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Why we need pre-exposure prophylaxis: incident HIV and syphilis among men, and transgender women, who have sex with men, Bangkok, Thailand, 2005-2015

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Abstract

We describe incident human immunodeficiency virus (HIV) and syphilis trends in men who have sex with men (MSM) and transgender women (TGW) presenting for HIV voluntary counseling and testing (VCT) services and sexually transmitted infection (STI) management at the Silom Community Clinic, Bangkok, Thailand. Clients underwent rapid HIV testing and syphilis rapid plasma reagin (RPR) testing. For incidence analysis, we included clients with >1 follow-up visit. Initial negative HIV with subsequent positive HIV defined incident HIV infection; incident syphilis infection was defined as negative RPR followed by positive RPR (titer ≥1:8) and confirmatory anti-*Treponema pallidum* antibodies. Calculation of incidence using Poisson regression assumed a uniform probability distribution throughout the serocon-version interval. From 15 September 2005 to 31 December 2015, we tested 10,158 clients for HIV and 10,324 for syphilis. Overall, 7109 clients tested HIV-seronegative and contributed 7157 person-years (PY). Three-hundred forty-seven incident HIV infections resulted in an incidence rate of 4.8 per 100 PY (95% confidence interval [CI] 4.4–5.4). We found an inverted U-shape trend of HIV incidence over time with a peak of 6.4 per 100 PY in quarter 2/2011 ($p < 0.01$) (Poisson with RCS function, $p = 0.001$). Overall, 8713 clients tested seronegative for syphilis and contributed 8623 PY. The

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Authors' contribution

All authors have participated in the study and have substantially contributed to the study. THH, WW, SP, AC, and PAM contributed to the conception and design of the study, analysis, and generation of data, and critical review of the manuscript. PAM did the main statistical analysis. WT contributed to the conception and design of the study, acquisition of data, analysis, and critical review of the manuscript. WC, SP, and WS contributed to the acquisition of data and critical review of the manuscript. MEC and EFD contributed to the analysis of data and critical review of the manuscript. All authors have read and approved the manuscript for publication.

Declaration of conflicting interests

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incidence of syphilis infection was 4.4 per 100 PY (95% CI 3.9–4.8). Despite an apparent decline in HIV incidence among MSM and TGW attending VCT services, syphilis incidence rose and remained high. Evaluating temporal trends of HIV and syphilis incidence provides an opportunity to evaluate epidemic trajectories and target limited program funding. We recommend focused HIV and STI prevention interventions for MSM in Bangkok.

Keywords

Men who have sex with men; HIV; syphilis; epidemiology

Introduction

Despite successful control of the human immunodeficiency virus (HIV) epidemic among heterosexual men in Thailand by the late 1990s,[1] and certified elimination of mother-to-child HIV transmission in 2016,[2] the continued spread of HIV in other high-risk groups, particularly men who have sex with men (MSM), and transgender women (TGW), remains concerning.[3,4] The first cross-sectional MSM HIV prevalence survey assessment conducted in Bangkok in 2003 revealed a largely unrecognized epidemic of HIV among MSM, with a prevalence of 17.3%.[5] Within a few years, HIV prevalence among MSM had risen to 28.3% using the same survey technique[6]; although incidence had not been assessed, it was estimated to be above 5 per 100 person-years (PY), with the prevalence remaining stable between 25 and 31% in subsequent study years.[7,8] Similarly, rates of syphilis among MSM have been high and increasing in recent years, in both high-income countries in North America,[9–11] Western Europe,[12] and some middle-income countries[13] including China,[14] as well as Thailand.[15,16]

Although the Thailand Ministry of Public Health (MOPH) conducts HIV surveillance, the incidence of HIV infection among MSM and TGW has not been easily determined. Incidence assays can provide accurate estimates of HIV incidence in some populations, but cross-sectional studies are unable to demonstrate the dynamic nature of the HIV epidemic over time. Longitudinal data give the best estimates of incidence and can provide the means to assess the potential impact of prevention interventions in a population.[17] Incidence data are most robust if quantifying HIV infections among repeatedly tested HIV-negative individuals. However, clients or participants in longitudinal assessments of HIV in a clinic or cohort study may not be representative of the general population of MSM.[18–22]

