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The High Risk of an HIV Diagnosis Following a Diagnosis of Syphilis: A Population-level Analysis of New York City Men

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Background. Epidemiologic studies have shown that syphilis is associated with risk for human immunodeficiency virus (HIV) infection. We used population-level syphilis and HIV data to quantify HIV incidence among men following primary or secondary (P&S) syphilis diagnoses and identify the highest-risk subgroups for intensified prevention, such as pre-exposure prophylaxis with antiretroviral medications.

Methods. Male cases reported to the New York City HIV/AIDS and Sexually Transmitted Disease (STD) surveillance registries were matched using a deterministic algorithm. We measured HIV incidence following P&S syphilis diagnosed between 2000 and June 2010 and identified risk factors for HIV infection using Cox proportional hazards models.

Results. Of 2805 men with syphilis contributing 11 714 person-years of follow-up, 423 (15.1%) acquired HIV; annual incidence was 3.61% (95% confidence interval [CI], 3.27%, 3.97%). HIV incidence was high among: men who have sex with men (MSM) (5.56%, 95% CI, 5.02%–6.13%); males with secondary compared with primary syphilis (4.10% vs 2.64%, $P < .0001$); and males diagnosed with another bacterial STD after syphilis (7.89%, 95% CI, 6.62%–9.24%).

Conclusions. HIV incidence among men diagnosed with syphilis is high; one in 20 MSM were diagnosed with HIV within a year. Our data have implications for syphilis and HIV screening and may be useful for further targeting HIV-negative populations for pre-exposure prophylaxis.

Keywords. syphilis; HIV incidence.

Human immunodeficiency virus (HIV) infection disproportionately affects men in the industrialized world, primarily gay men and other men who have sex with men (MSM) [1]. In 2012 in New York City (NYC), 79% of 3141 new HIV/AIDS diagnoses were among men, and 69% of new male diagnoses were among MSM [2]. NYC surveillance data also indicate a large burden of sexually transmitted diseases (STD) among men, with 96%–98% of primary and secondary (P&S) syphilis cases each year being male, and >80% of male cases being among MSM [3]. Significant overlap in subpopulations of NYC men affected by HIV and P&S syphilis, and large increases in disease rates over time have been reported [4]. Syphilis may be associated with a high risk for subsequent HIV infection because: (1) syphilis lesions are efficient portals of entry for the HIV virus; (2) HIV can be found in syphilis lesions; and (3) there are high rates of HIV co-infection among MSM with syphilis [5] (eg, 64% of NYC MSM diagnosed with P&S syphilis in 2013 reported being HIV-infected [3]), and with especially high HIV prevalence in certain sexual networks, a person who is exposed to a partner with syphilis is likely exposed to HIV during the same sexual encounter.

To prevent the spread of HIV, it is necessary to identify persons for prevention interventions such as

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pre-exposure prophylaxis (PrEP), the daily use of oral emtricitabine-tenofovir to prevent HIV acquisition. Recent studies examining predictors of HIV acquisition in large prospective cohorts, HIV vaccine efficacy trials, and clinic-based samples have found very high incidence rates among MSM engaging in unprotected receptive anal intercourse with HIV-positive/serostatus unknown partners or MSM with rectal bacterial STD [6–9], groups that have been incorporated in the US Public Health Service clinical practice guidelines for PrEP [10].

Given the epidemiologic link between syphilis and HIV, HIV-uninfected men who have had syphilis may be expected to have an elevated HIV risk. This has been demonstrated in recent analyses of surveillance data from Florida and prospective cohort data from the Pre-exposure Prophylaxis Initiative (iPrEX) study [11, 12]. We used population-level syphilis and HIV surveillance data to quantify HIV incidence in order to identify subgroups in need of intensified prevention efforts, such as PrEP, using the universe of men with P&S syphilis in NYC over a 10-year period.

