persons are of paramount importance in comprehensive HIV care.

In Singapore, the majority of all reported cases of primary and secondary syphilis in the general population are among men. The incidence per 100 000 population has increased drastically in recent years, from 3.8 in 2015 to 6.6 in 2017.<sup>10</sup> The predominant route of HIV infection is via sexual transmission in Singapore residents. The local HIV epidemiology is characterised by a preponderance of infections in men (male-to-female ratio of 9:1 or higher). In the late 1980s, the mode of transmission had been predominantly homosexual and bisexual. From the early 1990s to 2010, heterosexual transmission was the predominant mode of infection. Thereafter, MSM accounted for an increasing proportion of all newly diagnosed cases, from 51% in 2011 to 60% in 2017. As of end 2017, there were 7982 Singapore residents with HIV infection, of whom 1960 had died.<sup>11</sup>

A local study of over 793 HIV-infected patients who were referred for first-time care from 2006 to 2011 found that 98.4% received at least a single syphilis screening test during the 6-year period, and among 406 patients whose initial non-treponemal and treponemal test results were concordant, 12.3% had ever tested positive for syphilis.<sup>12</sup> The prevalence of syphilis was significantly higher in MSM, as compared with heterosexuals (18.1% vs 8.0%).<sup>12</sup> There have not been any studies on



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the incidence of syphilis seroconversion among HIV-infected patients in Singapore.

Given the implications of syphilis coinfection in HIV-infected persons, coupled with the pressing need to increase syphilis testing rates in high-risk groups, we sought to examine temporal trends and risk factors associated with incidence of syphilis among HIV-infected men in a 12-year period from 2006 to 2017.

## METHODS

### Study subjects

We conducted a retrospective cohort study using the records of HIV-infected patients on follow-up with the Clinical HIV Programme at the National Centre for Infectious Diseases (NCID), which is the largest referral and care centre for HIV in Singapore. Of 5279 newly diagnosed cases of HIV infections notified to the Ministry of Health, Singapore, between 2006 and 2017, 3327 (63.0%) had ever sought HIV care at the centre during this period. Majority of patients who received HIV care for the first time at NCID were newly diagnosed. Information that was routinely collected included demographic and epidemiological information, virological and immunological parameters, antiretroviral therapy (ART) and test results from biochemical investigations performed in the course of HIV care.

All patients seen at NCID with newly diagnosed HIV undergo syphilis testing and treatment as part of routine care. Thereafter, repeat or regular testing is guided by symptoms and/or ongoing sexual risk behaviour as reported to the care provider. Subjects included in this retrospective study were Singapore male residents diagnosed with HIV who had ever received HIV care at NCID between 2006 and 2017, with a negative syphilis result at baseline and at least one subsequent test during the 12-year period. We restricted the analyses to HIV-infected men to allow for a more homogenous group who comprises vast majority of reported HIV cases in Singapore.

Informed consent was not obtained as the clinical data collected was used as part of the care management of HIV patients. All data analysed for the study were anonymised.

### Statistical methods

Incidence of primary and secondary syphilis was defined as a positive rapid plasma regain (RPR) or venereal disease research laboratory (VDRL) test after a negative test result at baseline. Baseline referred to the date of first RPR or VDRL test, which is usually done as part of routine testing at the time of first presentation to HIV care. The period of observation was defined as the time between the first negative test and either the first positive or the last negative test for syphilis during the study period. Incidence rate of syphilis was calculated as number of newly diagnosed syphilis infections per 100 person-years of follow-up (PYFU).

We compared the baseline demographic and epidemiological characteristics among HIV-infected patients with and without incident syphilis using  $\chi^2$  or Fisher's exact test for categorical variables where appropriate.

Crude and adjusted HRs together with their 95% CIs were calculated based on Cox proportional hazards regression models. Multivariable analysis was used to determine independent risk factors for seroconversion of syphilis. We included age at HIV diagnosis and HIV transmission risk group as variables selected a priori based on scientific literature of similar epidemiological studies. Other variables with  $p < 0.10$  in the univariable regression analyses were entered as initial candidates and retained in

the final multivariable model only when  $p < 0.05$ . We checked the proportionality assumption of the multivariable Cox model by examining the parallelism between the log minus log function plots for different values of each covariate. No significant time-dependent covariates were found.

