Syphilis Testing Behavior Following Diagnosis With Early Syphilis Among Men Who Have Sex With Men—San Francisco, 2005–2008

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Background: In San Francisco, men who have sex with men (MSM) with early syphilis are at high risk of reinfection. We described syphilis testing behavior among MSM after diagnosis, identified factors associated with not testing, and developed algorithms to identify nontesters.

Methods: We used syphilis surveillance data from 2005 through 2008 to describe follow-up testing behavior among MSM with early syphilis and titers of nontreponemal serologic tests ≥1:16. We analyzed data from contact-tracing interviews to identify factors associated with not testing during the 1 to 6 months postdiagnosis. We developed and applied a multivariate model in a derivation set (2005–2006) and a validation set (2007–2008), respectively, calculating correct classification rates (CCR) to assess predictive ability and evaluating patient characteristics for potential interventions.

Results: Among 795 MSM, 260 (33%) did not have a follow-up syphilis test. Not testing was associated with being HIV-uninfected (risk ratio [RR]: 1.9, 95% confidence interval [CI]: 1.5–2.6), residing outside of San Francisco's gay-identified neighborhood (RR: 1.7, 95% CI: 1.0–2.9), and being diagnosed at the municipal sexually transmitted disease clinic (RR: 1.5, 95% CI: 1.2–2.0) (CCR derivation set, 71.6%; CCR validation set, 71.3%). An intervention focusing on MSM with those 3 characteristics would include 13% of syphilis cases among MSM and identify 26% of nontesters.

Conclusions: Although MSM in San Francisco are at high risk for syphilis reinfection, one-third of MSM diagnosed with syphilis did not test during the 1 to 6 months postdiagnosis. Interventions to encourage follow-up testing among persons with syphilis might contribute to more effective syphilis prevention and control efforts.

After reaching a historic nadir in 2000, the incidence of primary and secondary (P&S) syphilis in the United States increased annually through 2008.[1] That increase has been concentrated primarily among men who have sex with men (MSM), who accounted for 63% of P&S cases in 2008. A large proportion of MSM infected with P&S syphilis are coinfected with human immunodeficiency virus (HIV).[2–5] In San Francisco, reported cases of P&S syphilis increased 67% from 2007 (n = 204) to 2008 (n = 342).[6] More than 90% of cases during 2008 were among MSM, of whom 64% were coinfected with HIV.

Persons who are reinfected with sexually transmitted diseases (STDs) have been considered to comprise a core group that might sustain transmission in a population[7]; thus, interventions that focus on this group might reduce local community burden of disease. Whereas several studies have examined reinfection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis,*[8–12] few have explored repeat syphilis. Because syphilis is relatively rare, persons who are reinfected with syphilis might be more likely to disproportionately sustain endemic transmission than persons who are reinfected with *N. gonorrhoeae* or *C. trachomatis*. A study of early syphilis among MSM in San Francisco found that 6.7% of patients had a newly diagnosed syphilis infection within 1 year of diagnosis and treatment.[13] Others have reported rates of syphilis reinfection of 10% within 10 years in British Columbia,[14] 17.6% within 17 years in Seattle[15] and 42.7% within 1 year in Peru.[16]

The San Francisco Department of Public Health (SFDPH) recommends that sexually active MSM have a serologic test for syphilis every 3 to 6 months, and that persons diagnosed with syphilis have a serologic test for syphilis at 1, 3, 6, 9, and 12 months after diagnosis.[17] Serologic testing of syphilis patients after diagnosis allows for clinical follow-up to monitor post-treatment titer decline and can identify treatment failures and new cases. Despite guidelines on screening and follow-up testing for healthcare providers, and social marketing campaigns to promote syphilis testing among MSM,[18,19] syphilis incidence has remained high among MSM in San Francisco since 2002,[6] with increased rates of infection among persons who have previously been infected.[13]

Because MSM diagnosed with syphilis are more likely to acquire syphilis in the future compared with MSM not diagnosed with syphilis, it is critical that MSM diagnosed with syphilis regularly test for syphilis after they are diagnosed. Follow-up testing is important clinically because it can detect treatment failure, but treatment failure is rare. Follow-up testing is even more critical from a public health perspective because it can detect, as early as possible, new cases of syphilis in a population at high risk of syphilis. Therefore, our objective in this study was to describe and analyze syphilis testing behavior among those MSM who were previously infected with syphilis. Specifically, we aimed to describe syphilis testing behavior following diagnosis with early syphilis among MSM in San Francisco, to identify factors associated with not having a syphilis test following diagnosis, and to develop algorithms to

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prospectively identify likely nontesters for syphilis prevention and control efforts.

