PREVALENCE OF POSITIVE SYPHILIS SEROLOGY AMONG HIV-INFECTED PATIENTS: ROLE FOR ROUTINE SCREENING IN THAILAND

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Abstract. Data regarding syphilis screening in resource-limited settings is limited. We aimed to determine the prevalence and associated factors of positive syphilis serology in HIV-infected adult patients in an outpatient setting in Thailand. A cross sectional study was conducted among 178 HIV-infected patients. Ninety-eight patients (55%) were male; then median (interquartile range; IQR) age was 43 (36-49) years. The majority of the patients (84.3%) had a heterosexual risk. Three patients (1.7%) had a positive rapid plasma reagin (RPR) test (range, 1:2 to 1:16), 9 (5%) patients had a positive *Treponema pallidum* particle agglutination (TPPA) test, and 3 patients (1.7%) had positive results on both tests. On multivariate logistic regression analysis, a pruritic papular eruption [odds ratio (OR) 5.37; 95% confidence interval (CI): 1.09-26.38; p=0.038], current CD4 cell count (OR 1.22, per 50 cells/mm^3; 95% CI: 1.01-1.46; p=0.035), and using abacavir in the current regimen (OR 59.19; 95% CI: 2.15-1,628.68; p=0.016) were associated with positive syphilis serology. In conclusion, the prevalence of positive syphilis serology among Thai HIV-infected patients was low. Routine screening for syphilis in HIV-infected patients who are asymptomatic may need to be re-considered at the national level in this resource-limited setting.

Keywords: AIDS, HIV, syphilis, screening, Thailand

INTRODUCTION

Syphilis is a sexually transmitted disease (STD) caused by *Treponema pallidum* infection. Syphilis facilitates both human immunodeficiency virus (HIV) transmission and HIV acquisition, reflecting the complex interplay between the two diseases (Holmberg *et al*, 1988). For example, chancres cause epithelial and mucosal breaches, facilitating the transmission of HIV virions. *T. pallidum* and its pro-inflammatory components can induce expression of CCR5, the major co-receptor for HIV entry, on human monocytes within chancres, thereby enhancing the susceptibility of these cells to HIV infection (Sellati *et al*, 2000). Immune activation caused by syphilis infection stimulates HIV replication, resulting in a

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higher HIV RNA level and a lower CD4 cell count (Buchacz *et al*, 2004).

A significant proportion of syphilis infections in HIV-infected persons are asymptomatic (Winston *et al*, 2003; Cohen *et al*, 2005). However, untreated syphilis can have serious sequelae with significant morbidity. Syphilis in HIV-infected patients has a greater frequency of complications, such as neurosyphilis, and a higher rate of treatment failure (Johns *et al*, 1987). The clinical presentation of syphilis may differ between HIV-infected and HIV-uninfected patients. HIV-infected patients may present with multiple chancres that are deeper and slower to resolve than the solitary chancre typically seen in HIV-uninfected patients (French, 2007; Karp *et al*, 2009). Primary and secondary syphilis overlap more often in patients with HIV infection than in those without (Rompalo *et al*, 2001a,b).

The incidence of syphilis has risen in the past decade (CDC, 2006; Dougan *et al*, 2007), especially among men having sex with men (MSM) (McNicholl *et al*, 2008). Several factors may explain the greater incidence of syphilis infection in HIV-infected patients, such as the introduction of highly active antiretroviral therapy (HAART) resulting in longer survival and greater quality of life with resumption of sexual activity and increased risky sexual behavior (Bachmann *et al*, 2005; Dodds *et al*, 2007). Serologic testing is the primary tool for a diagnosing syphilis. Two types of serologic tests are required for diagnosis. First, there are treponemal tests, such as fluorescent treponemal antibody absorption (FTA-ABS), *T. pallidum* particle agglutination (TPPA) and immunoglobulin G against *T. pallidum* detected by enzyme immunoassay (EIA). Second, there are nontreponemal tests, such as the Venereal Disease Research Laboratory (VDRL) test or the rapid plasma reagin (RPR) test. The use of only one type of serologic test is insufficient to diagnose syphilis because each type of test has limitations. Therefore, persons with a reactive nontreponemal test should receive a treponemal test to confirm the diagnosis of syphilis (Workowski and Berman, 2010).