METHODS

Disease Surveillance Registries

The NYC HIV/AIDS surveillance registry contains information on NYC residents diagnosed with AIDS since 1981 and HIV infection or disease since 2000. Healthcare providers are required by law to report all new diagnoses of HIV and AIDS and all new HIV-related illnesses. Laboratories are required to report all positive Western blot and other diagnostic test results, HIV viral loads, CD4 counts, and viral nucleotide sequences results. A cumulative total of 216 164 HIV/AIDS cases were reported to the HIV/AIDS registry through 31 March 2011. The vital status of cases in the registry is routinely updated [2].

The NYC STD surveillance registry contains information on NYC residents diagnosed and reported with the following notifiable STD: syphilis, gonorrhea, chlamydia, lymphogranuloma venereum (LGV), chancroid, granuloma inguinale, and neonatal herpes. Diagnosing healthcare providers are legally required to report all new cases. Clinical laboratories are required to report positive laboratory tests for the 7 STD, as well as negative confirmatory syphilis tests. A total of 618 597 diagnoses of STD among 431 685 unique persons were reported to the STD registry between 1 January 2000 and 30 June 2010.

Match Process

We conducted a match of male cases in the STD registry (reported 1 January 2000–30 June 2010) with male cases in the HIV/AIDS registry (reported through 31 March 2011) using deterministic record linkage. Persons in the registries were matched based on 36 combinations of patient information (eg, name, birth date, social security number). Records that matched based on the strictest criteria of 7 combinations were accepted without further review. Records that matched on another set of 17 combinations were considered probable matches and manually reviewed by 2 trained staff, with inter-reviewer discrepancies settled by a third staff member; manual reviews required matches on gender and incorporated other patient demographic variables available in the disease registries (eg, race, ethnicity, address). Records that linked on the remaining 12 combinations or did not link on any were not acceptable matches, and those persons were considered as STD cases without HIV infection. Afterward, all persons with a death date before 1 January 2000 were removed from the matched data set.

Analytic Methods

Our outcome of interest was incident HIV infection, measured as an HIV diagnosis reported to the HIV/AIDS registry, following syphilis reported to the STD registry between 1 January 2000 and 30 June 2010. Accordingly, we excluded men from our analytic cohort if they had an HIV diagnosis date before 2000 in the matched dataset. Given that 95% of individuals seroconvert 2–8 weeks after HIV infection, we also excluded men whose HIV diagnosis dates were <60 days after their syphilis diagnosis dates to minimize the possibility of including those who acquired syphilis and HIV at the same time. For men with multiple P&S syphilis infections, follow-up for HIV started at the time of diagnosis of their last (most recent) infection. We conducted Kaplan–Meier survival analysis to account for varying times to HIV diagnosis. For men diagnosed with HIV, HIV-free time-at-risk was calculated as the interval between syphilis diagnosis date and HIV diagnosis date; those without a new HIV diagnosis during the analytic period were presumed HIV uninfected and censored on 31 March 2011, or death date for deaths before 1 April 2011.

We calculated HIV incidence estimates for subgroups defined by age, race/ethnicity, transmission risk, stage of syphilis (primary vs secondary), other bacterial STD, year of syphilis diagnosis, and syphilis diagnostic setting (STD clinic provider vs other providers). Age was assigned as the age at time of syphilis diagnosis. Transmission risk was assigned using the Centers for Disease Control and Prevention (CDC) transmission risk categories, and categorized as: (1) sex with men (MSM), including MSM reporting a history of injection drug use (IDU); (2) heterosexual contact/sex with women (MSW); (3) IDU; and (4) other or unknown risk. Risk category assignments were based on information in the HIV registry, or sex of partners gleaned during syphilis case interviews and recorded in the STD registry. Other bacterial STD was classified as: (1) "none (syphilis only)" when the patient had no diagnoses of chlamydia, gonorrhea, or LGV reported to the STD registry at or after the time of syphilis diagnosis, (2) "concurrent with syphilis" if there were

Table 1. Risk of New Human Immunodeficiency Virus Diagnosis Following a Primary or Secondary Syphilis Diagnosis for Men in New York City, by Demographic/Behavioral Characteristic