METHODS

Study Population

Laboratories are legally required to report reactive syphilis serologic test results on specimens obtained from San Francisco residents to SFDPH, as mandated by Title 17, CA Code of Regulations §2500, §2593, §2641 to 2643, and §2800 to 2812. SFDPH staff review all reported reactive tests among San Francisco residents and prioritize patients for interview who are most likely to be newly infected with syphilis.[20] During interviews, SFDPH staff follow Centers for Disease Control and Prevention methods[21] to elicit contact information for sex partners, classify stage of syphilis, and collect data on patient demographics (e.g., sexual orientation and race/ethnicity) and behaviors (e.g., drug use). Interviewed persons are asked for the number, gender, and contact information of sex partners from the critical period, which is 3, 6, and 12 months for primary, secondary, and early latent syphilis, respectively, and represents the period during which patients were most likely infectious to partners. Each patient's HIV-infection status is assessed by self-report if test results are not documented.

We used data from syphilis interviews of MSM, defined as men who identified as gay or bisexual or who reported ever having sex with men, who were residents of San Francisco and diagnosed with early syphilis from 2005 through 2008. For patients with multiple interviews during the period, we used data from the most recent interview. We searched SFDPH surveillance records to assess whether patients had a documented history of syphilis and reviewed surveillance data on laboratory-reported reactive serologic tests to assess syphilis testing behavior during the 1 to 6 months following diagnosis (i.e., 23–190 days following diagnosis to allow a 1-week window on either end). SFDPH has access to nonreactive results from syphilis serologic tests that are conducted by the San Francisco Public Health Laboratory, but nonreactive syphilis serologic tests are not reported to SFDPH by other laboratories. To maximize the likelihood that follow-up serologic tests would remain reactive and thus be reported, we excluded patients whose serologic titers on the day of diagnosis were $<$1:16[22] or who had no available titer data. To assess whether excluding those patients might introduce bias, we compared the distribution of race/ethnicity, age, and HIV-infection status among excluded patients with the distribution of those factors among patients who were included in the analysis.

Statistical Analysis

To describe syphilis testing behavior following diagnosis of early syphilis, we calculated the proportion of patients who had at least 1 documented syphilis test during the 1 to 6 months following diagnosis. Because we aimed to develop algorithms to prospectively identify likely nontesters, we divided patients into a derivation data set and a validation data set.[23] We used patients diagnosed during 2005 and 2006 (derivation set) to identify factors associated with not testing and develop a prediction model, and patients diagnosed during 2007 and 2008 (validation set) to assess the ability of those factors to prospectively identify nontesters in a set of data not used to develop the model.[24]

To identify factors associated with not testing, we used chi-square tests to compare demographic, clinical, and behavioral characteristics of patients who did and did not test for syphilis during the 1 to 6 months following diagnosis. For demographic characteristics, we assessed age (categorized as $<$25, 25–34, 35–44, or $\geq$45), sexual orientation (gay, bisexual, or straight), and race/ethnicity (white, Hispanic, Asian, black, or other). We also assessed whether patients resided in San Francisco's gay-identified neighborhood where the gay men's health clinic is located, hypothesizing that those patients might test more frequently than MSM residing elsewhere. For clinical characteristics, we assessed stage of syphilis, documented history of syphilis, diagnosis with *N. gonorrhoeae* or *C. trachomatis* infection at the visit during which syphilis was diagnosed, HIV-infection status (HIV-infected, HIV-uninfected, or HIV status unknown), and the healthcare setting in which syphilis was diagnosed (municipal STD clinic, managed care organization, gay men's health clinic, HIV care clinic, or other). For behavioral characteristics, we assessed recreational drug use in the 12 months before diagnosis (methamphetamine, inhaled nitrites, or cocaine), lifetime history of injection drug use, number of male sex partners during the infectious period (dichotomized to $<$5 or $\geq$5), and venues for meeting those partners (bathhouses/sex clubs or Internet).

