

Use of the Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) to Identify Recently Acquired HIV Infections in Men With Early Syphilis in Los Angeles County

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Background: Syphilis outbreaks among men who have sex with men (MSM) in the United States, many of whom are HIV infected, have prompted increased concern for HIV transmission.

Methods: To identify whether men are acquiring HIV concomitantly or within the critical period of syphilis infection, banked *Treponema pallidum* particle agglutination–positive serum specimens from men with early syphilis infection were screened for HIV-1 antibody. Samples that were positive for HIV antibody were then tested with a less sensitive (LS) HIV-1 antibody enzyme immunoassay (serologic testing algorithm for recent HIV seroconversion [STARHS]) to identify HIV infections that occurred on average within the previous 6 months.

Results: Of the 212 specimens banked from men with early syphilis, 74 (35%) were HIV-positive. Of these, 15 tested non-reactive by the LS assay. Twelve of these 15 were considered to be recent infections by the LS assay and testing history. Eleven (92%) of the recent infections were among MSM. One man had primary syphilis, 6 (50%) had secondary syphilis, and 5 (42%) had early latent syphilis. Eight men (67%) reported sex with anonymous partners, and 3 (25%) reported consistent condom use. The estimated HIV incidence was 17% per year (95% confidence interval [CI]: 12%–22%) among all men with early syphilis, and it was 26% per year (95% CI: 91%–33%) among MSM.

Conclusions: Syphilis epidemics in MSM may be contributing to HIV incidence in this population. The STARHS can be applied as a surveillance tool to assess HIV incidence in various at-risk populations, but further studies are necessary for validation.

Key Words: syphilis, men who have sex with men, HIV incidence, serologic testing algorithm for recent HIV seroconversion assay, sexual risk

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The reported number of HIV diagnoses increased in 29 states from 1999 to 2002, with a 17% increase documented among men who have sex with men (MSM), suggesting a possible resurgence of HIV transmission in this at-risk group.¹ There are an estimated 45,000 persons living with HIV and AIDS in Los Angeles County (LAC) who are aware of their status and an estimated 9000 persons with HIV who do not know their status. As of December 2003, the epidemic of HIV/AIDS in LAC remains predominantly among males (89%), people of color (63%), and MSM (70%).²

A concurrent epidemic of syphilis among MSM has been ongoing in LAC since early 2000.³ During 2003, 704 cases of early syphilis were diagnosed in LAC, with 464 (66%) occurring among MSM. HIV-seropositive men made up 60% of these early syphilis cases diagnosed among MSM.⁴ These coinfection rates are of significant concern, given the increased risk of HIV transmission associated with a sexually transmitted disease (STD) such as syphilis.⁵ Recently reported data among MSM diagnosed with incident HIV and an STD in San Francisco support this risk.⁶ In addition, reports of increases in unsafe sexual behaviors among MSM groups^{7–9} suggest further transmission opportunities for HIV and other STDs in these populations.

To evaluate the contribution of the ongoing syphilis epidemic to incident HIV infections among MSM, we applied STARHS to stored blood specimens of men diagnosed with early syphilis.

METHODS

Study Population

The LAC Public Health Laboratory (PHL) performs syphilis testing on samples received from the 13 publicly funded STD clinics in LAC from community-based organizations and from other public facilities. Beginning in January

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of 2002 through April 2004, 212 rapid plasma reagin (RPR)–positive and *Treponema pallidum* particle agglutination assay (TP-PA)–positive specimens of men diagnosed with primary, secondary, or early latent syphilis were banked and frozen at the LAC PHL for purposes of detecting recent HIV infection. Identifying information was removed from all cases before testing.

Field interview records obtained on early syphilis cases were reviewed for demographic, behavioral, and clinical data and linked to cases before removal of identifying information. Demographic data included age, race/ethnicity, zip code of primary residence, self-reported HIV serostatus, HIV testing history, and history of incarceration. Sexual behavioral data included self-reported anal sex, oral sex, sex with anonymous partners, venues for meeting sex partners, consistent condom use within the previous 12 months, and intravenous and nonintravenous drug use as practiced during the “critical period” of syphilis infection defined in the syphilis case definition.¹² Sex with anonymous partners was defined as oral or anal sex with a person for whom no identifying information was available to the syphilis patient. Clinical data included stage of syphilis, symptoms present at time of diagnosis, treatment information, and follow-up laboratory testing results.

This anonymous unlinked survey was conducted as part of the epidemic disease control activities to contain syphilis and HIV transmission. As a non-research activity, it was exempt from human subjects review. Informed consent for HIV antibody and STARHS testing was not obtained.

