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Human Immunodeficiency Virus Diagnosis After a Syphilis, Gonorrhea, or Repeat Diagnosis Among Males Including non–Men Who Have Sex With Men: What Is the Incidence?

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Background: The release of the first drug for human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) in 2012 marked the beginning of a new era of HIV prevention. Although PrEP is highly efficacious, identifying and ultimately increasing uptake among the highest risk male subgroups remains a challenge.

Methods: Public health surveillance data from 2009 to 2016 was used to evaluate the risk of an HIV diagnosis after a syphilis (ie, primary, secondary, or early latent), gonorrhea, and repeat diagnoses among urban males, including men who have sex with men (MSM) and non-MSM in Baltimore City.

Results: Of the 1531 males with 898 syphilis diagnoses and 1243 gonorrhea diagnoses, 6.8% (n = 104) were subsequently diagnosed with HIV. Within 2 years, 1 in 10 syphilis or gonorrhea diagnoses were followed by an HIV diagnosis among MSM, and 1 in 50 syphilis or gonorrhea diagnoses were followed by an HIV diagnosis among non-MSM. Among non-MSM with gonorrhea, the rate of HIV incidence was 5.36 (95% confidence interval, 2.37–12.14) times higher in those with (vs. without) a subsequent syphilis diagnosis or gonorrhea diagnosis.

Conclusions: Local health care providers should offer PrEP to MSM diagnosed with syphilis or gonorrhea and to non-MSM with a previous gonorrhea diagnosis at time of a syphilis or gonorrhea diagnosis. The high proportion and short time to an HIV diagnosis among MSM after a syphilis or gonorrhea diagnosis suggest immediate PrEP initiation.

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Conflicts of Interest: None declared.

Sources of Funding: This study was supported by the Centers for Disease Control and Prevention grants (Co-PIs: Jennings, Chaulk) entitled Understanding Syphilis Transmission in the United States (1U01PS005171-01), Health Department Demonstration Projects for Comprehensive Prevention, Care, Behavioral Health, and Social Services for Men Who Have Sex with Men of Color at Risk for and Living with HIV Infection (PS15-1509), Health Department Demonstration Projects to Reduce HIV Infections and Improve Health Outcomes for Men Who Have Sex with Men of Color at Risk for and Living with HIV Infection (PS15-1506), and Community Approaches to Reducing STDs. This study was also supported by the Center for Disease Control STD Surveillance Network (PS13-1306) (co-PIs: Schumacher, Chaulk).

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Received for publication April 16, 2018, and accepted December 1, 2018.
DOI: 10.1097/OLQ.0000000000000964

The release of the first drug for human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) in 2012 marked the beginning of a new era of HIV prevention. Preexposure prophylaxis has been shown to be highly efficacious in reducing the acquisition of HIV,[1] and is indicated for men who have sex with men (MSM) and heterosexual men or women who report risky sexual behavior (ie, high number of sexual partners or commercial sex work) or a recent bacterial sexually transmitted infection (STI).[2] The Centers for Disease Control (CDC) estimates that nearly 1 in 4 US sexually active MSM and 1 in 200 sexually active US heterosexuals are indicated for PrEP based on these guidelines.[2,3] Preexposure prophylaxis uptake across MSM communities has been varied, but on average, 51% of MSM with gonorrhea in the CDC sexually transmitted disease (STD) Surveillance Network (SSuN), reported being prescribed PrEP.[4] Compared with MSM, less is known about PrEP scale up and barriers to PrEP engagement among high-risk heterosexual males as they are generally underrepresented and poorly defined in US HIV prevention research.[5] Preexposure prophylaxis–eligible heterosexual males (herein referred to as non-MSM) may represent an important subgroup that bridges high HIV prevalence networks with lower prevalence networks, playing a key role in sustaining HIV transmission among heterosexuals.[6]

An important barrier to PrEP scale up may be health care providers' ability to identify high-risk individuals.[7] Classification into a high-risk subgroup often relies on the self-report of behaviors such as inconsistent condom use, high numbers of sexual partners, or HIV serodiscordant sexual partnerships. These behaviors are subject to recall and social desirability bias,[8,9] and can be challenging for health care providers to assess during clinic or primary care visits.[10] Instead, it may be more effective for health care providers to ask clients or assess medical histories for diagnosis or repeat diagnosis with syphilis and gonorrhea to identify males at risk for HIV and potentially eligible for PrEP. Evidence suggests that syphilis and gonorrhea increase the transmission efficiency of HIV,[11,12] and bacterial STIs (ie, syphilis, gonorrhea, chlamydia) may serve as a biomarker of condomless sex and membership in a high-risk sexual network.[13] Additionally, bacterial STIs are relatively

easy to screen for and, when diagnosed, are routinely captured in medical records.