We assessed trends in the incidence of HIV and syphilis infections from 2005 to 2015 among MSM and TGW attending the Silom Community Clinic (SCC) located in central Bangkok. Since 2005 the clinic has provided an MSM-friendly environment and rapid voluntary counseling and testing (VCT). Services include testing and treatment for common sexually transmitted infections (STIs), counseling, and referral to care for HIV treatment.[7,23] Pre-exposure prophylaxis (PrEP) against HIV was recommended in the Thai national guidelines in 2013,[24] but demonstration projects in focused urban areas did not occur until 2015.[25] Few if any participants were using PrEP prior to March 2016 when SCC started providing PrEP to clients. Previous analysis of participant data from 2005 to 2011 reported

an HIV incidence of 6.3 per 100 PY and syphilis incidence of 3.6 per 100 PY.[7,26] Updates in temporal trends of HIV and syphilis incidence provide an opportunity to evaluate the trajectory of these epidemics among MSM and TGW over the last decade in Bangkok. In addition, we evaluated factors associated with incident infections that may support public health prevention efforts.

Methods

Study participants and procedures

Between 15 September 2005 and 31 December 2015, we asked MSM and TGW clients attending SCC for VCT services' basic demographic data at the initial visit. Thai men and TGW, aged ≥18 years, who reported oral or anal sex with another man in the past six months, were eligible for inclusion in this analysis. As VCT services were offered confidentially and anonymously, we did not ask clients to reveal their gender identity and we analyzed both MSM and TGW as one group. Clients were asked to repeat HIV and syphilis testing every six months if HIV-negative (a policy incorporated into the 2010 Thai National Guidelines).[24,27] At each visit, clients were screened for HIV-1 antibody in whole blood using a rapid test and, if positive, were further tested with consecutive HIV-1 rapid tests (Determine™, Abbott, USA; DoubleCheck™, Organics Ltd, Israel or SD Bioline™, Standard Diagnostics, Inc., Korea; and Capillus™ HIV-1/2, Trinity Biotech, USA or HIV1/2 Core™, Core Diagnostic, UK), in accordance with Thai National Guidelines' rapid HIV testing algorithm. An initial negative rapid HIV test result with a subsequent positive rapid HIV result during a follow-up visit defined incident HIV infection. All clients with incident HIV infection were referred for treatment to a Thailand MOPH HIV site according to the Thailand HIV treatment guidelines.

Clients were also screened for incident syphilis infection at each visit with a rapid plasma reagin (RPR) test, and if reactive, were tested for RPR titer (Macro-Vue™ RPR 18 mm Circle Card Test; Becton Dickinson Microbiology Systems, Sparks, Maryland, USA). If the RPR was reactive, we tested for anti-*Treponema pallidum* antibodies (Determine™ Syphilis TP; Inverness Medical Japan, Chiba, Japan) in serum. A positive RPR with a titer ≥1:8 and positive anti-*T. pallidum* antibodies were considered evidence of syphilis.[13] An initial negative RPR with a subsequent positive RPR (titer ≥1:8) and confirmatory anti-*T. pallidum* antibodies during a follow-up visit defined incident syphilis infection. Clients with incident syphilis were treated at SCC according to Thailand treatment guidelines. We defined a cure to be a fourfold decrease in a follow-up RPR over six months.

The provision of VCT services at SCC was determined to be a public health program activity by the Office of the Associate Director of Science, CDC, and as such, this analysis was exempt from CDC Institutional Review Board review.

Statistical analysis

For incident HIV or syphilis infection during the time frame of assessment, we conducted a descriptive analysis of client demographic characteristics with comparisons using Wilcoxon nonparametric tests and Chi square tests. We calculated exact Poisson 95% confidence

intervals (CIs) for HIV incidence per 100 PY. An alpha = 0.05 was used to perform two-sided significance testing, and 95% CIs were constructed for measures of effect.

