

# Risk Factors for Repeat Syphilis in Men Who Have Sex With Men, San Francisco

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**Background:** Syphilis incidence has increased dramatically in the United States since 2000, occurring primarily among men who have sex with men (MSM) and disproportionately affecting those with human immunodeficiency virus (HIV) infection. The continued increases in syphilis rates among MSM signals the need for enhanced prevention methods. We undertook a study to examine the rate of repeat syphilis infection among MSM in San Francisco and to identify risk factors associated with syphilis reinfection that may inform additional prevention strategies.

**Methods:** We developed a retrospective cohort of all cases of primary, secondary, and early latent syphilis among MSM diagnosed in San Francisco in 2001 and 2002. We evaluated data through the end of 2003 to determine all cases of syphilis reinfection, defined as a new infection that occurred within 1 year after prior syphilis infection and treatment.

**Results:** We found that 6.7% (42/624) of cases had a repeat syphilis infection within 1 year. HIV infection was associated with an increased risk of repeat infection (OR = 4.7; CI, 1.8–12.0). No differences in age, race, number of period sex partners, illicit substance use, or partner meeting venues were observed between cases with and without repeat infection.

**Conclusions:** Our study revealed that HIV-infected MSM with syphilis represent an at-risk group for repeat syphilis infection. Targeting increased screening and risk reduction interventions to HIV-infected MSM in care could reduce the overall incidence of syphilis among MSM.

After declining to historically low rates in 2000, syphilis incidence has increased dramatically in the United States. From 2000 to 2006, the syphilis rate increased by 50% from 2.1 cases to 3.3 cases per 100,000 population.<sup>1</sup> This resurgence has occurred primarily among men who have sex with men (MSM), who are estimated to constitute over 60% of the cases of primary and secondary syphilis in the United States.<sup>2,3</sup> Large cities with established populations of MSM have been most

affected by the epidemic, with syphilis outbreaks reported in cities including Boston, Chicago, Los Angeles, San Francisco, NY, Miami, and Seattle.<sup>4–10</sup> The increased incidence of syphilis among MSM has been associated with a high prevalence of human immunodeficiency virus (HIV) coinfection. Reports from several cities indicate that 20% to 60% of MSM with syphilis have concurrent HIV.<sup>2,10–12</sup> In San Francisco, 90% of syphilis cases occur in MSM, of whom 65% are coinfecting with HIV. Syphilis cases have been associated with meeting partners in venues such as bathhouses, sex clubs, adult bookstores, and on the Internet.<sup>13–14</sup> Methamphetamine use, particularly when combined with Viagra, has also been associated with syphilis infection.<sup>15</sup> The increase in syphilis among MSM parallels reports of increased rates of other sexually transmitted diseases (STDs) and high-risk sexual behavior among MSM,<sup>16–17</sup> which may in part be due to increased substance use, fatigue over safer sex messages, or a decreased concern about HIV-infection in the era of antiretroviral therapy.<sup>18</sup>

Despite ongoing public health efforts to prevent syphilis, including innovative public awareness campaigns and Internet-based prevention interventions,<sup>12,19–20</sup> infection rates among MSM have increased over the last 8 years. Epidemic syphilis among MSM is now the dominant obstacle to the goal of eliminating syphilis in the United States.<sup>21</sup> Moreover, the syphilis epidemic has important implications for HIV infection because syphilis is estimated to increase the transmission of HIV up to 5-fold and may facilitate HIV acquisition.<sup>22–24</sup> New prevention strategies directed toward high-risk groups are needed to better control the current syphilis epidemic. Studies of other STDs, particularly gonorrhea, have shown that disease can be sustained by a core group of people with repeated infections who are essential targets of infection control efforts.<sup>25</sup> A similar core group of individuals with repeated syphilis infections may maintain a syphilis reservoir in the MSM community and thereby contribute to increasing infection rates. We undertook a study to examine the rate of repeat syphilis infection among MSM in San Francisco and to identify risk factors associated with syphilis reinfection that may identify a core group of high-frequency transmitters who warrant additional public health interventions.