All  $p$  values reported were two sided, and statistical significance was taken as  $p < 0.05$ . Statistical analyses were performed using the IBM SPSS Statistics for Windows, V.24.0.

## RESULTS

Among the 3,327 HIV-infected patients seen under the Clinical HIV Programme from 2006 to 2017, 2258 were excluded from the analysis on incidence of syphilis for the following reasons: 542 did not have any syphilis tests, 1153 had only one syphilis test, 515 were tested positive at baseline and 48 women tested negative at baseline—none had incident syphilis (online supplementary figure). A total of 1069 HIV-infected male patients who had been routinely tested for syphilis at least once following their negative baseline test between 2006 and 2017 were included in the study, and they contributed 4284 person-years during the follow-up period. The median follow-up time per patient was 3.64 years (IQR 1.72–5.88).

There were 266 cases of incident syphilis, giving an overall incidence of 6.21 per 100 PYFU (95% CI 5.49 to 7.00). The incidence of syphilis per 100 PYFU increased significantly from 1.21 (95% CI 0.33 to 3.10) in 2010 to 10.09 (95% CI 7.60 to 13.14) in 2016, and then surged to 26.04 (95% CI 19.97 to 33.40) in 2017 (figure 1A). The median time between HIV diagnosis and incidence of syphilis seroconversion was 3.89 years (IQR 1.86–6.11). Among the 266 men with incident syphilis, about three-quarters (76%) had at least another positive result for syphilis subsequent to their first positive RPR or VDRL test as of end 2017.

The overall incidence of syphilis seroconversion was 9.00 per 100 PYFU (95% CI 7.86 to 10.27) in MSM, significantly higher than that of men infected with HIV via heterosexual mode of transmission, which was 2.22 per 100 PYFU (95% CI 1.54 to 3.10). Both groups showed significant increases in incidence rate of syphilis during the study period (figure 1B). Among MSM, the incidence per 100 PYFU jumped from 14.77 (95% CI 10.89 to 19.58) in 2016 to 35.85 (95% CI 26.70 to 47.42) in 2017. Among men infected with HIV via heterosexual mode of transmission, the largest increase was from 2.67 per 100 PYFU (95% CI 0.87 to 6.24) in 2016 to 14.29 per 100 PYFU (95% CI 7.38 to 24.95) in 2017. The annual incidence rate of syphilis was significantly higher among MSM compared with men infected with HIV via heterosexual mode of transmission during the period from 2014 to 2017.

### Characteristics of HIV-infected men with and without incident syphilis

HIV-infected men aged 25–44 years at HIV diagnosis comprised 54.9% of the study sample (table 1). The mean age was 38 years (SD 12, range 17 to 82). About three-quarters (75.7%) were Chinese and 62.7% were unmarried. The main mode of HIV transmission was via sexual exposure (93.5%). More than half (55.2%) had CD4  $> 200$  cells/mm<sup>3</sup>, and 62.5% were known to be not virologically suppressed ( $> 200$  copies/mL) at time of HIV diagnosis while 35.3% did not have viral load measurements within 6 months of HIV diagnosis.

Compared with HIV-infected men without incident syphilis, a significantly higher proportion of those who had incident syphilis were aged 15–34 years at HIV diagnosis (60.2% vs



**Figure 1** Annual incidence of syphilis seroconversion among HIV-infected men who attended the national referral centre for HIV in Singapore, 2006–2017. (A) Overall. (B) HIV-infected MSM and men infected with HIV via heterosexual mode of transmission. MSM, men who have sex with men; PYFU, person-years of follow-up.

40.2%), unmarried (70.7% vs 60.0%), infected with HIV via homosexual/bisexual mode of transmission (83.8% vs 50.2%) and had CD4 >200 cells/mm<sup>3</sup> at time of HIV diagnosis (66.9% vs 51.3%).

Among 242 HIV-infected men with incident syphilis who had HIV viral load measurements within 6 months of their syphilis seroconversion, 76.0% had undetectable viral load (<50 copies/mL) at the time they were tested positive for syphilis, while 6.6% had viral load between 50 and 200 copies/mL. There were no significant differences in the proportions with undetectable viral load and virological suppression ( $\leq 200$  copies/mL) between MSM and men infected with HIV via heterosexual mode of transmission (figure 2).