We used a multivariable log-binomial model to calculate unadjusted and adjusted risk ratios (RRs) and 95% confidence intervals (CIs) of not testing for syphilis during the 23 to 190 days following diagnosis. All factors that were significantly associated with not testing in bivariate analysis ($P < 0.1$) were considered for inclusion in the multivariable model. We collapsed categories for HIV-infection status (HIV-uninfected/unknown compared with HIV-infected), and we did not include sexual orientation because there were too few patients ($n = 4$ in the derivation set) who were straight-identified to evaluate that characteristic. To simplify the model, we removed variables that were not statistically significant ($P > 0.05$) when doing so did not negatively impact model fit, as measured by likelihood ratio tests.[25] We used the predicted probabilities to apply the final model to the validation set, calculating the correct classification rate for the model in each set to assess predictive ability. Patients with predicted probabilities of not testing $>$0.5 were classified as predicted nontesters, whereas the remaining patients were classified as predicted testers. The correct classification rate is the proportion of observed outcomes that are correctly predicted by the model.

To develop algorithms to prospectively identify nontesters, we assessed all possible combinations of patient characteristics remaining in the final model for potential interventions among patients unlikely to seek follow-up testing for syphilis. For each algorithm, we used the validation set to calculate the proportion of nontesters identified (i.e., sensitivity) and the proportion of the total sample included. An efficient algorithm for an intervention would maximize the proportion of nontesters identified while minimizing the proportion of the sample included. We also calculated the ratio of percent of identified nontesters to percent of included patients for each combination of characteristics to measure the incremental benefit or decrement in efficiency for each algorithm. A ratio $>$1 indicated that focusing resources on syphilis patients with a particular characteristic or combination of characteristics would identify more nontesters than would be expected by chance, with higher ratios indicating increasing efficiency.

RESULTS

From 2005 through 2008, 1501 MSM in San Francisco were diagnosed with early syphilis, of whom 1147 (76%) were interviewed. Of 1039 (91%) patients with available titers, 795

TABLE 1. Characteristics of Men Who Have Sex With Men Diagnosed With Early Syphilis (n = 795), by Syphilis Testing Behavior During 1–6 Months After Diagnosis—San Francisco, 2005–2008*

Characteristic	At Least 1 Syphilis Serologic Test 1–6 Months After Diagnosis, n (Row %)	No Syphilis Serologic Test 1–6 Months After Diagnosis, n (Row %)
Total	535 (67)	260 (33)
Demographic		
Age, yr		
<25	24 (53)	21 (47)
25–34	113 (60)	75 (40)
35–44	237 (70)	103 (30)
≥45	161 (73)	61 (27)
Sexual orientation		
Gay	512 (69)	230 (31)
Bisexual	16 (39)	25 (61)
Straight	5 (83)	1 (17)
Race/ethnicity		
White	340 (68)	157 (32)
Hispanic	102 (68)	48 (32)
Asian	42 (67)	21 (33)
African American	35 (56)	27 (44)
Other	15 (71)	6 (29)
Residence in gay-identified neighborhood		
Yes	107 (76)	34 (24)
No	428 (65)	226 (35)
Clinical		
Stage		
Primary	64 (70)	27 (30)
Secondary	302 (66)	157 (34)
Early latent	169 (69)	76 (31)
History of syphilis		
Yes	170 (76)	53 (24)
No	365 (64)	207 (36)
Concurrent NG or CT infection		
Yes	56 (52)	51 (48)
No	479 (70)	209 (30)
HIV status		
Infected	388 (77)	115 (23)
Uninfected	137 (50)	137 (50)
Unknown	10 (56)	8 (44)
Healthcare setting of diagnosis		
STD clinic	134 (52)	126 (48)
Managed care organization	52 (67)	26 (33)
Gay men's health clinic	48 (75)	16 (25)
HIV care clinic	35 (85)	6 (15)
Other	266 (76)	86 (24)
Behavioral		
Drug use, past 12 mo		
Methamphetamine	164 (70)	70 (30)
Inhaled nitrites	69 (69)	31 (31)
Cocaine	41 (68)	19 (32)
Injection drug use, ever		
Yes	61 (67)	30 (33)
No	447 (67)	220 (33)
No. sex partners, infectious period†		
<5	289 (65)	156 (35)
≥5	232 (70)	101 (30)
Venues for meeting sex partners		
Bathhouses or sex clubs	97 (81)	23 (19)
Internet	232 (68)	110 (32)

*Data were collected during contact-tracing interviews, using the most recent interview for persons with multiple interviews. Cases with nontreponemal titer <1:16 were excluded. Column frequencies might not sum to total because of missing data.