## MATERIALS AND METHODS

We reviewed all cases of primary, secondary, and early latent syphilis among MSM in San Francisco reported in the county STD registry in 2001 and 2002. Our outcome was syphilis reinfection, defined as a new infection that occurred within 1 year after a primary, secondary, or early latent syphilis infection first identified in 2001 or 2002. Data were evaluated through the end of 2003 to determine all cases of repeat syphilis within 1 year. Although there is no standard definition in the medical literature for categorizing a repeat syphilis infection within a specific time period, we defined syphilis reinfection as

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a second infection in 1 year, because we felt that those individuals with a repeat infection in that period may represent persons in a core sexual network that would be particularly important for targeted public health interventions.

Syphilis infection was identified by testing patient's sera with rapid plasma reagin (RPR) or Venereal Disease Research Laboratory, and confirming reactive specimens by treponemal specific particle agglutination. Disease investigation staff at the San Francisco Department of Public Health determined if patients had a repeat syphilis infection if they met all of the following criteria based on CDC guidelines:<sup>26</sup> (1) the patient had received treatment for a prior case of primary or secondary syphilis and had demonstrated a response to treatment by at least a 4-fold decline in serologic titers, (2) the patient had new seroreactivity or a 4-fold increase in RPR or Venereal Disease Research Laboratory titers after treatment of the prior infection, and (3) the patient had a clinical history consistent with a repeat infection, including a plausible sexual exposure and clinical symptoms consistent with syphilis. Those patients who failed to have a 4-fold decline of nontreponemal test titers within 6 months after therapy for primary or secondary syphilis were classified as treatment failure and were not considered cases of reinfection. All patients were treated per standard recommendations when the diagnosis of syphilis was made.<sup>26</sup>

As part of routine public health practice, public health staff obtained demographic and behavioral data at the time of the initial syphilis diagnosis through a standardized interview per San Francisco Department of Public Health protocols. These questions included information about partner frequency, meeting venues, and substance use in the period before infection (3 months for primary syphilis, 6 months for secondary syphilis, and 12 months for early latent syphilis). To compare partner frequency among stage groupings, the number of reported sex partners was averaged to a 3-month period for those with secondary or early latent syphilis. MSM categorization was determined by a man's report of having any male partners in the year before infection rather than self-identified sexual orientation. HIV status was determined by self-report and review of public health records. Additional information was obtained from available public health data.

We evaluated the baseline demographic, clinical, and behavioral characteristics obtained at the time of the initial syphilis diagnosis to predict syphilis reinfection. Univariate and multivariate logistic regression were performed using Stata 9.1 (StataCorp. College Station, TX). This analysis was conducted as a part of the public health response to syphilis in San Francisco and was classified as nonresearch, in accordance with the human experimentation guidelines of the US Department of Health and Human Services.

## RESULTS

Between January 2001 and December 2002, 624 MSM were diagnosed with primary, secondary, or early latent syphilis in San Francisco. Sixty-three percent (394/624) were HIV-infected, with a median age of 38 years. Sixty-four percent (401/624) were white, 18% (112/624) were Hispanic, 8% (53/624) were black, and 7% (45/624) were Asian or Pacific Islander. Twenty-four percent (151/624) had primary syphilis, 44% (275/624) had secondary syphilis, and 32% (198/624) had early latent syphilis. The number of sex partners in the 3-month period before the diagnosis of infection was reported as 1 or 2 by 37% (230/624), 3 to 5 by 20% (125/624), 6 to 10 by 14% (87/624), or over 10 by 13% (80/624) of cases; partner data were unknown in 16% (102/624). Twenty-six percent (162/

624) reported meeting partners on the Internet and 28% (173/624) met partners in commercial sex venues, including sex clubs, bathhouses, or adult bookstores. Injection drugs were used by 4% (24/624), and amphetamines were used by 21% (132/624). Two percent (14/624) gave money or drugs in exchange for sex and 3% (19/624) received money or drugs in exchange for sex (Table 1).

Among these cases of primary, secondary, or early latent syphilis, 42 patients (6.7%) had a repeat syphilis infection within 1 year. Comparing data obtained at the first diagnosis of syphilis, no differences in age, race, stage of syphilis, number of period sex partners, illicit substance use, or partner meeting venue were observed between those cases with and without repeat infections (Table 1). HIV infection was associated with an increased risk of repeat syphilis infection (OR = 4.7; CI, 1.8–12.0), which remained significant when adjusted for age and race/ethnicity (OR = 5.2; CI, 2.0–13.7).