Syphilis Case Definition

Early syphilis consisted of all reported primary, secondary, and early latent syphilis cases. The diagnosis of primary syphilis was made by the presence of 1 or more ulcers at the site of exposure and the demonstration of exposure to *T. pallidum* by a reactive serologic test for syphilis. Secondary syphilis was diagnosed by the presence of characteristic dermatologic lesions and a reactive nontreponemal test (titer > 1:4). The diagnosis of early latent syphilis was made in persons with evidence of having acquired the infection within the previous 12 months based on 1 or more of the following criteria: documented negative test result in the last 12 months, 4-fold or greater increase in titer of a nonreactive treponemal test during the previous 12 months, history of symptoms consistent with primary or secondary syphilis during the previous 12 months, history of sexual exposure to a partner who had confirmed infectious syphilis, or reactive nontreponemal and treponemal tests from a person whose only possible exposure occurred within the preceding 12 months.¹²

Laboratory Methods

Syphilis serologic testing was performed with the RPR assay; confirmatory testing was performed with the use of the TP-PA on samples that had an RPR titer of greater than or equal to 1:1. Serum specimens with positive RPR and/or TP-PA results were screened for HIV-1 antibodies by a conventional sensitive EIA (Vironostika HIV-1 MicroElisa). Repeatedly reactive specimens were confirmed to be positive

by Western blot analysis. Samples that were positive for HIV antibody were then tested with a less sensitive (LS) HIV-1 antibody EIA.^{10,11} Specimens that had a mean standard optical density (SOD) of 1.00 or less were defined as “nonreactive” and interpreted to represent HIV infection occurring, on average, within the previous 170 days (95% confidence interval [CI]: 145–200 days), and those that had a mean SOD >1.00 were defined as “reactive” and interpreted to represent HIV infections occurring, on average, greater than 170 days from the sample collection date.^{10,11}

Statistical Methods

Data were analyzed using the SAS statistical package, version 8.0 (SAS Institute, Cary, NC). The recently infected HIV proportion was calculated as the number of recently HIV-infected persons divided by the number of HIV-uninfected plus recently HIV-infected persons. Annual HIV incidence among MSM with early syphilis was calculated by multiplying the proportion of recently HIV-infected MSM (11 of 90; Table 1) by the correction factor of $(365.25/170) \times (100)$.^{10,11}

RESULTS

During January 2002 through April 2004, 1721 cases of early syphilis were diagnosed in LAC; 1426 (83%) of these occurred among men. Of the cases occurring among men, 1114 (78%) were in MSM (see Table 1). Two hundred twelve specimens from men with early syphilis that were diagnosed through the LAC PHL were used for this study. One hundred forty (66%) of these men were MSM by self-report; for 31 (14%), data on sexual orientation were not available.

Of the 212 specimens banked from men with early syphilis, 74 were HIV-positive by standard testing algorithms. Fifteen of these 74 specimens tested “nonreactive” by the LS assay. Of these 15 cases, 3 were determined to be old infections as demonstrated by information on the date of the first HIV-positive test result collected during field interviews. Eleven (92%) of the recent infections were among MSM. One man (8.3%) had primary syphilis, 6 (50%) had secondary syphilis, and 5 (42%) had early latent syphilis. Eight men (67%) reported sex with anonymous partners, and 3 (25%) reported using a condom (see Table 1). The annualized HIV incidence was 17% (95% CI: 12%–22%) among men with early syphilis. Among the group of MSM with early syphilis, the annualized HIV incidence was 26% (95% CI: 19%–33%).

DISCUSSION

Our results suggest a high rate of HIV acquisition occurring among this group of MSM with early syphilis in comparison to the percentage of MSM newly diagnosed with HIV in LAC. Available comparison data showed that the percentage of MSM tested for HIV (non-STARHS testing) at publicly funded sites with newly diagnosed HIV infection was 4.1% (615 of 15,161 MSM) in 2002.¹³ These results may seem to conflict with the recent population-based data analyzed from San Francisco and Los Angeles that found no measurable increase in the number of HIV infections occurring among MSM during the periods of higher syphilis rates among MSM in these areas.¹³ The fundamental difference in study design

TABLE 1. Demographic and Behavioral Characteristics of All Men With Early Syphilis in Los Angeles County (N = 1426) and the Study Population (N = 212) According to HIV Infection Status