Calculation of incidences per quarter assumed a uniform probability distribution throughout the serocon-version interval between the last negative and first positive HIV and syphilis test results.[28] Participants were excluded from one cohort analysis or the other due to a lack of testing for one disease or lack of follow-up testing. We did not examine reinfection or multiple events. We evaluated temporal trends in HIV and syphilis incidence by quarter using a restricted cubic spline (RCS) function for time using three knots, in a Poisson regression with robust standard errors.[29,30] The RCS function provides flexible fitting of curve shapes for continuous predictors in regression models, allows assessment of linearity, and graphically characterizes the association between the outcome and the predictor. The number of knots chosen was based on the recommendation that three to five knots are sufficient in practice.[30] We performed all statistical analysis using Stata/SE 13.1 (Stata Press, College Station, Texas, USA).

Role of the funding source

The funder of the study had no role in study design, data gathering, analysis, or interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study population

Overall, 11,057 MSM and TGW visited SCC VCT from 15 September 2005 to 31 December 2015; 10,158 were tested for HIV and 10,324 for syphilis (Figure 1). The number of first visits gradually increased during the first several years the clinic first offered services (2005–2009), to subsequently larger annual increases in the number of visits (2010–2013), and a stabilization in the number of visits through 2015. Among the 7109 clients who were seronegative for HIV, 3097 (43.6%) had a follow-up HIV test (Table 1). Among the same 3097 clients, 257 (8.3%) had syphilis infection at baseline. Among the 8713 clients who were seronegative for syphilis, 3357 (38.5%) had a follow-up syphilis test. Among the same 3357 clients, 779 (23.2%) tested positive for HIV at their first clinic visit. Overall, the overlap was 59.7%, with 16.9% only in the HIV analysis and 23.4% only in the syphilis analysis (Figure 2).

The 3097 clients who initially tested HIV-seronegative and had a follow-up visit contributed 7157 PY of follow-up (Table 2). The 3357 clients who initially tested seronegative for syphilis and had a follow-up visit contributed 8623 PY of follow-up. The median age at first registration for both groups was 27 years (interquartile range [IQR] 23–32 years) and most were Thai nationals. The median HIV testing time interval between visits (between initial and follow-up, and all follow-up visits) was 193 days (25/75 IQR 105–367 days) and the median syphilis testing time interval between visits was 278 days (25/75 IQR 162–464 days). Among the HIV-seronegative group, just over half (1809 [58.4%]) had a previous

HIV testing history; only 1645 (49.0%) of those tested for syphilis reported a previous test for HIV.

HIV incidence

Among the 3097 clients initially HIV-seronegative, 347 incident HIV infections occurred, with a median time between last negative and first positive HIV test result of 358 days (IQR 171–824 days). The median number of HIV tests done before seroconversion was three (IQR 2–4) tests. The overall HIV incidence was 4.8 per 100 PY (95% CI 4.4–5.4) (Table 2). Among the 347 incident HIV infections, 344 (99.1%) had a CD4 count at the time of HIV diagnosis: 95 (27.6%) had a CD4 count of <350 cells/μl, 108 (31.4%) had a CD4 count of 350–500 cells/μl, and 141 (41.0%) had a CD4 count of >500 cells/μl. For the 95 with a CD4 <350 cells/μl, the median number of tests before sero-converting was two (IQR 2–3), and the median time between last negative and first positive test result was 248 (IQR 119.5–575) days. For the 141 with a CD4 >500 cells/μl, the median number of tests before sero-converting was three (IQR 2–4), and the median time between last negative and first positive test result was 183 (IQR 91–385) days ($p = 0.003$ comparing median time).

HIV incidence was significantly higher among younger persons aged 18–21 years (6.9 per 100 PY) and aged 22–29 years (5.7 per 100 PY) compared with 3.0 per 100 PY for those aged ≥30 years, $p < 0.001$. Over the entire period, HIV incidence fluctuated from 2.5 to 6.4 per 100 PY each quarter. Analysis noted two trends, an increased HIV incidence until quarter 2/2011, followed by stabilization in quarter 3/2011 and then a decline (inverted U-shape curve over time) through quarter 4/2015 (Figure 3) at a rate of 3.8 per 100 PY. Poisson regression of the time trend using an RCS function adjusted for age showed both a significant linear effect ($p = 0.0001$), and a nonlinear effect ($p = 0.0001$) (Table 2), with clients aged 18–21 years being at more significant risk for incident HIV infection (relative risk [RR] 2.3, 95% CI 2.0–2.7).