## DISCUSSION

Our study examined the rate and risk factors of repeat syphilis infection among MSM with early syphilis in San Francisco in 2001 and 2002. We found that 6.7% of patients had repeat infection within 1 year of a prior syphilis infection, and the single factor predicting reinfection was HIV-infection, conferring a nearly 5-fold greater risk. To date, there are no published reports of rates or risk factors of repeat syphilis in other locations in the United States since the beginning of the HIV epidemic. Data presented at the 2006 National STD Conference from an analysis of repeat syphilis among MSM in Chicago found a similar rate of repeat syphilis infection (8.5%) and also identified HIV infection along with white race as risk factors for multiple syphilis infections.<sup>27</sup> Similarly, research presented at the Annual Conference of the British HIV Association in 2006 concluded that HIV infection was a predictor of syphilis reinfection in MSM in the United Kingdom.<sup>28</sup> Given the strong association between HIV and syphilis reinfection found in our study and others, there is a large population of HIV-infected MSM potentially at risk for repeated syphilis infections who may also represent a core group of transmitters integral in sustaining the current syphilis epidemic.

Although several studies report that some HIV-infected patients may fail to respond serologically to syphilis treatment, we do not believe that cases of treatment failure were likely to be misclassified as repeat infection in our study. The determination of repeat infection was made based on new seroreactivity or a 4-fold rise in nontreponemal titers from a patient's prior serology and a sexual history consistent with a new infection. Studies describing treatment failure have generally reported a slow or incomplete serologic response rather than an increase in nontreponemal titers. For example, Yinnon et al. followed 64 HIV-positive patients after syphilis treatment and found that they were more likely to have a slower decline in RPR titer levels compared to matched HIV-negative controls, but no cases showed an increasing titer after treatment were described.<sup>29</sup> Similarly, Rolfs et al. observed that serologically defined treatment failures were more common among HIV-infected patients, but found only 1 (1%) treatment failure demonstrating an increase in RPR over the lowest titer following treatment among 101 HIV-infected patients studied.<sup>30</sup> Malone et al. reported that 2 of 13 HIV-infected patients with primary or secondary syphilis, seen at a naval medical center between 1985 and 1991, did demonstrate a 4-fold titer rise after standard treatment, occurring at 7 and 22 months after treatment.<sup>31</sup> However, it is unclear if those were cases of treatment

TABLE 1. Risk Factors for Repeat Syphilis, San Francisco

Characteristic	Overall (N = 624)	No Repeat Infection (N = 582)	Repeat Infection (N = 42)	Crude OR (95%CI)	Adjusted OR (95% CI)*
HIV status—N (%)					
Positive	394	357 (91%)	37 (9%)	4.7 (1.8–12.0)	5.2 (2.0–13.7)
Negative	230	225 (98%)	5 (2%)	Ref	Ref
Age (yrs), median (range)	38 (16, 66)	38 (16, 66)	38 (24, 56)	0.99 (0.95–1.03)	0.97 (0.92–1.01)
Race/Ethnicity—N (%) <sup>†</sup>					
Asian/PI	45	41 (91%)	4 (9%)	1.4 (0.4–4.0)	1.3 (0.4–4.0)
African American	53	48 (91%)	5 (9%)	1.4 (0.5–3.9)	1.3 (0.5–3.7)
Hispanic	112	107 (96%)	5 (4%)	0.6 (0.2–1.7)	0.6 (0.2–1.6)
White	401	374 (93%)	27 (7%)	Ref	Ref
Syphilis stage—N (%)					
Primary	151	143 (95%)	8 (5%)	0.9 (0.3–2.2)	—
Secondary	275	253 (92%)	22 (8%)	1.3 (0.7–2.8)	—
Early latent	198	186 (94%)	12 (6%)	Ref	—
Sex partners—N (%) <sup>‡</sup> (3-mo period)					
1–2	230	217 (94%)	13 (6%)	Ref	—
3–5	125	115 (92%)	10 (8%)	1.4 (0.6–3.4)	—
6–10	87	84 (97%)	3 (3%)	0.6 (0.2–2.1)	—
Over 10	80	76 (95%)	4 (5%)	0.9 (0.3–2.8)	—
Partner meeting venue					
Internet—N (%)					
Yes	162	152 (94%)	10 (6%)	0.88 (0.42–1.8)	—
No	462	430 (93%)	32 (7%)	Ref	—
Commercial sex venue—N (%) <sup>§</sup>					
Yes	173	165 (95%)	8 (5%)	0.6 (0.27–1.3)	—
No	451	417 (93%)	34 (7%)	Ref	—
Drug use					
Injection drugs used—N (%)					
Yes	24	22 (92%)	2 (8%)	1.3 (0.3–5.6)	—
No	600	560 (93%)	40 (7%)	Ref	—
Amphetamines used—N (%)					
Yes	132	122 (93%)	10 (7%)	1.2 (0.6–2.5)	—
No	492	460 (94%)	32 (6%)	Ref	—
Exchange for Sex					
Gave money/drugs for sex—N (%)					
Yes	14	12 (86%)	2 (14%)	2.4 (0.5–11.0)	—
No	610	570 (94%)	40 (6%)	Ref	—
Received money/drugs for sex—N (%)					
Yes	19	17 (90%)	2 (10%)	1.7 (0.4–7.4)	—
No	605	565 (93%)	40 (7%)	Ref	—