†Infectious period was based on stage of syphilis at diagnosis: 3 months for primary, 6 months for secondary, and 12 months for early latent.

HIV indicates human immunodeficiency virus; NG, *Neisseria gonorrhoeae*; CT, *Chlamydia trachomatis*; STD, sexually transmitted disease.

(77%) had a titer ≥1:16 at diagnosis. A comparison of patients with titers ≥1:16 (n = 795) with patients who were excluded because of no available titer or titers <1:16 (n = 244) identified no differences in the distribution of race/ethnicity, age, or HIV-infection status (data not shown). Of the 795 patients included in the analysis, most had secondary syphilis (58%), were white (63%), and were HIV-infected (63%) (Table 1). The median age was 40 years (interquartile range, 33–45). More than one-quarter (28%) had a documented history of syphilis, and 13% were diagnosed with *N. gonorrhoeae* or *C. trachomatis* infection at the time of syphilis diagnosis. The healthcare settings in which syphilis was most commonly diagnosed were the municipal STD clinic (33%), a managed care organization (10%), the gay men's health clinic (8%), and an HIV care clinic (5%). Almost one-third (29%) reported methamphetamine use in the past 12 months.

Of the 795 syphilis patients interviewed and having a titer ≥1:16 at diagnosis, 260 (33%) did not have a documented syphilis test during the 1 to 6 months following diagnosis. Among the patients who did have a test during the 1 to 6 months following diagnosis, the median days between diagnosis and testing was 70 (interquartile range, 42–112).

In bivariate analysis of patients in the derivation set (n = 377), not having a syphilis test (34% of patients in the derivation set) was significantly associated with *N. gonorrhoeae* or *C. trachomatis* infection at the time of syphilis diagnosis, compared with not having one of those infections (RR: 1.7, 95% CI: 1.3–2.4); residing outside of San Francisco's gay-identified neighborhood, compared with residing in that neighborhood (RR: 2.0, 95% CI: 1.2–3.3); being HIV-uninfected or of unknown HIV status, compared with being HIV-infected (RR: 2.2, 95% CI: 1.6–2.9); being diagnosed at the STD clinic, compared with being diagnosed elsewhere (RR: 1.9, 95% CI: 1.4–2.4); cocaine use in the past 12 months, compared with not using cocaine in the past 12 months (RR: 1.6, 95% CI: 1.1–2.4); having no documented history of syphilis, compared with having a prior episode (RR: 1.5, 95% CI: 1.0–2.1); and not meeting partners at bathhouses or sex clubs, compared with meeting partners at those venues (RR: 1.6, 95% CI: 0.9–2.8) (Table 2).

In multivariable analysis, not having a follow-up syphilis serologic test remained significantly associated with residing outside of San Francisco's gay-identified neighborhood (RR: 1.7, 95% CI: 1.0–2.9); being HIV-uninfected or of unknown HIV status (RR: 1.9, 95% CI: 1.5–2.6); and being diagnosed at the STD clinic (RR: 1.5, 95% CI: 1.2–2.0). The model in the derivation set correctly classified 71.6% of nontesters and testers. When the same model was applied to the validation set (n = 418), 71.3% of nontesters and testers were correctly classified.

The proportion of nontesters identified and patients included by all possible combinations of the patient characteristics remaining in the final model, and the ratios of percent of identified nontesters to percent of included patients, are shown in Figure 1. The ideal algorithm for an intervention would maximize the proportion of nontesters identified while minimizing the proportion of patients included, and thus would be situated at the upper left corner of the figure. An intervention focusing on MSM who are diagnosed at the STD clinic, or not HIV-infected, or residing outside of San Francisco's gay-identified neighborhood (algorithm I; Fig. 1, Table 3) would identify the highest proportion of nontesters (95%) and would include 90% of syphilis patients (ratio, 1.06) (Table 3). An intervention focusing on MSM who are diagnosed at the STD clinic or not HIV-infected (algorithm F) would identify 78% of nontesters and include 54% of patients (ratio, 1.44). An intervention focusing on MSM who are diagnosed at the STD clinic, and not HIV-infected, and residing outside of San Francisco's gay-identified neighborhood (algorithm A) would identify 26%

TABLE 2. Factors Associated With Not Having a Syphilis Test During 1–6 Months After Diagnosis—San Francisco, 2005–2006*†