Although associations between bacterial STIs (ie, syphilis, gonorrhea, chlamydia) and a subsequent HIV diagnosis have been identified among MSM, there have been varying estimates of the relative risks of HIV associated with bacterial STIs among MSM,[14–17] conflicting evidence on HIV risks related to repeat STI infections among MSM,[18–20] and little is known about the risks of an HIV diagnosis after syphilis diagnosis or gonorrhea diagnosis among non-MSM.[21–23] This variability in evidence suggests that the relationships between prior STIs and HIV risk may depend on local transmission networks and disease prevalence, and more evidence is needed to guide local recommendations for eligible PrEP clients, including non-MSM.

The HIV and STI burden in Baltimore City, MD, is high. In 2016, the Baltimore-Columbia-Towson statistical area ranked 14th in the United States for HIV incidence with a rate of 19.0 infections per 100,000 people.[24] In 2016, Baltimore City's primary and secondary syphilis rate was 3.6-fold higher than the national rate (31.7 per 100,000 vs. 8.7 per 100,000), and gonorrhea rate was 3.9-fold higher than the national rate (568.3 per 100,000 vs. 145.8 per 100,000).[25]

The overall goal of this article is to inform local efforts by health care providers and public health practitioners to eliminate HIV transmission through the effective delivery of PrEP to populations at greatest risk. Specifically, the objectives were to evaluate the risk of an HIV diagnosis after a syphilis (ie, primary, secondary, or early latent), gonorrhea, and repeat diagnosis among urban males including MSM and non-MSM.

MATERIALS AND METHODS

Study Population

Public health surveillance data on all reports of syphilis (ie, primary, secondary or early latent), and gonorrhea (all anatomical sites) from January 1, 2009, to December 31, 2015, and all reports of HIV between January 1, 2009, and December 31, 2016 were obtained from the Baltimore City Health Department (BCHD). Information used was collected through routine morbidity reporting and disease control activities, which include partner services interviews for early syphilis cases and SSuN-enhanced surveillance interviews for a random sample of gonorrhea cases.[26]

A retrospective study cohort of HIV uninfected males diagnosed with syphilis with at least 1 partner services interview or diagnosed with gonorrhea with at least 1 SSuN interview during the study period was used to examine time from a syphilis and separately, a gonorrhea diagnosis to HIV diagnosis. To ensure that individuals were newly infected in 2009, a conservative 60-day run-in period, January 1, to March 1, 2009, was used and thus, the follow-up time period started March 1, 2009. In addition, individuals were excluded if an HIV diagnosis was reported within 30 days of the first syphilis or separately gonorrhea diagnosis date to reduce the likelihood that HIV was acquired simultaneously. Individuals were followed until the date of an HIV diagnosis, as reported to the BCHD, or were administratively censored on December 31, 2016.

All analyses were conducted at the diagnosis level, and time at risk was taken as the time interval between each syphilis or gonorrhea diagnosis and HIV diagnosis or administrative censure, herein referred to as diagnosis-years. Therefore, individuals receiving multiple syphilis or gonorrhea diagnoses over the study period could contribute multiple records in our study cohort for each diagnosis that occurred longer than 30 days before an HIV diagnosis and: (1) was a different bacterial diagnosis; or (2) occurred longer than 30 days after a diagnosis of the same bacterial infection. Individuals who were codiagnosed with syphilis and gonorrhea at the same time contributed multiple records for those diagnoses.

Measures

Syphilis and gonorrhea were the primary exposures and were analyzed separately. Covariates included age, race, MSM status, number of syphilis or gonorrhea diagnoses during the study period, number of sex partners during the critical period, and diagnosing provider. For age, we categorized individuals as adolescents and young adults (<25) or adults (≥25). Race was categorized as black or other. Individuals were classified as MSM if they ever self-identified as gay/bisexual or reported sex with male partners during partner services or SSuN interviews. Individuals were classified as non-MSM if they were never classified as MSM based on these criteria at any syphilis or gonorrhea diagnosis. For each diagnosis included, we created a binary indicator variable, repeat syphilis or gonorrhea, to denote whether that diagnosis was the first or a repeat syphilis or gonorrhea diagnosis reported within an individual during the study period. The number of sex partners was defined by the critical period and categorized as 0 to 1, 2, and 3 or greater. As per standard health department protocols, the critical period was defined as 3 months for gonorrhea diagnoses and 3, 6, and 12 months for primary, secondary, and early latent syphilis, respectively. Diagnosing provider types were defined as: publically funded STI clinics, private health care providers (primary care and other specialty health care practices), hospitals, emergency departments and urgent care centers, detention centers, and outreach (health department or community-based organizations offering STI testing in non–health care facilities). Any providers not meeting one of the above definitions was classified as other.