Characteristic	Number of P&S Syphilis Cases	Percent of P&S Syphilis Cases (%)	Number of Newly Diagnosed HIV Cases	Person-years at Risk	Annual HIV Incidence (%)	95% CI (HIV Incidence)
Total	2805	100.0	423	11714.18	3.61	3.27–3.97
Age						
13–19	178	6.3	35	646.12	5.42	3.77–7.53
20–24	449	16.0	73	1654.75	4.41	3.46–5.51
25–29	484	17.3	83	1897.18	4.37	3.48–5.42
30–34	472	16.8	80	2107.84	3.80	3.01–4.72
35–39	489	17.4	76	2284.96	3.33	2.62–4.16
40–44	345	12.3	43	1511.29	2.85	2.06–3.83
45–49	186	6.6	23	742.20	3.10	1.96–4.65
50+	202	7.2	10	869.84	1.15	.55–2.11
Race/ethnicity						
White	751	26.8	126	3064.03	4.11	3.43–4.90
Black	898	32.0	169	3597.64	4.70	4.02–5.46
Hispanic	642	22.9	94	2480.61	3.79	3.06–4.64
Other/unknown[a]	514	18.3	34	2571.90	1.32	.93–1.83
Sexual behavior/risk						
MSM	1884	67.2	389	7000.55	5.56	5.02–6.14
MSW	373	13.3	20	1661.05	1.20	.73–1.86
Other, IDU, unknown	548	19.5	14	3052.57	0.46	.25–.77

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug users; MSM, men who have sex with men; MSW, men who have sex with women; P&S, primary or secondary syphilis.

[a] Includes Native American/Alaskan Native, Asian, Hawaiian/Pacific Islander, and men of multiple, other, and unknown races.

diagnoses of any of those 3 infections with specimen collection dates matching the collection date associated with the syphilis diagnosis, or (3) "syphilis and subsequent STD" if there were any of the 3 diagnoses after the syphilis diagnosis.

Univariate and multivariate Cox proportional hazards models were used to analyze contributions of risk factors to HIV diagnosis. For the models, age at syphilis diagnosis was grouped as "<35 years" vs "≥35 years." Other bacterial infection was collapsed into: (1) none, vs (2) concurrent with, or subsequent to syphilis. Analyses were performed using SAS 9.1 (SAS Institutes, Cary, North Carolina), conducted using de-identified records collected for surveillance purposes and not involving human subjects, and were not subject to review by the NYC Department of Health and Mental Hygiene Institutional Review Board [13].

RESULTS

Between 1 January 2000 and 30 June 2010, 6053 men with P&S syphilis were reported to the STD registry. Of those, 3081 (51%) had an HIV diagnosis date before 1 January 2000 recorded in the HIV registry and an additional 167 were reported with HIV <60 days after their syphilis diagnosis. The remaining 2805 men lacking evidence of prior or concurrent HIV infection comprised our analytic cohort. Of them, 111 (4%) had more than 1 P&S syphilis diagnosis. The median age was 33 years (range, 14–86), and approximately one-quarter were non-Hispanic white, one-quarter Hispanic, and one-third non-Hispanic black. Two-thirds of men were classified as MSM, 13.3% as MSW, and 19.5% with IDU, unknown, or other risk (Table 1). Over two-thirds of the cohort (1946/2805) had secondary syphilis diagnoses. Overall, 82.4% of men were reported with only P&S syphilis during the analytic period, whereas 3.7% had a concurrent, and 14.0% a subsequent bacterial STD diagnosis (Table 2).

The 2805 men with syphilis contributed 11 714 person-years of follow-up time (mean: 4.2 years). A total of 423 men (15.1%) were newly diagnosed with HIV during the analytic period, and median time to HIV diagnosis was 1.6 years (range: 60 days–8.6 years). The annual HIV incidence for all men diagnosed with P&S syphilis was 3.61%. Risk of being diagnosed with HIV did not change appreciably with age, although older men (≥50 years) had lower annual incidence (1.15%) than men aged 13 through 44 years (range 2.85%–5.42%). HIV incidence was similar across the major race/ethnicity groups (range 3.79%–4.70%), and lower among men of other/unknown races (1.32%). Incidence was substantially higher for MSM (5.56%) compared to MSW (1.20%) and men with other, IDU, and unknown risk (0.46%) (Table 1). Men diagnosed with