#### Factors associated with syphilis incidence

Univariate Cox regression analyses indicated that men of younger age, Malay ethnicity, HIV exposure via MSM contact and HIV diagnosis in the periods later than 2006–2008 were at higher risk of incident syphilis, while the risk of syphilis seroconversion was significantly lower in those who were ever married (table 2).

In the multivariable Cox regression model, risk factors for incident syphilis were: age 15–24 years at HIV diagnosis (adjusted HR (aHR) 1.64, 95% CI 1.05 to 2.56) versus  $\geq 45$  years, being Chinese (aHR 1.82, 95% CI 1.01 to 3.29) versus Indian and other minority ethnic groups, HIV exposure via MSM (aHR 3.29, 95% CI 2.22 to 4.87) versus heterosexual mode, and HIV diagnosis in later periods of 2009–2011 (aHR 1.96, 95% CI 1.41 to 2.74), 2012–2014 (aHR 3.96, 95% CI 2.68 to 5.83) and

2015–2017 (aHR 7.94, 95% CI 4.52 to 13.95) versus 2006–2008 (table 2).

#### DISCUSSION

This study revealed an increasing trend of syphilis incidence in HIV-infected men, especially among MSM in Singapore. The most drastic increase was in 2017, with the incidence of 26.04 per 100 PYFU being more than 2.5 times that in 2016 (figure 1A). Rising trends of syphilis incidence with greater increases in more recent years were also seen in HIV cohort studies conducted in Asia,<sup>2</sup> the USA<sup>13</sup> and Canada.<sup>14</sup> Comparisons of syphilis incidence per 100 PYFU with that of other studies are shown in online supplementary table.

The reasons for the resurgence of syphilis are likely to be multifactorial. Possible factors contributing to the rise in syphilis seroconversion include increased awareness of STIs and the need for testing,<sup>15</sup> and the availability of effective HIV antiretroviral treatment<sup>16</sup> and pre-exposure prophylaxis leading to changes in risk perception and hence changes in sexual behaviour.<sup>17</sup> As per the treatment guidelines for STIs published by the US Centers for Disease Control and Prevention and the European AIDS Clinical Society, HIV-infected individuals are recommended to undergo syphilis testing at least once a year.<sup>18,19</sup> Routine testing for syphilis among people living with HIV (PLHIV) is routinely practised in South Korea, Taiwan and Hong Kong, whereas in Japan and the Philippines, tests are performed only when patients are symptomatic or infection is otherwise suspected.<sup>2</sup> In Singapore, specific national guidelines for syphilis testing in PLHIV

**Table 1** Demographic and epidemiological characteristics of HIV-infected men with and without incident syphilis who attended the national referral centre for HIV in Singapore, 2006–2017