Current guidelines published by the Centers for Disease Control and Prevention (CDC), European AIDS Clinical Society (EACS) and Thai National guideline on HIV/AIDS diagnosis and treatment recommend a syphilis test at first diagnosis of HIV infection. The first two guidelines also recommend a syphilis test at least yearly among HIV-infected patients, but in practice, many HIV-infected patients do not have this repeat testing performed. Data regarding syphilis screening in a resource-limited setting is limited. Thus, we aimed to determine the prevalence of positive syphilis serology among HIV-infected patients in Thailand who are actively followed up in a tertiary care setting and are asymptomatic for syphilis infection.

MATERIALS AND METHODS

A cross sectional study was conducted at an outpatient clinic of a university hospital in Bangkok, Thailand. Inclusion criteria were: 1) an HIV-infected adult patient (>15 years old) followed at Ramathibodi Hospital between February and November 2012; 2) having no clinical signs or symptoms of syphilis at the time of screening; 3) being willing and able to give written informed consent. The study was reviewed and approved by the local institutional review board. We calculated the sample size from the incidence of syphilis among HIV-infected

MSM in Thailand, reported in 2010 as 8.3% (McNicholl *et al*, 2008). We were unable to find the prevalence of syphilis among non-MSM HIV-infected Thai patients. Using Jacob Cohen's formula for prevalence studies (Cohen, 1977), we estimated the sample size of our study should be 117 patients. We added approximately 10% for missing data and/or unavailable data to give a total sample size of at least 130 patients.

The patients' characteristics and laboratory results were obtained from medical records and an electronic database. Patient data collected included sex, age, previous AIDS-defining conditions, underlying disease, marital status, history of other sexually transmitted disease, sexual activity, HIV prevention method, HAART regimen, CD4 cell count, HIV RNA level and co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). Syphilis serology was performed using RPR (Lab 21 Healthcare, Cambridge, United Kingdom) and TPPA (SERODIA® TPPA, Fujirebio, Tokyo, Japan). Patients with both a positive RPR and TPPA were diagnosed with having syphilis infection and treated according to current recommendations. If a patient had a positive RPR test but a negative TPPA test, the RPR test was repeated in 4 weeks to determine if there was a fourfold rise in the titer. Patients with only a positive TPPA test were considered as having a previous syphilis infection.

Categorical data were presented as percentages. Continuous data were presented as median and interquartile range (IQR). Categorical variables were compared using the chi-square test or Fisher's exact test. Numerical variables were compared using the Wilcoxon rank sum (Mann-Whitney) test. Logistic regression analysis was used to determine the factors associated with positive syphilis serology, either RPR or TPPA. The odds ratio (OR) and its 95% confidence interval (CI) were estimated. Variables selected by univariate analyses with a p-value <0.05, and those considered as possible associated factors on the basis of prior research were included in the final multivariate logistic regression model using backward stepwise selection after assessment of multicollinearity of variance inflation factors. The ones that attained significance were retained in the model. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata 11 software (StataCorp, 2009. Stata Statistical Software: Release 11. StataCorp LP, College Station, TX).

RESULTS

A total of 178 HIV-infected patients were included in the analysis. The median (IQR) age of subjects was 43 (36-49) years; 98 of patients (55%) were male. Forty-one percent of patients had a previous AIDS-defining illness and 39.3% patients had other co-morbidities, such as dyslipidemia (14.6%) and hypertension (12.4%). Ten of 169 patients (5.9%) and 5 of 159 patients (3.2%) had positive HBsAg and anti-HCV test results, respectively. For HIV exposure risks, 150 patients (84.3%) had a heterosexual risk, 26 (14.6%) had a homosexual risk, and 2 (1.1%) were intravenous drug users. The median (IQR) current CD4 cell count was 413 (272-559) cells/mm^3; 88.8% of patients had an undetectable HIV RNA level.