Syphilis incidence

Among 3357 clients initially seronegative for syphilis, 376 (11.2%) had incident syphilis infection, with a median time between last negative and first positive serology test result of 337 days (IQR 168–784 days). The median number of syphilis tests performed before seroconverting was five (IQR 3–7). The overall incidence of syphilis infection was 4.4 per 100 PY (95% CI 3.9–4.8) (Table 2). Syphilis incidence was significantly higher in the younger age groups (4.9 per 100 PY for those aged 18–21 years, 4.8 per 100 PY for those aged 22–29 years) compared with 3.5 per 100 PY for those aged ≥30 years, $p < 0.001$. Syphilis incidence rose and peaked in quarter 2/2011 at 5.9 per 100 PY, then remained steady in the range of 4.2 per 100 PY in quarter 3/2011 to 5.5 per 100 PY in quarter 4/2015 (Figure 4). Poisson regression of the estimated temporal trend using an RCS function found a significant nonlinear time trend ($p = 0.001$). Age was also significant ($p < 0.0001$), with clients aged 22–29 years being at greater risk for incident syphilis infection (RR 1.4, 95% CI 1.2–1.5) (Table 2).

Incidence trends

The evaluation of the ecologic relationship between the two trend curves of HIV and syphilis incident infections using correlation (regression) analyses found a Pearson correlation of 0.75, a moderately high positive association between the two curves. However, when we divided the time into two periods, quarter 4/2005-quarter 3/2011 and quarter 4/2011-quarter 4/2015, the correlation was high during the first period (Pearson = 0.87) and low during the second period (Pearson = 0.10).

Discussion

Fifteen years have passed since the recognition of a high prevalence of HIV infection among MSM in Bangkok. Subsequent biannual surveys by the Thailand MOPH showed an increase and then stabilization of HIV prevalence in the sampled population between 25 and 31%.[6–8,31] In this study of VCT clients at a large MSM and TGW clinic in Bangkok, conducted between 2005 and 2015, we found both HIV and syphilis incidence among clients to reach a peak of 5–6 per 100 PY in 2011, reflective of ongoing epidemics of HIV and syphilis infections in this population. Despite a recent drop in the number of new HIV infections in this population tested, the incidence continues to be alarmingly high. Most alarming, the youngest adults, aged 18–21 years, had the highest rate of incident infections for both HIV (more than twice the incidence than for those over 30) and syphilis, a concerning trend.[16] Due to high-risk behavior, vulnerability to STIs is substantial albeit preventable for young people.

The overall HIV incidence rate found among MSM and TGW in the cohort period, in the context of the Thai epidemic, is 18 times as high as in the general population of the Thailand Eastern seaboard as seen in the placebo arm of the RV144 trial between 2003 and 2008,[32] and nearly 200 times as high as the estimated incidence of 0.03% in 2011 among adults in Thailand.[33] This ongoing high HIV incidence contrasts sharply with the history of the HIV epidemic among Thai heterosexuals. The rate of HIV infection in the general Thai population was brought under control by systematic interventions including the widespread use of barrier methods.[1] The epidemic among MSM and TGW, however, subsequently increased and continues unabated. Two earlier reports derived from this dataset from 2005 through 2011 showed increasing incidence among MSM.[7,26] Our data are similar to the high burden of infection among MSM found in an acute HIV infection study at the Bangkok Thai Red Cross anonymous clinic between 2006 and 2007, with 60% of new infections among MSM.[34] Similarly, a study of VCT repeat testers in Chiang Mai, Northern Thailand during 2008–2009 found an HIV incidence of 8.2 per 100 PY.[35]

Our data from 2010 to 2015 show a decline in HIV incidence among the population accessing services at SCC, raising the possibility that transmission may have slowed over the past five years. This was unlikely due to increased coverage of antiretroviral therapy (ART) in the MSM population, as the UNAIDS 2016 Prevention Gap Report showed that only 10% of HIV-infected MSM were estimated to be covered by ART between 2013 and 2015.[36] Prevention messaging could also have had an effect, with a resultant change in behavior.[37] Social media can be used as a medium for prevention messaging, although we know of only one official Thai online intervention prior to 20 1 4.[38] Anecdotal evidence suggests that

during the study period MSM and TGW increased use of social networking apps and websites to find casual sexual partners, behavior found to be associated with increased risk of HIV.[39]