Characteristic	All n (%)	Incident syphilis n (%)	No incident syphilis n (%)	P value
All	1069 (100.0)	266 (100.0)	803 (100.0)	
Age at HIV diagnosis (years)				<0.0005
15–24	177 (16.6)	65 (24.4)	112 (13.9)	
25–34	306 (28.6)	95 (35.7)	211 (26.3)	
35–44	281 (26.3)	71 (26.7)	210 (26.2)	
45–54	205 (19.2)	25 (9.4)	180 (22.4)	
55–64	81 (7.6)	8 (3.0)	73 (9.1)	
65+	19 (1.8)	2 (0.8)	17 (2.1)	
Ethnic group				0.055
Chinese	809 (75.7)	205 (77.1)	604 (75.2)	
Malay	171 (16)	49 (18.4)	122 (15.2)	
Indian	51 (4.8)	7 (2.6)	44 (5.5)	
Others	38 (3.6)	5 (1.9)	33 (4.1)	
Marital status				<0.0005
Never married	670 (62.7)	188 (70.7)	482 (60.0)	
Married	182 (17.0)	19 (7.1)	163 (20.3)	
Separated/divorced/widowed	66 (6.2)	3 (1.1)	63 (7.8)	
Unknown	151 (14.1)	56 (21.1)	95 (11.8)	
HIV transmission risk group				<0.0005
Heterosexual	374 (35.0)	34 (12.8)	340 (42.3)	
Homosexual	496 (46.4)	173 (65.0)	323 (40.2)	
Bisexual	130 (12.2)	50 (18.8)	80 (10.0)	
IDU	5 (0.5)	1 (0.4)	4 (0.5)	
IDU and sexual	34 (3.2)	4 (1.5)	30 (3.7)	
Others and unknown	30 (2.8)	4 (1.5)	26 (3.2)	
Period of HIV diagnosis				0.277
2006–2008	301 (28.2)	72 (27.1)	229 (28.5)	
2009–2011	376 (35.2)	100 (37.6)	276 (34.4)	
2012–2014	272 (25.4)	72 (27.1)	200 (24.9)	
2015–2017	120 (11.2)	22 (8.3)	98 (12.2)	
Prior AIDS diagnosis				0.217
No	808 (75.6)	209 (78.6)	599 (74.6)	
Yes	261 (24.4)	57 (21.4)	204 (25.4)	
Ever on ART				1.000
Yes	1051 (98.3)	262 (98.5)	789 (98.3)	
No	18 (1.7)	4 (1.5)	14 (1.7)	
Ever used recreational or illicit drugs*				0.242
No	231 (21.6)	62 (23.3)	169 (21.0)	
Yes	136 (12.7)	40 (15.0)	96 (12.0)	
Unknown	702 (65.7)	164 (61.7)	538 (67.0)	
CD4 (cells/mm <sup>3</sup> at HIV diagnosis†				<0.0005
≤200	419 (39.2)	69 (25.9)	350 (43.6)	
201–350	251 (23.5)	82 (30.8)	169 (21.0)	
>350	339 (31.7)	96 (36.1)	243 (30.3)	
Not available	60 (5.6)	19 (7.1)	41 (5.1)	
Viral load (copies/mL) at diagnosis†				0.113
>200	668 (62.5)	180 (67.7)	488 (60.8)	
≤200	24 (2.2)	4 (1.5)	20 (2.5)	
Not available	377 (35.3)	82 (30.8)	295 (36.7)	

\*Includes ecstasy, insufflated amyl nitrites or 'poppers', erectile dysfunction medications like sildenafil, amphetamines, cannabis, heroin, cocaine, barbiturates/benzodiazepines, opium, psychedelic psilocybin mushrooms, solvents, lysergic acid diethylamide.

†Within ±6 months of HIV diagnosis.

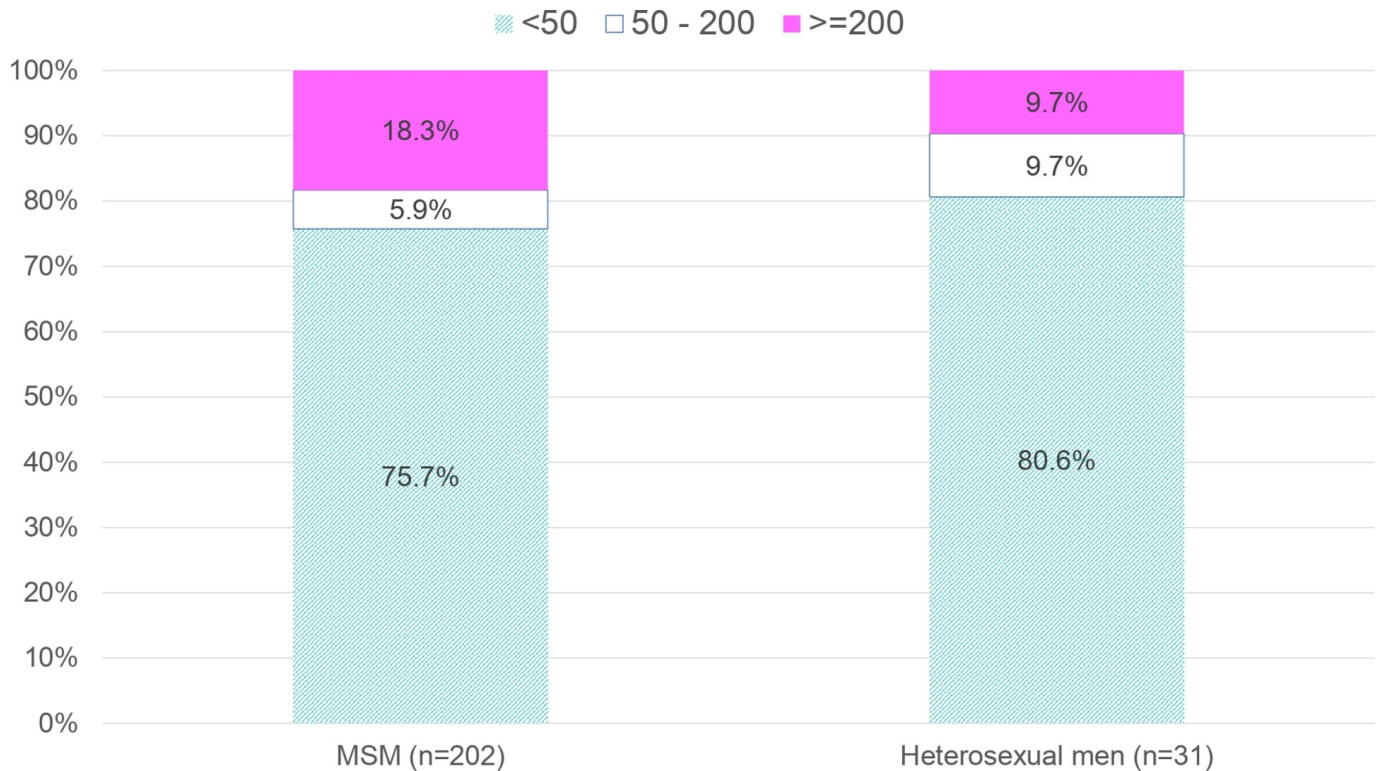
ART, antiretroviral therapy; IDU, intravenous drug use.