Table 2. Risk of New Human Immunodeficiency Virus Diagnosis Following a Primary or Secondary Syphilis Diagnosis for Men in New York City, by Characteristics Related to Syphilis Infection

Characteristic	Number of P&S Syphilis Cases	Percent of P&S Syphilis Cases (%)	Number of Newly Diagnosed HIV Cases	Person-years at Risk	Annual HIV Incidence (%)	95% CI (HIV Incidence)
Syphilis stage						
Primary	859	30.6	103	3905.50	2.64	2.15–3.20
Secondary	1946	69.4	320	7808.68	4.10	3.66–4.57
Other bacterial infections						
None (syphilis only)	2310	82.4	281	9718.04	2.89	2.56–3.25
STD[a] concurrent with syphilis	103	3.7	12	348.96	3.44	1.77–6.01
Syphilis and subsequent STD[a]	392	14.0	130	1647.18	7.89	6.59–9.37
Year of syphilis						
2000	47	1.7	9	430.40	2.09	.95–3.97
2001	133	4.7	31	1085.93	2.85	1.94–4.05
2002	186	6.6	52	1333.22	3.90	2.91–5.11
2003	231	8.2	58	1503.69	3.86	2.93–4.99
2004	274	9.8	44	1665.15	2.64	1.92–3.55
2005	255	9.1	53	1283.46	4.13	3.09–5.40
2006	272	9.7	40	1164.34	3.44	2.45–4.68
2007	360	12.8	45	1236.88	3.64	2.65–4.87
2008	443	15.8	61	1121.37	5.44	4.16–6.99
2009	406	14.5	24	691.97	3.47	2.22–5.16
Jan–June 2010	198	7.1	6	197.78	3.03	1.11–6.60
Syphilis diagnosing provider						
STD clinic	1007	35.9	158	4266.36	3.70	3.15–4.33
Other	1798	64.1	265	7447.82	3.56	3.14–4.01

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; P&S, primary or secondary; STD, sexually transmitted disease.

[a] STD include chlamydia, lymphogranuloma venereum, and gonorrhea.

secondary syphilis had more than 1.5 times the annual HIV incidence of those diagnosed with primary syphilis (4.10% vs 2.64%). HIV incidence among men with bacterial STD diagnosed after the syphilis diagnosis (7.89%) was more than twice the incidence among those with only syphilis (2.89%) or with concurrent infections (3.44%). HIV risk did not differ appreciably by year of syphilis diagnosis or syphilis diagnosing provider (Table 2).

The multivariate model showed that among men with syphilis, race/ethnicity, MSM risk transmission category, secondary syphilis, and other bacterial STD were independently associated with a new HIV diagnosis (Table 3). In the adjusted model: non-Hispanic white, non-Hispanic black, and Hispanic men each had similar HIV risk, twice that of men with other or unknown races/ethnicities; MSM had a 9-fold risk of HIV infection compared to men with other, unknown, or IDU risk (adjusted hazard ratio [aHR] 8.88; 95% confidence interval [CI], 5.20–15.18); men with secondary syphilis diagnoses had higher risk compared to men with primary syphilis (aHR 1.37; 95% CI, 1.10–1.72); and men with concurrent or subsequent STD had a 2-fold risk compared to those with only syphilis (aHR 2.03; 95% CI, 1.65–2.50).

DISCUSSION

We found that men in NYC who have been diagnosed with P&S syphilis are at high risk for HIV, with more than 1 in 30 diagnosed with HIV within a year of syphilis infection. Annual HIV incidence in NYC (3.6%) exceeded that found in a similar analysis from Florida (2.3%) [11]. It has been estimated that at an annual HIV incidence rate of 2.4%, 41% of men who are HIV-negative at age 18 will be seropositive by age 40 [14]. The HIV incidence we measured among NYC men who had had P&S syphilis portends an eventual HIV prevalence of even greater magnitude. Estimates such as ours point to the need for more effective primary HIV prevention efforts among all men with P&S syphilis and especially for MSM and men with syphilis followed by other bacterial STD.