Statistical Testing

Summary statistics were produced to characterize the individuals with a syphilis diagnosis or gonorrhea diagnosis during the study period overall and by type of diagnosis. Because of differences in composition between the groups (ie, significantly different by age, race, MSM status, number of syphilis and gonorrhea diagnoses, and diagnosing provider $P < 0.05$ not shown), primary analyses were stratified by syphilis or gonorrhea. Stratified cumulative incidence curves based on Kaplan-Meier survival functions were used to describe the probability of a new HIV diagnosis from a syphilis or gonorrhea diagnosis by MSM status and type of STI diagnosis and separately, by MSM status and first or repeat syphilis diagnosis and gonorrhea diagnosis.

The HIV incidence rates were calculated by dividing the total number of new HIV diagnoses by the total time at risk from a syphilis or gonorrhea diagnosis to either an HIV diagnosis or administrative censoring. Incidence rate ratios (IRR) and corresponding 95% confidence intervals (CI) clustered at the individual level were calculated using generalized estimated equations (GEE) to compare HIV incidence rates by MSM status after syphilis and gonorrhea diagnoses separately. Similarly, we compared HIV incidence rates by age category and repeat versus first syphilis or gonorrhea diagnosis; however, these analyses were stratified by type of STI diagnosis and MSM status. All analyses were conducted using Stata 14.0 (Stata Corp, College Station, TX). This study used routine public health surveillance information and was considered exempt from human subjects research by the Johns Hopkins Medicine IRB.