do not yet exist. However, in practice NCID recommends that syphilis testing be performed at least once a year for all HIV-infected individuals at risk of infection. The results of this study supported alignment of regular syphilis screening in Singapore with international recommendations.

The overall testing rate per 100 PYFU based on the presence of annual non-treponemal syphilis tests among HIV-infected men

who attended the national referral centre for HIV in 2006–2017 was 35.4 (95% CI 34.5 to 36.4) (data not shown). Our study highlights the importance of increased testing to diagnose initial and repeat episodes of syphilis in sexually active persons with HIV infection.

Surveillance of the prevalence and incidence of STIs among PLHIV serves as an indicator of the level of ongoing high-risk



**Figure 2** Distribution of HIV viral load at time of syphilis seroconversion among HIV-infected MSM and men infected with HIV via heterosexual mode of transmission with incident syphilis who attended the national referral centre for HIV in Singapore, 2006–2017. MSM, men who have sex with men.

sexual activity and potential HIV transmission to uninfected sexual partners. In Singapore, the rates of voluntary HIV testing and condom use are low among the high-risk groups of MSM and heterosexual men who engaged in commercial sex.<sup>20</sup> In the USA and Western Europe, the surge of new syphilis cases among MSM has been attributed to increased sexual activities including seroadaptive behaviours (including serosorting and seropositioning, which refer to the selection of sexual partners and positions to be of concordant HIV serostatus) and the increased frequency of condomless sex.<sup>21 22</sup> Transmission of syphilis can still occur if there are chancres in an area not covered by the condom.

The rise in incidence of syphilis over time could also be explained by the increased use of online and geospatial social networking mobile applications to facilitate casual and anonymous sexual contacts, especially among MSM.<sup>23</sup> In Singapore, outreach-based HIV testing projects in venues frequented by MSM conducted by Action for AIDS (AfA), a local non-governmental HIV/AIDS community-based organisation, found that sex-on-premises venues such as saunas or bath houses were the most popular place to meet sexual partners, and internet/mobile devices ranked second as a means to facilitate contact.<sup>24</sup>

HIV exposure via MSM contact was the common independent risk factor associated with syphilis incidence in our study and that of other studies in Asia<sup>2</sup> and the USA<sup>13</sup> (online supplementary table). The recommended frequency of syphilis testing is higher for HIV-infected patients deemed to be at high risk in Taiwan and for MSM in Hong Kong.<sup>2</sup> In Singapore, efforts aimed at reducing the spread of HIV and STIs among at-risk MSM and heterosexual men are being undertaken by various organisations through educational outreach activities and social support via collaboration with community partnerships and public stakeholders.