The majority of the patients (60%) were in a relationship and 19 (10.7%) had a history of a sexually transmitted disease. Only 1 patient had a previously positive RPR test. Ninety-nine patients (55.6%), 45 patients (25.3%), and 34 patients (19.1%)

Table 1
Characteristics of 178 HIV-infected study patients.

Characteristics	Total (*N*=178)	Syphilis serology positive (*N*=9)	Syphilis serology negative (*N*=169)	*p*-value
Median (IQR) age in years	43 (36-49)	50 (37-57)	43 (36-49)	0.265
Male gender, *n* (%)	98 (55.1)	7 (77.8)	91 (53.8)	0.189
Underlying disease, *n* (%)	70 (39.3)	4 (44.4)	66 (39)	0.740
HIV exposure risk, *n* (%)				0.423
Heterosexual	150 (84.3)	9 (100)	141 (83.4)	
Homosexual	26 (14.6)	0 (0)	26 (15.4)	
Intravenous drug use	2 (1.1)	0 (0)	2 (1.2)	
History of previous STD, *n* (%)	19 (10.7)	0 (0)	19 (11.2)	0.600
Previous AIDS-defining illness, *n* (%)	73 (41)	3 (33.3)	70 (41.4)	0.739
Positive HBsAg, *n* (%)	10 (5.9)	0 (0)	10 (6.2)	1.000
Positive anti-HCV, *n* (%)	5 (3.2)	1 (12.5)	4 (2.6)	0.230
Symptoms related to AIDS, *n* (%)				
Fever	77 (43.3)	3 (33.3)	74 (43.8)	0.734
Weight loss	57 (32.0)	3 (33.3)	43 (32.0)	1.000
Oral candidiasis or oral hairy leukoplakia	29 (16.3)	1 (11.1)	28 (16.6)	1.000
Pruritic papular eruption	30 (16.8)	4 (44.4)	26 (15.4)	0.045
Chronic diarrhea	5 (2.8)	0 (0)	5 (3.0)	1.000
HIV protection, *n* (%)	73 (41.0)	3 (33.3)	70 (41.4)	0.739
Median (IQR) current CD4, cell count, cells/mm^3	413 (272-559)	593 (339-680)	403 (272-557)	0.186
Patients with undetectable HIV RNA, *n* (%)	158 (88.8%)	8 (88.9%)	150 (88.8%)	0.432

IQR, interquartile range; STD, sexual transmitted disease.

had no, 1-2 times/month, and >2 times/month sexual activity. Surprisingly, 59% of patients did not use any method of HIV prevention. Only 3 patients (1.7%) and 9 patients (5%) had a positive RPR test (range, 1:2 to 1:16) and a positive TPPA test, respectively, while 3 patients (1.7%) had positive results on both serology tests. No patient had a four-fold rise in titer when the RPR test was repeated. There were no statistically significant difference in baseline characteristics between patients with and without a positive syphilis test, except pruritic papular eruption (PPE), which was significantly more common among those with positive syphilis serology (44.4% *vs* 15.4%, p=0.045). The baseline characteristics of the subjects stratified by syphilis serology status are shown in Table 1.

On univariate logistic regression analysis, a history of having PPE (OR 4.33; 95% CI: 1.09-17.24; p=0.037) and using abacavir in the current antiretroviral regimen (OR 21.0; 95% CI: 1.20-367.1; p=0.037) were associated with having positive syphilis serology. Using backward stepwise multivariate logistic regression analysis, PPE

Table 2
Predictive factors for positive syphilis serology on univariate logistic regression analysis.