Characteristic	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
No documented history of syphilis	1.5 (1.0–2.1)	—
Concurrent NG or CT infection	1.7 (1.3–2.4)	—
Resided outside of gay-identified neighborhood	2.0 (1.2–3.3)	1.7 (1.0–2.9)
HIV-uninfected or unknown status	2.2 (1.6–2.9)	1.9 (1.5–2.6)
Diagnosed at STD clinic	1.9 (1.4–2.4)	1.5 (1.2–2.0)
Cocaine use, past 12 mo	1.6 (1.1–2.4)	—
Did not meet partners at bathhouses or sex clubs	1.6 (0.9–2.8)	—

*Univariate and multivariable log-binomial analyses were conducted in derivation set (n = 377).
†All comparisons were for persons with vs. without the characteristic listed.
RR indicates risk ratio; CI, confidence interval; NG, *Neisseria gonorrhoeae*; CT, *Chlamydia trachomatis*; HIV, human immunodeficiency virus; STD, sexually transmitted disease.

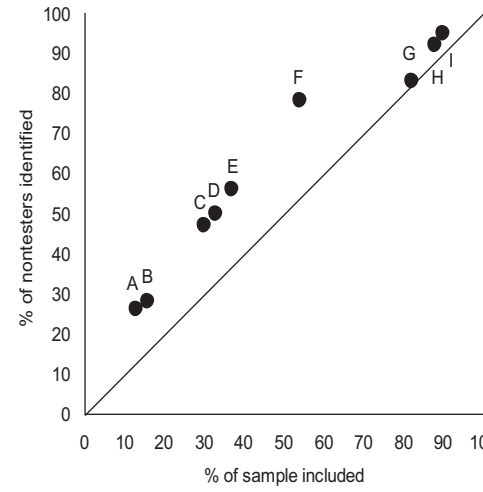

Figure 1. Proportion of nontesters identified and patients included by selected characteristics—San Francisco, 2005–2008. Criteria were evaluated in validation set (n = 418). A, Diagnosed at STD clinic, and not HIV-infected, and reside outside of gay-identified neighborhood. B, Diagnosed at STD clinic and not HIV-infected. C, Reside outside of gay-identified neighborhood and not HIV-infected. D, Diagnosed at STD clinic. E, Not HIV-infected. F, Diagnosed at STD clinic or not HIV-infected. G, Reside outside of gay-identified neighborhood. H, Reside outside of gay-identified neighborhood or not HIV-infected. I, Diagnosed at STD clinic, or not HIV-infected, or reside outside of gay-identified neighborhood.

TABLE 3. Proportion of Nontesters Identified and Patients Included, and Ratio of Percent of Identified Nontesters to Percent of Included Patients, by Selected Criteria—San Francisco, 2005–2008*

Characteristic(s)	% of Sample	% Nontesters	Ratio of % Nontesters Identified to % of Sample
A. Diagnosed at STD clinic, and not HIV-infected, and reside outside of gay-identified neighborhood	13	26	2.00
B. Diagnosed at STD clinic and not HIV-infected	16	28	1.75
C. Reside outside of gay-identified neighborhood and not HIV-infected	30	47	1.57
D. Diagnosed at STD clinic	33	50	1.52
E. Not HIV-infected	37	56	1.51
F. Diagnosed at STD clinic or not HIV-infected	54	78	1.44
G. Reside outside of gay-identified neighborhood	82	83	1.01
H. Reside outside of gay-identified neighborhood or not HIV-infected	88	92	1.05
I. Diagnosed at STD clinic, or not HIV-infected, or reside outside of gay-identified neighborhood	90	95	1.06

*Criteria were evaluated in validation set (n = 418).
HIV indicates human immunodeficiency virus; STD, sexually transmitted disease.

of nontesters and include 13% of patients, providing the highest ratio of identified nontesters to included patients (ratio 2.00).

DISCUSSION

In this analysis, we found that 33% of MSM diagnosed with early syphilis in San Francisco from 2005 through 2008 did not have a documented test for syphilis during the 1 to 6 months following diagnosis, despite local recommendations to test for syphilis at 1, 3, and 6 months after diagnosis and for sexually active MSM to screen for syphilis every 3 to 6 months. Three factors were independently associated with not having a documented test after diagnosis: being diagnosed at the STD clinic, not being HIV-infected, and residing outside of San Francisco's gay-identified neighborhood. The model identifying these factors correctly classified 71.6% of testers and nontesters in the derivation set and 71.3% when applied to the validation set, suggesting that it has moderate ability to prospectively identify nontesters for syphilis prevention and control efforts.