	All Male Early Syphilis N (%)	STARHS		HIV-Negative Specimens N (%)
		Non Reactive (early infection) N (%)	STARHS Reactive (late infection) N (%)	
Total	1426	12	62*	138
Sexual orientation				
MSM	1035 (73)	10 (83)	42 (68)	70 (51)
MSM/W	79 (6)	1 (8.3)	8 (13)	9 (7)
MSW	153 (11)	0 (0)	2 (3.2)	38 (28)
Refused	4 (0.3)	0 (0)	1 (1.6)	0 (0)
Unknown	155 (11)	1 (8.3)	9 (15)	21 (15)
Stage				
Primary	232 (16)	1 (8.3)	6 (9.6)	32 (23)
Secondary	553 (38)	6 (50)	30 (48)	47 (34)
Early latent	641 (45)	5 (42)	26 (42)	59 (43)
Age (y)				
<20	28 (2)	0 (0)	3 (4.8)	8 (6)
20–29	275 (19)	7 (58)	12 (19)	38 (28)
30–39	610 (43)	2 (16)	38 (61)	51 (37)
40–49	388 (27)	2 (16)	7 (11)	27 (20)
50+	125 (9)	1 (8.3)	2 (3.2)	14 (10)
Race/ethnicity				
White	615 (43)	4 (33)	17 (27)	34 (25)
African American	178 (12)	2 (17)	9 (15)	23 (17)
Latino	528 (37)	5 (42)	25 (40)	54 (39)
Other/mixed	105 (7)	1 (8.3)	11 (18)	27 (20)
HIV status†				
Positive	705 (62)	6 (50)	42 (68)	1 (0.7)
Negative	437 (38)	3 (25)	5 (8)	93 (67)
Behavioral risk factors				
Anal insertive	760 (74)	7 (58)	37 (60)	48 (35)
Anal receptive	735 (72)	9 (75)	39 (63)	43 (32)
Oral sex	974 (93)	9 (75)	54 (87)	83 (60)
Anonymous sex‡	779 (75)	8 (67)	35 (56)	62 (45)
Condom use§	286 (31)	3 (25)	10 (16)	21 (15)
Incarceration	54 (5.7)	1 (8)	4 (6)	7 (5)
IDU¶	31 (3)	0 (0)	2 (3)	2 (1.4)
Non-IDU#	284 (28)	3 (25)	18 (29)	36 (26)
Venues				
Bathhouses	232 (25)	3 (25)	14 (23)	19 (14)
Bars/clubs	391 (41)	3 (25)	17 (27)	29 (21)
Dancehalls	11 (1.2)	0 (0)	0 (0)	1 (0.7)
Internet	195 (21)	2 (17)	10 (16)	17 (12)
Motels	24 (2.6)	0 (0)	0 (0)	3 (2)
Parks	48 (5.2)	0 (0)	3 (5)	7 (5)
Streets	82 (8.7)	2 (17)	1 (1.6)	14 (10)

*Includes 3 of 15 specimens testing nonreactive by the STARHS assay and determined by field interview data to be late infections.

†Self-reported.

‡Anonymous partner is defined as a sexual partner for whom the syphilis patient was unable to provide any type of identifying or locating information.

§Condom use is reported as consistent use within the past 12 months after field interview.

||Incarceration in the previous year.

¶Intravenous drug use includes use of injectable forms of heroin, methamphetamines, cocaine, and other drugs.

#Nonintravenous drug use includes the use of oral, inhaled, and/or smoked forms of marijuana, methamphetamines, poppers/nitrates, viagra, ketamine, ecstasy, and cocaine.

IDU indicates injection drug use; MSM/W, men who have sex with men and women.

may account for these discrepancies, given that population-based analyses may not be sensitive enough to identify risks to individuals from relatively rare diseases such as syphilis.

These results are of public health concern given the number of metropolitan areas in the United States experiencing rising syphilis rates among MSM populations at risk or coinfecting with HIV.^{3,9,14} Counseling messages to persons with early syphilis should include information on the increased risk of HIV transmission in the setting of a concomitant STD. Integrated HIV/STD testing efforts should be fostered to identify new cases of HIV and other STDs such as syphilis and to prevent further transmission of these preventable diseases. Public health attention should remain focused on educational efforts to providers, community-based organizations, and persons at risk so as to prevent increases in HIV rates in association with syphilis epidemics and increases in risk behaviors.

Our study has strengths and limitations. It is the first study of its kind to use the STARHS testing algorithm to estimate HIV incidence among men with early syphilis infection. The STARHS testing algorithm may misclassify some persons with long-standing HIV infection and/or HIV-infected persons on antiretroviral therapy as recently HIV infected.^{11,15} Indeed 3 of our subjects testing nonreactive with STARHS reported having long-standing HIV infection. The percentage of newly diagnosed HIV infections is currently the only available proxy for HIV incidence among MSM in LAC and does not necessarily reflect HIV incidence trends. Sample size limited our ability to recognize significant behavioral or demographic associations with recent HIV infection as determined by STARHS. Finally, our results were obtained from men with early syphilis diagnosed in LAC and thus should not be generalized to other at-risk groups

Our findings highlight the ongoing need for HIV incidence monitoring in areas with high syphilis morbidity, particularly among MSM at high risk for HIV infection and other STDs such as syphilis. STARHS should be considered a relatively simple and cost-effective epidemiologic tool that may be used by local health departments for assessment of HIV incidence in well-characterized populations with information available on previous HIV testing history. The use of other S/LS strategies that can increase the predictive value of correctly identifying recently infected persons¹⁶ and improve the validity of STARHS is needed, particularly in light of our findings that 20% (3 of 15) of the persons testing as having recently acquired infections by the S/LS test were incorrectly classified. Not all men had complete HIV test results available. Further research using the STARHS testing algorithm and larger sample sizes is needed to identify demographic and behavioral characteristics associated with early HIV infection among persons with early syphilis.

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