Characteristics	Odds ratio	95% Confidence interval	*p*-value
Age, per 5 years	1.19	0.87-1.62	0.265
Female gender	0.33	0.07-1.65	0.178
Being married	5.12	0.13-1.98	0.332
Having a prior AIDS-defining illness	0.71	0.17-2.92	0.632
HIV protection	0.71	0.17-2.92	0.632
Co-morbidity	1.25	0.32-4.82	0.747
CD4 cell count at diagnosis of HIV, per 50 cells/mm^3	1.02	0.85-1.23	0.806
HIV RNA at diagnosis of HIV, per 10^3 copies/ml	0.99	0.99-1.00	0.775
Current CD4 cell count, per 50 cells/mm^3	1.13	0.97-1.31	0.100
Current HIV RNA per 10^3 copies/ml	1.00	0.99-1.02	0.292
History of having a pruritic papular eruption	4.40	1.11-17.48	0.035

(OR 5.37; 95% CI: 1.09-26.38; p=0.038), current CD4 cell count (OR 1.22, per 50 cells/mm^3; 95% CI: 1.01-1.46; p=0.035) and using abacavir in the current antiretroviral regimen (OR 59.19; 95% CI: 2.15-1,628.68; p=0.016) were all associated with having positive syphilis serology.

DISCUSSION

This study demonstrated a low prevalence of asymptomatic syphilis infection among HIV-infected patients followed in an out-patient setting at a tertiary care hospital in Bangkok, Thailand. This low prevalence may be due to some biases such as small sample size or few MSM patients. Most subjects in this study were male and had a heterosexual HIV risk. Fewer than 2% of asymptomatic syphilis patients were positive on RPR screening, similar to a study from the Netherlands who found the prevalence of syphilis of less than 1% in HIV-infected heterosexuals (Heiligenberg *et al*, 2012b). However, another study from the Netherlands among HIV-infected MSM found a prevalence of 5% (Heiligenberg *et al*, 2012a). None of the HIV-infected MSM in our study had positive syphilis serology. This result may be due to the small number of MSM in our study (14.6%) and/or a difference in sexual activity. Among MSM in the present study, 84.6% had no sexual activity (data not shown). Current recommendations of the US CDC and EACS include testing for syphilis at first diagnosis of HIV infection and at least yearly among HIV-infected patients. This recommendation may be appropriate for high risk HIV-infected patients such as MSM (McNicholl *et al*, 2008).

We also found that having a history of PPE, the current CD4 cell count and using abacavir were associated with having positive syphilis serology. PPEs, regarded by the WHO stage II HIV disease, usually manifests in HIV-infected patients with low CD4 counts (Lakshmi *et al*, 2008). Patients with PPE should be considered

as having advanced HIV disease. The higher the current CD4 cell count in our study the greater the likelihood of positive syphilis serology. A possible reason in these patients might be because they are healthier and more likely to have greater sexual activity and risk for acquisition of syphilis. We do not have a good explanation for why patients taking abacavir are at greater risk for positive syphilis serology.

There were some limitations to this study. First, the sample size was calculated based on the prevalence of syphilis infection among HIV-infected MSM in Thailand. This prevalence may not reflect the prevalence found in our study population. Therefore, the sample size might have been too small. Second, we tested the serology only once in this cross sectional study. If we had performed several tests over a longer time, the prevalence may have been higher due to changing sexual activity over time (Bissessor *et al*, 2010). Despite these limitations, this is the first study of asymptomatic syphilis among HIV-positive patients in a tertiary care setting in Thailand, which can inform syphilis surveillance systems.

In conclusion, the prevalence of positive syphilis serology, both RPR and TPPA, among HIV-infected Thai patients was low. Routine screening for syphilis in HIV-infected patients who are asymptomatic may need to be re-considered in resource-limited settings, especially where heterosexual risk is a major HIV transmission route. A larger prospective study is needed to determine the true prevalence and incidence of positive syphilis tests in HIV-infected Thai patients. Patients with some factors, such as having a history of PPE, a high current CD4 cell count, or current use of abacavir, should have regular syphilis screening.

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