In contrast, the incidence of syphilis was initially high, reached a peak during the study period, and was sustained over time. This is consistent with the global epidemic of syphilis among MSM, a trend that is not abating.[40,41] Syphilis is a recognized risk factor for transmission and acquisition of HIV infection because of both biologic and behavioral factors.[42] Incident syphilis infections are a marker of ongoing high-risk sexual behaviors in the population, which may contribute to the HIV epidemic.[43] Globally, syphilis infection rates are high among both HIV-infected[11] and HIV-uninfected MSM,[9] can be asymptomatic as well as undetected, and can lead to 'bridging' between the MSM population and the general community. Continued syphilis screening and treatment for MSM and TGW, including prompt partner notification and treatment, will support prevention of HIV and STIs.

If the incidence in the MSM and TGW Thai HIV epidemic is indeed declining as we found, this is welcome news, a promising sign that the high HIV incidence rates seen in the 2000s may have stabilized or even declined. The strength of this analysis is the duration of the longitudinal assessment, and a continual infusion of young MSM, although we cannot rule out a cohort effect. However, previous assessments of the incidence in VCT clients demonstrated a similar incidence to a cohort study.[23] The HIV incidence trend in the VCT population described here also fit trends seen elsewhere among MSM, especially in Asia.[44,45] The U.S. has noted recent declines in estimated HIV incidence (no longer directly measured by CDC)[46,47] which may indicate impact of prevention strategies such as PrEP and antiretroviral treatment to reduce onward transmission.[48]

Although the SCC advises VCT clients to return for follow-up, many elect not to return. In this cohort, <50% of VCT clients returned for follow-up of either HIV or syphilis test results, and less for syphilis testing. Some officials in Thailand consider this better-than-expected follow-up without incentives or integrated health care delivery. In addition to being an opportunity for referral if needed, HIV testing is a decision point for conducting risk assessments and providing high-impact prevention interventions such as PrEP to reduce HIV transmission in these key populations.[49] According to CDC guidelines, PrEP management also includes regular STI testing[50] and is an opportunity to test and treat syphilis more frequently. We also noted a significant testing interval difference, the sero-converters with a lower CD4 count (<350 cells/μl) had a wider interval between testing than those who had a higher CD4 count (>500 cells/μl), indicating that testing messages still need to be received by those with more advanced infection.

With this expanded incidence trend line we are making a stronger argument for the need for PrEP in the national health plan, since this high incidence (even if it declined in later years) was in a country with a well-established and long-term commitment to treatment access for all. Given the high efficacy found in major PrEP trials among MSM,[51–53] scale-up of PrEP is needed nationwide in Thailand for all MSM and TGW. The announcement in early 2018 that the Thailand National Health Security Office is set to approve payment for PrEP as part

of a prevention package is a welcome sign that PrEP will be financially accessible to all MSM and TGW in Thailand who are at substantial risk of infection.

There are limitations to our study. For one, clients who continued to follow-up in the clinic may not be representative of the general MSM and TGW populations in Bangkok. For example, they may be motivated to follow-up because of self-recognition of ongoing risk behavior, higher knowledge, or other reasons. Our VCT services construct an open cohort, in that clients can enroll, repeat test, and follow-up (or not) as they prefer. Thus, we are not able to draw any conclusions about the causal relationship between the two incident infections. The incidence of syphilis could be underestimated. Incident syphilis cases could have been missed since our definition of incident syphilis is specific but not sensitive as it was based on seroconversion. Persons who had evidence of previous infection would be excluded with this definition, persons with a history of syphilis in a serofast state could become reinfected, and newly infected persons with RPR ≤1:4 would be missed. VCT services are offered to all who come to the clinic, but we were unable to separate the MSM and TGW into distinct groups. We agree that there is a strong need for more transgender-specific data. Testing visits varied from a median of 193 days (6.3 months) for HIV testing to 278 days (9.1 months) for syphilis testing; verification of the specific time of incident infection may be limited by the time frame between visits. In addition, the uniform probability distribution is an approximation that would not capture any recency bias toward exposure events prior to or prompting a VCT visit. Lastly, we collected minimal behavioral data and are thus unable to assess if behavioral factors in a changing client base were responsible for the shift in incidence.