HIV-uninfected syphilis patients were more likely than HIV-infected patients to not have a follow-up test for syphilis after diagnosis. Follow-up testing rates might have been higher among syphilis patients with HIV infection because they might be more likely to have an established source of healthcare than HIV-uninfected syphilis patients. In San Francisco, recommendations that HIV-infected MSM be screened for syphilis with every CD4 T cell count or HIV viral load[26] might also have resulted in increased syphilis testing in that group. In addition, syphilis patients diagnosed at the STD clinic were less likely to have had a syphilis test following diagnosis compared with patients diagnosed in other healthcare settings. Patients who test for syphilis at the STD clinic might be less likely to have health insurance or be engaged in primary care than patients diagnosed in the private sector, resulting in less frequent testing. These findings have identified areas for intervention within our own STD clinic, and programs are being considered to improve follow-up testing among patients diagnosed in that setting. We also found that patients who resided outside of San Francisco's gay-identified neighborhood were less likely to test for syphilis following diagnosis. That neighborhood has been the primary focus of SFDPH's social marketing campaigns and is home to a gay men's health clinic that diagnoses approximately 10% of San Francisco's early syphilis cases. Our findings suggest that those interventions might have been successful, and that MSM residing in other areas of San Francisco should also be the focus of messages to test for syphilis and efforts to provide easier access to testing.

Prediction models have been used to develop selective screening criteria and focused interventions among STD patients,[27–29] and algorithms based on those models can provide evidence-based projections of real-world impact. Depending on resource availability, the set of algorithms we present here can guide the design of interventions to prevent and control syphilis among MSM in San Francisco. For example, if we only have sufficient funding to implement an intervention to promote follow-up testing among 30% of MSM diagnosed with early syphilis in San Francisco, we might choose to focus resources on patients who are diagnosed at the STD clinic (33% of sample), thus identifying 50% of nontesters. When public health resources devoted to syphilis prevention and control are scarce, data-driven programmatic decision-making can increase the effectiveness of local health department activities.

There are at least 3 limitations to our analysis. First, excluding patients whose serologic titers at diagnosis were $<$1:16 could have introduced bias by eliminating more patients in primary stage. However, a comparison of excluded patients with those who were included in the analysis showed no differences in the distribution of race/ethnicity, age, or HIV-infection status (data not shown). Second, we might have missed serologic tests following syphilis diagnosis among patients whose serologic syphilis tests reverted to nonreactive and might therefore not have been reported to SFDPH. Although this could have resulted in overestimating the proportion of patients who did not test for syphilis, approximately 90% of patients with titers $\geq$1:16 at diagnosis will not have seroreverted within 6 months.[22] Third, we used local data from San Francisco, where the syphilis epidemic is largely among MSM. Our findings might not be generalizable to other settings, particularly where syphilis cases are not primarily among MSM or the frequency of syphilis testing is substantially different from that of the population we examined. However, our methods can be replicated in jurisdictions where data are routinely collected on reactive serologic syphilis tests.

In San Francisco, it is recommended that MSM have a serologic test for syphilis every 3 to 6 months and that persons

diagnosed with syphilis have follow-up serologic tests to assess treatment adequacy at 1, 3, 6, 9, and 12 months after diagnosis. In this analysis of follow-up testing of MSM diagnosed with early syphilis from 2005 through 2008, one-third had no documented syphilis serologic test during the 1 to 6 months after diagnosis. MSM who were HIV-uninfected, diagnosed at the STD clinic, and residing outside of San Francisco's gay-identified neighborhood were less likely to be tested following diagnosis with early syphilis. To help prevent and control syphilis, interventions are needed to increase adherence to follow-up testing recommendations among MSM diagnosed with syphilis. One such intervention, developed by the County of San Diego and Family Health Centers of San Diego and called "We All Test," offers incentives to HIV-infected MSM diagnosed with syphilis to register to receive e-mail and/or text message reminders every 3 or 6 months to get tested for syphilis.[30] An evaluation of that program is underway. Other jurisdictions should also consider interventions with the same goal as part of syphilis prevention and control efforts.

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