Table 3. Univariate and Multivariate Hazard Ratios for Human Immunodeficiency Virus Diagnosis Among Men With Primary and Secondary Syphilis, New York City, 2000–2010

Characteristic	Univariate HR	95% CI	Multivariate HR	95% CI
Age (years)				
<35	1.48	1.22–1.81	1.13	.92–1.39
≥35	1		1	
Race/ethnicity				
White	1		1	
Black	0.90	.69–1.17	0.96	.73–1.26
Hispanic	1.14	.90–1.43	1.19	.94–1.51
Other/unknown[a]	0.32	.22–.47	0.46	.31–.67
Sexual behavior/risk				
MSM	10.92	6.40–18.61	8.88	5.20–15.18
MSW	2.49	1.26–4.93	1.99	1.00–3.96
Other, IDU, or unknown	1		1	
Syphilis stage				
Primary	1		1	
Secondary	1.49	1.20–1.86	1.37	1.10–1.72
Other bacterial infections				
None (syphilis only)	1		1	
STD[b] concurrent with or subsequent to syphilis	2.46	2.01–3.00	2.03	1.65–2.50

Abbreviations: CI, confidence interval; HR, hazard ratio; IDU, injection drug users; MSM, men who have sex with men; MSW, men who have sex with women; STD, sexually transmitted disease.

[a] Includes Native American/Alaskan Native, Asian, Hawaiian/Pacific Islander, and men of multiple, other, and unknown races.

[b] STD include chlamydia, lymphogranuloma venereum, and gonorrhea.

We were surprised to find little variation in annual HIV incidence rates among men with syphilis by race/ethnicity, or by age. A study of HIV incidence rates among men in Florida showed black–white rate ratios of 5.5 for MSM and 16 for MSW [15], and we have previously reported extremely high case rates of both new HIV and P&S syphilis diagnoses among black and young MSM and MSW in NYC [4]. Furthermore, epidemiologic studies have consistently identified black race/ethnicity as an independent risk factor for HIV seroconversion [16, 17]. The relatively uniform risk of HIV following syphilis infections across groups defined by race/ethnicity and by age in this analysis suggests that men who acquire syphilis are involved in the highest-risk partnerships or sexual networks and/or have risk behaviors that are more influential with regard to HIV risk than demographic factors otherwise associated with HIV acquisition.

As expected, MSM had the highest HIV incidence (5.4%), but our measure exceeded overall incidence estimates from many other studies (2%–3% [9, 14, 16]) and instead approximated rates reported for subpopulations at the highest risk for HIV, such as young black MSM who have participated in the HIV Prevention Trials Network 061 Study [6] or the National HIV Behavioral Surveillance System [17]. Also, and not surprisingly, indicators of ongoing risky behaviors, such as STD diagnoses subsequent to P&S syphilis infection and secondary rather than primary syphilis diagnoses, were associated with a greater risk for incident HIV. Bacterial STD diagnoses almost certainly indicate a lack of consistent/correct condom use, a shared risk factor for the sexual transmission of HIV. A diagnosis of syphilis during its secondary stage may result when initial infection is introduced in the anorectum, where transient and painless chancres can go unnoticed and not diagnosed as primary lesions. The occurrence of anorectal lesions suggests condomless receptive anal sex, a practice that very well could continue after treatment for syphilis and has been associated with a higher risk for HIV [18].

A new syphilis diagnosis in an HIV-negative man offers a key opportunity for PrEP initiation. A recent study by Buchbinder and colleagues to identify MSM populations that would benefit the most from PrEP showed a population attributable fraction (PAF) for syphilis of approximately 10%; of 11 other HIV-associated risks that were examined, only condomless receptive anal intercourse and reporting more than 5 recent sex partners had higher PAFs [19]. The investigators estimated that approximately 30 persons with prior syphilis infection would need to be on PrEP for a year to prevent 1 HIV infection. In June 2014, New York Governor Andrew Cuomo announced the state's successful negotiations with pharmaceutical companies that represent 70% of the HIV antiretroviral market to reduce costs of the medications, thereby expanding access to PrEP. Currently CDC recommends PrEP for MSM with recent (past 6 months) histories of bacterial STD [10]. Our data, however, show that a substantial proportion of individuals who acquire HIV are diagnosed well after their syphilis diagnoses, and we suggest that all men in NYC with a new P&S syphilis diagnosis be considered for this prevention strategy, even if that diagnosis occurred more than 6 months ago.