In 2013, for the first time, the Thai MOPH issued national guidelines for implementing HIV prevention among MSM and TGW, which were reiterated again in 2017.[24] The testing practice recommended in 2013 had been recommended at SCC VCT services since its inception in 2005, making the SCC VCT cohort a valuable and unique source of incidence data for the evaluation and monitoring of new HIV infections among the MSM population in Bangkok.

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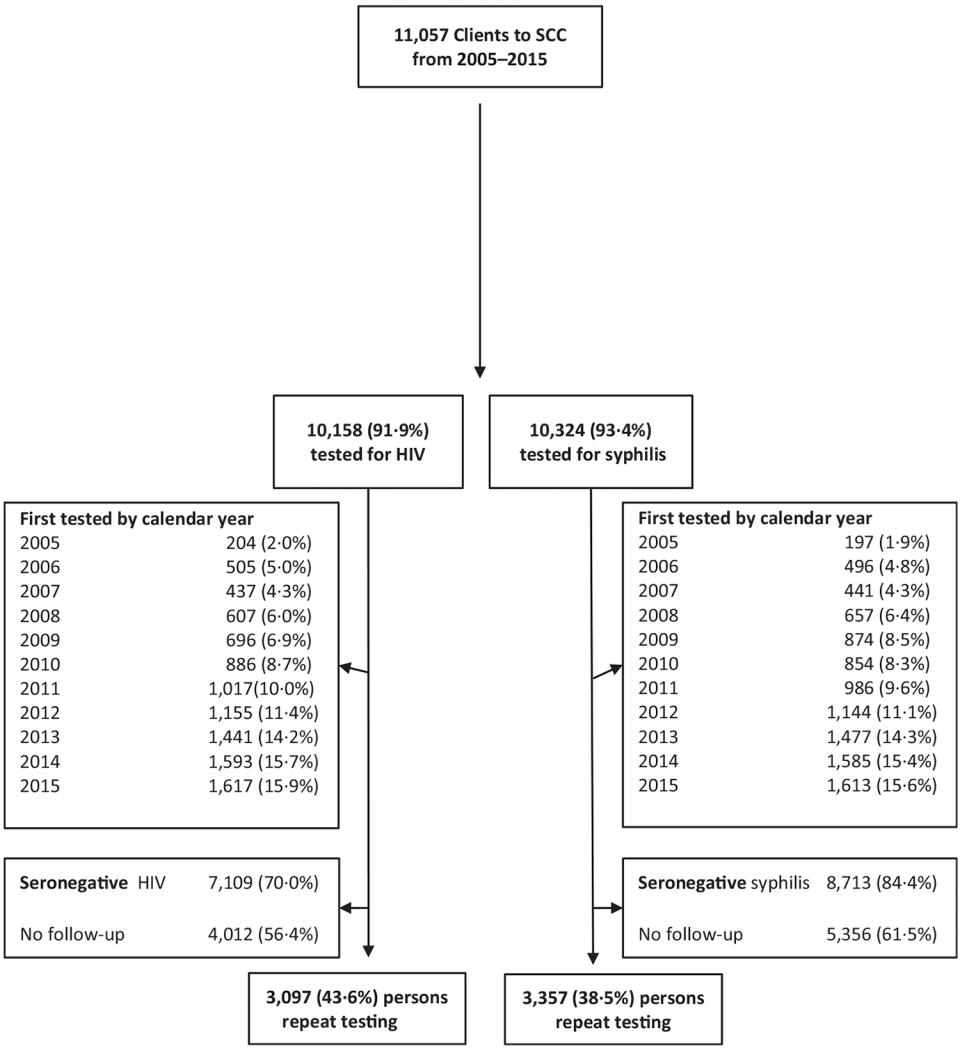

Figure 1.

HIV and syphilis screening by year among MSM, and TGW, presenting for VCT (for HIV) at the SCC in Bangkok, Thailand, 2005–2015.

SCC: Silom Community Clinic.