\*Adjusted for HIV status, age, race/ethnicity.

<sup>†</sup>Missing data for 13 (2%) cases.<sup>‡</sup>Missing data for 102 (16%) cases.<sup>§</sup>Commercial sex venue includes adult bookstores, bathhouses, and sex clubs.

failure or reinfection because the study was a retrospective chart review, which may have limited the authors' access to a relevant clinical history needed to distinguish a new infection from treatment failure. Although it is possible that some cases in our study may represent treatment failure and not a true reinfection, these cases are unlikely to account for the strong association between HIV infection and syphilis reinfection we observed. Future studies utilizing molecular methods to distinguish among strains of *Treponema pallidum* could potentially help to clarify the frequency of treatment failure in the HIV-infected population.<sup>32</sup>

Several factors might explain our finding that there is an increased risk of repeat syphilis infection among persons with HIV infection. There is likely a higher prevalence of syphilis in the HIV-infected population, leading to a higher risk of infection due to increased exposure to others with syphilis. The phenomenon of serosorting, in which HIV-infected men are more likely to have sex, and in particular unprotected anal sex,

with others of similar HIV status might be a useful strategy to reduce HIV transmission but may actually increase the spread of STDs like syphilis.<sup>33–36</sup> Immunosuppression secondary to HIV infection could also limit the host's defenses against *T. pallidum*, possibly elevating the risk of acquiring syphilis infection.<sup>37</sup> Finally, because HIV-infected persons are more likely to be in routine medical care than HIV-negative persons, they might be more likely to be screened for syphilis, increasing the chance of identifying a second infection within 1 year.

Our study found no association between repeat infection and several baseline factors associated with the risk of initial syphilis infection reported in other studies, including meeting partners on the Internet, methamphetamine use, and nonwhite race.<sup>15</sup> Our results might indicate that the prevalence of syphilis in a person's sexual network is more important than these other risk factors, particularly if HIV-infected men serosort with others of the same HIV status. It is also possible that the risk factors reported at the time of first syphilis infection might not

predict persistence of those risk factors, suggesting that some patients might alter their behaviors after being diagnosed with syphilis. Finally, the small sample size of repeat infections might also have limited our study's power to detect an association among those factors. Our sample might also underestimate the incidence of repeat syphilis cases since it is possible that some patients had a second infection that was diagnosed more than 1 year from initial infection but was actually acquired earlier, was diagnosed outside of San Francisco, or was not diagnosed due to inadequate follow-up.

Despite these limitations, our study highlights the important association between HIV infection and syphilis and suggests there is an opportunity for targeted public health interventions among HIV-infected MSM presenting with syphilis infection. Provider-focused interventions, including patient education and increased screening, may be particularly effective because many HIV-infected MSM are likely to be under the care of a clinician.<sup>38</sup> Our results also underscore the importance of current CDC recommendations for routine and frequent syphilis screening in all sexually active HIV-infected patients,<sup>39</sup> particularly if they have had a prior syphilis infection. Many HIV care providers now screen for syphilis in sexually active MSM with every CD4 T-cell measurement. Focusing public health interventions and future prevention research on MSM with syphilis and HIV infection might help reduce reinfection and the overall incidence of disease among MSM.

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