The risk of HIV acquisition following syphilis infection among MSM, men with subsequent STD, and men with secondary syphilis indicates the importance of frequent STD and HIV screening. The CDC recommends that all sexually active MSM who are HIV-negative or not tested within the previous year be screened for HIV at least annually [20]. Given the substantial HIV risk that we measured, healthcare providers should conduct more frequent HIV screening for their HIV-negative patients who have had syphilis, perhaps as often as every 3–6 months. During our study period, approximately one-third of P&S syphilis cases were diagnosed and reported from public STD clinics. With US healthcare reform, patients may increasingly

access primary care clinicians for STD care, and it is important, even in the PrEP era, for providers diagnosing STD to continue to counsel patients on the effectiveness of condoms in preventing HIV transmission. It is also critical for providers to take comprehensive sexual histories and routinely screen for STD that disproportionately affect MSM and often are asymptomatic, such as syphilis and extragenital (rectal and oral) chlamydia and gonorrhea. Because it can be difficult to clinically distinguish between the chancres of primary syphilis and other ulcerative diseases, all patients who have genital, anal, or perianal ulcers should be evaluated with a serologic test for syphilis; the US Food and Drug Administration's recent waiver for a rapid screening test for syphilis will enable screening in a greater variety of healthcare settings and should contribute to a higher rate of detection [21].

Our study has limitations. First, both our exposure and outcome of interest were diagnosed infections. Men without additional STD reports due to lack of testing after syphilis or migration out of NYC were presumed STD-free. True HIV incidence may have been underestimated if men did not have an HIV test during the follow-up period, or if men were diagnosed with HIV outside of NYC and not reported to the NYC HIV registry. Second, we cannot be sure that men who were diagnosed with HIV after syphilis actually acquired HIV after syphilis; determining the timing of HIV acquisition would require data from laboratory-based tests to distinguish recent from established infections [22, 23], which were only incorporated in routine surveillance starting in 2005 and increasingly complete in the later years of this study. We could have overestimated risk if men who were diagnosed with syphilis were already HIV-infected at that time but were not tested until later; these men were not at risk of acquiring HIV and should not have been included in follow-up. Third, estimates of HIV risk among syphilis cases with concurrent or subsequent STD may have been affected by the under-ascertainment of certain STD. A lack of availability and/or use of extragenital tests for chlamydia and gonorrhea results in missed diagnoses and underreported STD. By counting the most recent P&S syphilis infection in our analysis, we did not assess the association between repeat syphilis infections (observed for 4% of our cohort) and incident HIV. Estimates of HIV risk among syphilis cases with other STD may also have been affected by better ascertainment of HIV infection if they were more likely to have been tested for HIV at the time of STD diagnosis. Finally, underreporting is a possibility even with electronic laboratory reporting; any unreported HIV diagnoses, or missing syphilis reports among men in the cohort that could have shortened the follow-up period would have led to underestimating true HIV incidence.

After years of relatively stable rates, P&S syphilis infections among men in the United States are on the rise [24]. Substantial HIV prevalence among men with P&S syphilis coupled with the high HIV incidence we have shown has implications for ongoing HIV transmission. Although HIV acquisition among men with syphilis may not drive substantial increases in HIV incidence among the general population, it can certainly greatly increase the probability of HIV infection in selected sexual networks. Consideration of promising HIV prevention strategies (eg, PrEP) and maximizing use of existing effective interventions (eg, frequent repeat HIV testing) will be necessary to reduce the rate of HIV in this group.

Notes

Disclaimer. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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