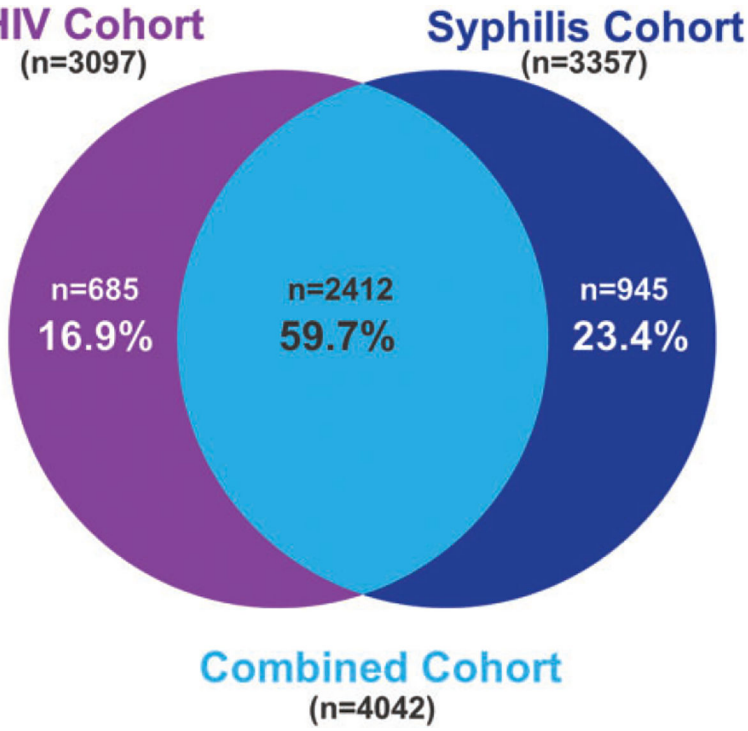

Figure 2:
Quarterly HIV incidence from quarter 4/2005 to quarter 4/2015, using a RCS curve, in the VCT cohort of MSM, and TGW, 18 years and older at first test, Bangkok, Thailand.

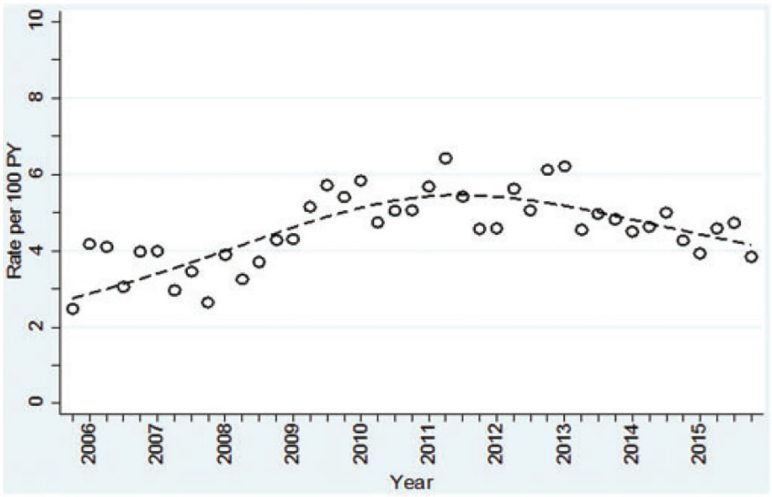

Figure 3.

Quarterly syphilis incidence (first episode), from quarter 4/2005 to quarter 4/2015, using a RCS curve, in the VCT cohort of MSM, and TGW, 18 years and older at first test, Bangkok, Thailand.

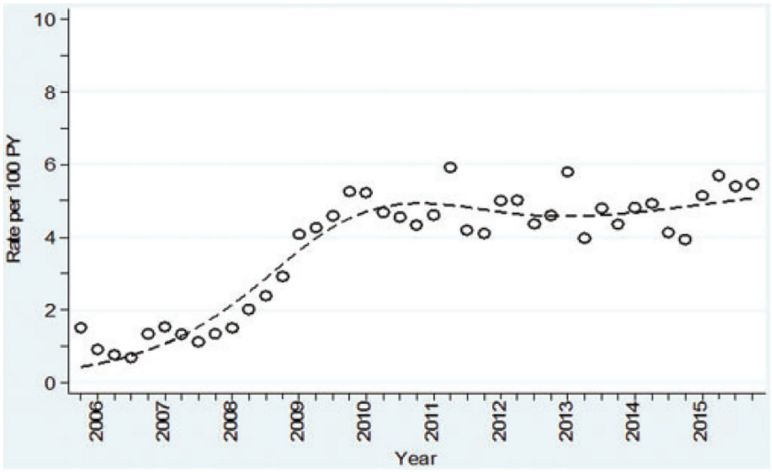

Figure 4.