In our study, diagnosis of HIV in later calendar years during the study period was a significant factor associated with syphilis incidence. This indicated the need for syphilis testing at the earliest opportunity, including those on their first medical appointment for HIV care after being diagnosed with HIV. Increasing the frequency of testing and increasing testing among men who previously had no previous testing could help reduce the risk of contracting syphilis.<sup>25</sup> Moreover, increasing the frequency and coverage of syphilis screening in HIV-infected MSM receiving HIV care, relative to current standard of care, would be highly cost-effective.<sup>26</sup> Many promising and novel interventions have been identified to boost frequency and coverage of syphilis testing, including modification of default clinical procedures, provision of self-testing and point-of-care testing, venue-based screening and community-based testing services via mobile testing units.<sup>27</sup> In order to make voluntary HIV testing more accessible and convenient in Singapore, AfA launched the first Mobile Testing & Counselling Service on 7 December 2011, which provides anonymous HIV testing on wheels.<sup>28</sup>

In our study, about three-quarters of HIV-infected men with incident syphilis had undetectable viral load at the time they were tested positive for syphilis, and there was no significant difference in the proportion between MSM and heterosexual men (figure 2). While a study found no evidence of STIs altering the paradigm of ‘Undetectable=Untransmittable’ (‘U=U’) among HIV-positive MSM on ART in Thailand, those with STIs had higher levels of anogenital HIV RNA at the time of diagnosis, especially prior to commencement of ART.<sup>29</sup> This underscores the importance of integrating asymptomatic STI screening as part of universal treatment as prevention strategies.

We acknowledge several limitations in this study. Our study population was confined to patients seen at a single centre for HIV care and may not be representative of HIV-infected individuals

**Table 2** Syphilis incidence rate, crude and adjusted hazards ratios for syphilis incidence among HIV-infected men who attended the national referral centre for HIV in Singapore, 2006–2017

Characteristic	No. of incident syphilis/PYFU	Incidence per 100 PYFU (95% CI)	Univariable model			Multivariable model*		
			cHR	(95% CI)	P value	aHR	(95% CI)	P value
Age at HIV diagnosis (years)								
15–24	65/685	9 (7 to 12)	3.02	(2.00 to 4.56)	<0.0005	<b>1.64</b>	<b>(1.05 to 2.56)</b>	<b>0.031</b>
25–34	95/1304	7 (6 to 9)	2.23	(1.51 to 3.29)	<0.0005	1.40	(0.92 to 2.14)	0.118
35–44	71/1170	6 (5 to 8)	1.84	(1.22 to 2.76)	0.003	1.35	(0.88 to 2.06)	0.174
45+	35/1125	3 (2 to 4)	1.00	Referent		1.00	Referent	
Ethnic group								
Chinese	205/3296	6 (5 to 7)	3.11	(0.97 to 3.11)	0.064	<b>1.82</b>	<b>(1.01 to 3.29)</b>	<b>0.046</b>
Malay	49/659	7 (6 to 10)	4.00	(1.13 to 4.00)	0.020	1.85	(0.97 to 3.52)	0.063
Indian and others	12/330	4 (2 to 6)	1.00	Referent		1.00	Referent	
Marital status								
Single	188/2759	7 (6 to 8)	1.00	Referent				
Ever married	22/983	2 (1 to 3)	0.34	(0.22 to 0.52)	<0.0005			
Unknown	56/543	10 (8 to 13)	1.56	(1.16 to 2.10)	0.004			
HIV transmission risk group								
Heterosexual	34/1533	2 (2 to 3)	1.00	Referent		1.00	Referent	
MSM	223/2477	9 (8 to 10)	4.16	(2.90 to 5.97)	<0.0005	<b>3.29</b>	<b>(2.22 to 4.87)</b>	<b>&lt;0.0005</b>
IDU	1/21	5 (0 to 27)	1.96	(0.27 to 14.31)	0.509	2.15	(0.28 to 16.24)	0.459
Sexual and IDU	4/135	3 (1 to 8)	1.36	(0.48 to 3.84)	0.560	1.48	(0.52 to 4.20)	0.464
Others and unknown	4/117	3 (1 to 9)	1.43	(0.51 to 4.04)	0.498	1.44	(0.51 to 4.07)	0.492
Period of HIV diagnosis								
2006–2008	72/1714	4 (3 to 5)	1.00	Referent		1.00	Referent	
2009–2011	100/1623	6 (5 to 7)	2.01	(1.45 to 2.79)	<0.0005	<b>1.96</b>	<b>(1.41 to 2.74)</b>	<b>&lt;0.0005</b>
2012–2014	72/797	9 (7 to 11)	4.13	(2.83 to 6.02)	<0.0005	<b>3.96</b>	<b>(2.68 to 5.83)</b>	<b>&lt;0.0005</b>
2015–2017	22/150	15 (9 to 22)	9.38	(5.39 to 16.32)	<0.0005	<b>7.94</b>	<b>(4.52 to 13.95)</b>	<b>&lt;0.0005</b>
Prior AIDS diagnosis								
No	209/3368	6 (5 to 7)	1.00	Referent				
Yes	57/917	6 (5 to 8)	1.00	(0.75 to 1.35)	0.976			
Ever on ART								
Yes	262/4249	6 (5 to 7)	1.00	Referent				
No	4/35	11 (3 to 29)	2.42	(0.90 to 6.54)	0.081			

\*Adjusted for age at HIV diagnosis, ethnic group, HIV transmission risk group and period of HIV diagnosis. Significant associations in the multivariable model were highlighted in bold.

IDU, intravenous drug use; PYFU, person-years of follow-up; aHR, adjusted HR; cHR, crude HR.

on follow-up at other healthcare institutions. However, the Clinical HIV Programme at NCID sees the largest number of HIV-infected patients in Singapore. Hence, our study provides a reasonable indication of the trend of incident syphilis in PLHIV. Testing for STIs is not consistently carried out during the course of HIV care at NCID (though enhancements to practice recommendations are underway), and treatment information is not available in the clinical database. As such, the incidence rate of syphilis could have been underestimated or overestimated due to considerations such as varying frequency of testing over time, the use of improved or new diagnostic methods, and proportions of asymptomatic syphilis infections and patients lost to follow-up. As our study relied solely on laboratory investigations to identify incident syphilis, those with prior history of syphilis infection but were not captured in medical records and diagnosis of syphilis by a different healthcare provider could have been misclassified as incident syphilis. Apart from the reported HIV exposure category, information on sexual behaviour and history of other STIs was not available for our study. However, this may be a key confounder in the assessment of risk factors associated with syphilis seroconversion.

This study relied on non-treponemal tests. Institutional practice guidelines recommend the use of non-treponemal tests for screening of syphilis, and positive results are confirmed with the use of treponemal tests, in accordance with national STI screening recommendations. The definition of incident cases of syphilis differed between studies; some based it on positive non-treponemal tests (RPR or VDRL) with prior negative result,<sup>2 13</sup> while others required both non-treponemal and treponemal test results.<sup>8 9 13 14</sup> In addition, a few studies included reinfections in the definition of incident syphilis based on a fourfold or greater increase in RPR titre.<sup>8 9 13 14</sup> The use of both types of serological tests is recommended for syphilis diagnosis, as false-positive non-treponemal test results can arise due to detectable antibodies produced by other unrelated medical conditions.<sup>18</sup> The sensitivity of non-treponemal tests has been reported to be 78%–86% for detecting primary syphilis infection, 100% for detecting secondary syphilis infection and 95%–98% for detecting latent syphilis infection, while the specificity ranges from 85% to 99%.<sup>30</sup>

In conclusion, the increasing trend of incident syphilis in HIV-infected men observed in our study highlights the need for

regular STI screening and enhanced behavioural interventions in Singapore. Younger age at HIV diagnosis, being Chinese, HIV exposure via MSM and HIV diagnosis in more recent calendar years were independently associated with incidence of syphilis. In order to alleviate the burden of syphilis coinfection in PLHIV, concerted efforts to reduce risky sexual activity should target those identified to be at increased risk of STIs.

### Key messages

- ▶ The annual incidence rate of syphilis in HIV-infected men has been on the rise, and it is higher among MSM than in heterosexual men.
- ▶ There is a need for regular STI screening and enhanced behavioural interventions among HIV-infected men in Singapore.
- ▶ The frequency of syphilis testing should be increased for HIV-infected patients deemed to be at higher risk, particularly among MSM.

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