Quarterly syphilis incidence (first episode), from quarter 4/2005 to quarter 4/2015, using a RCS curve, in the VCT cohort of MSM, and TGW, 18 years and older at first test, Bangkok, Thailand.

Table 1.

Characteristics of clients with initial negative HIV or syphilis test result,[a] and a follow-up test, in the VCT cohort of men who have sex with men, and transgender women, Silom Community Clinic, Bangkok, Thailand, 2005–2015.

	HIV		Syphilis	
Characteristics	**n**	**%**	**N**	**%**
Repeat testing[b]	3097	100.0	3357	100.0
Incident infections	347	11.2	376	11.2
Age group (yrs) at time of incident infection				
18–21	543	17.5	540	16.1
22–29	1472	47.5	1647	49.1
≥30	1082	34.9	1170	34.9
Thai nationality, at first clinic visit	2729	88.1	3002	89.4
Born in Greater BMA	1239	40.0	1322	39.4
Living in Greater BMA, at first clinic visit	2776	89.6	3017	89.9
Moved to Greater BMA, at first clinic visit	1573	50.8	1735	51.7
History of prior HIV testing, at first clinic visit	1809	58.4	1645	49.0
Year of first test				
2005 (quarter 4 only)	88	2.8	99	2.9
2006	197	6.4	192	5.7
2007	136	4.4	156	4.6
2008	210	6.8	264	7.9
2009	268	8.7	366	10.9
2010	276	8.9	304	9.1
2011	391	12.6	412	12.3
2012	387	12.5	469	14.0
2013	437	14.1	464	13.8
2014	503	16.2	503	15.0
2015	204	6.6	128	3.8

BMA: greater Bangkok Metropolitan Area; VCT: voluntary counseling and testing.

[a] Given the definition of how incident infection was determined, this table does not summarize characteristics by year of incident infection.

[b] Clients who repeated HIV testing may not be the same persons as clients who repeated syphilis testing.

Table 2.

Poisson regression results for assessing temporal trends for HIV and syphilis incidence, in the VCT cohort of men who have sex with men, and transgender women, Silom Community Clinic, Bangkok, Thailand 2005–2015.

Variable	Incident infections	PY	Rate	(95% CI)	RR	(95% CI)	*p* value (adjusted)
HIV							
Overall	347	7157	4.84	(4.35–5.39)			
Time (trend)							
Overall							<0.001
time_RCS_linear							<0.001
time_RCS_spline							<0.001
Age group (yrs)							
30+	80	2707	2.96	(2.35–3.68)	1.0		
22–29	189	3319	5.69	(4.91–6.57)	1.92	(1.67–2.22)	
18–21	78	1132	6.89	(5.45–8.60)	2.31	(1.95–2.74)	<0.001
Syphilis							
Overall	376	8623	4.36	(3.93–4.82)			
Time (trend)							
Overall							<0.001
time_RCS_linear							<0.001
time_RCS_spline 1							<0.001
time_RCS_spline 2							<0.001
Age group (yrs)							
30+	113	3195	3.54	(2.91–4.26)	1.0		
22–29	200	4135	4.84	(4.19–5.55)	1.36	(1.20–1.54)	
18–21	63	1293	4.87	(3.74–6.23)	1.35	(1.15–1.59)	<0.001

CI: confidence Interval; PY: person-years; RCS: restricted cubic spline; RR: rate ratio; VCT: voluntary counseling and testing.

Note: (1) No estimates are given for the RCS function as they are not directly interpretable; (2) adjusted p value is from model including time represented by RCS and age; and (3) time_RCS_spline is a nonlinear component of RCS.