RESULTS

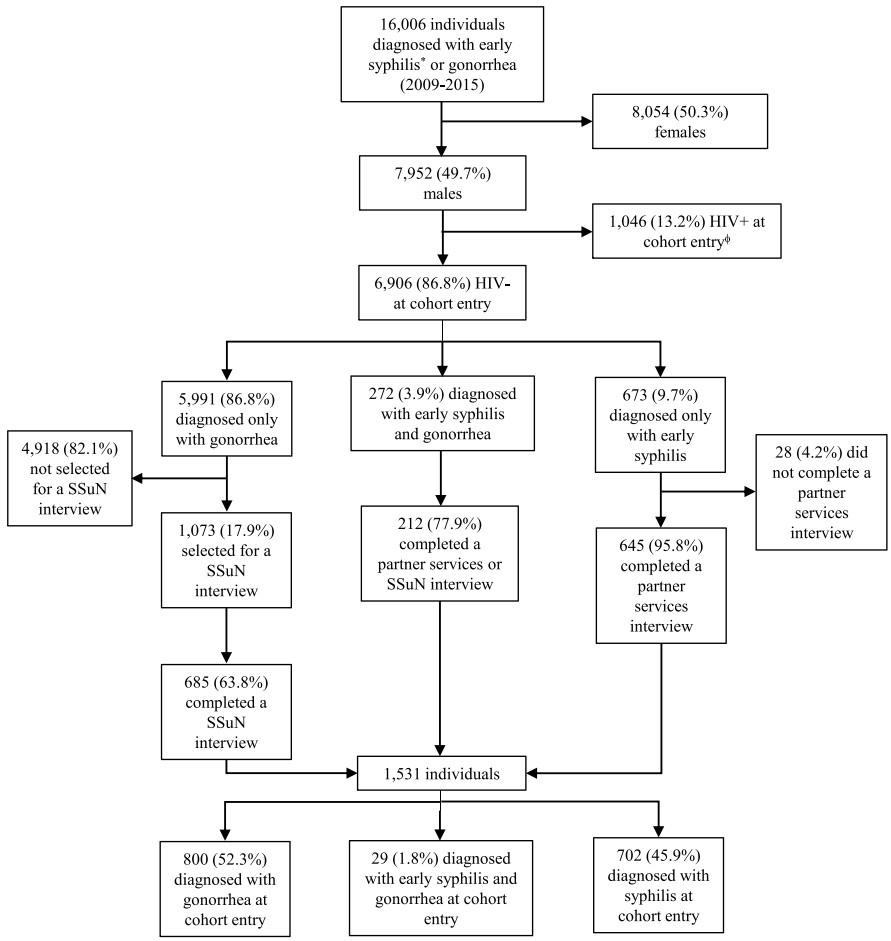
Study Population

Between January 2009 and December 2015, the BCHD received 2443 reports of syphilis and 17,290 reports of gonorrhea diagnoses among 16,006 individuals. Among these 16,006 individuals, 43.1% (n = 6906) were HIV-negative males, among whom 22.2% (n = 1531) received either a partner services interview for a syphilis diagnosis or a SSuN interview for a gonorrhea diagnosis and were included in this analysis. At cohort entry, 45.9% (n = 702) were diagnosed with syphilis, 52.3% (n = 800) were diagnosed with gonorrhea, and 1.8% (n = 29) were codiagnosed with syphilis and gonorrhea (Fig. 1). On average, individuals were 30 years old (SD: 11.6) at the time of their first diagnosis, 86.9% of individuals were black (n = 1331), 38.8% identified as MSM (n = 594), 39.6% reported 0–1 sex partners (n = 482), and 36.7% were diagnosed at an STI clinic (n = 792). A repeat syphilis and gonorrhea diagnoses was reported in 26.1% (n = 399) individuals (Table 1). Among syphilis diagnoses, 19.8% (n = 139), 42.2% (n = 296), and 37.8% (n = 265) were diagnosed during the primary, secondary, and early latent stages of infection, respectively. Among gonorrhea diagnoses, 4.4% were diagnosed from a positive rectal swab (n = 35).

Cumulative HIV Incidence by Syphilis or Gonorrhea Diagnosis and Repeat Diagnoses

A total of 2141 syphilis and gonorrhea diagnoses were reported and comprised the analytic sample; 898 (41.9%) were syphilis diagnoses and 1243 (58.1%) were gonorrhea diagnoses, contributing a total of 8587 diagnosis-years of follow-up. Fifty-six percent of repeat diagnoses represented a gonorrhea diagnosis followed by another gonorrhea diagnosis, 21.1% were a syphilis diagnosis followed by a gonorrhea diagnosis, 16.0% were a gonorrhea diagnosis followed by a syphilis diagnosis and 7.2% represented a syphilis diagnosis followed by another syphilis diagnosis. The median time between repeat diagnoses was 6.2 months (25th, 75th percentiles: 2.3 months, 1.7 years).

Among MSM, approximately 1 in 10 syphilis or gonorrhea diagnoses were followed by an HIV diagnosis within 2 years, and cumulative HIV incidence varied little between syphilis and gonorrhea diagnoses. Among non-MSM, 1 in 50 syphilis or gonorrhea diagnoses were followed by an HIV diagnosis within 2 years



* Early syphilis includes primary, secondary, and early latent syphilis
¶ Individuals were excluded if they were diagnosed with HIV before their cohort entry diagnosis or were diagnosed with HIV ≤ 30 days after their cohort entry diagnosis

Figure 1. Flow diagram of the study cohort.

TABLE 1. Characteristics of Males Overall and by Syphilis and/or Gonorrhea Diagnosis at Their Cohort Entry, Baltimore City, 2009–2015

		Cohort Entry Diagnosis		
	Overall (N = 1531)	**Syphilis (n = 702)**	**Gonorrhea (n = 800)**	**Syphilis and Gonorrhea (n = 29)**
Age at cohort entry, mean (SD)	30 (11.6)	33 (12.3)	27 (10.1)	25 (6.2)
<25 y, n (%)	659 (43.0)	201 (28.6)	442 (55.3)	16 (55.2)
≥25 y, n (%)	872 (57.0)	501 (71.4)	358 (44.7)	13 (44.8)
Race				
Black, n (%)	1331 (86.9)	569 (81.1)	737 (92.1)	25 (86.2)
Other, n (%)	200 (13.1)	133 (19.0)	63 (7.9)	4 (13.8)
MSM status*				
MSM, n (%)	594 (38.8)	337 (48.0)	231 (29.0)	26 (89.7)
Non-MSM, n (%)	928 (60.6)	365 (52.0)	560 (70.0)	3 (10.3)
Syphilis or gonorrhea diagnoses during study period				
1 syphilis or gonorrhea, n (%)	1132 (73.9)	620 (88.4)	512 (63.9)	0 (0.0)
>1 syphilis or gonorrhea, n (%)	399 (26.1)	82 (11.6)	288 (36.1)	29 (100.0)
Sex partners during critical period*,†				
0–1, n (%)	485 (39.6)	259 (36.9)	223 (27.8)	3 (10.3)
2, n (%)	369 (30.1)	179 (25.5)	186 (23.2)	4 (13.8)
≥3, n (%)	371 (30.3)	183 (26.1)	179 (22.4)	9 (31.0)
Diagnosing provider*				
STI clinics, n (%)	562 (36.7)	230 (32.8)	309 (39.1)	23 (79.3)
Private provider, n (%)	310 (20.3)	186 (26.5)	120 (15.2)	4 (13.8)
Hospitals, n (%)	297 (19.4)	62 (8.8)	235 (29.2)	—
Emergency departments and urgent care centers, n (%)	166 (10.8)	76 (10.8)	89 (11.1)	1 (3.5)
Detention centers, n (%)	89 (5.8)	75 (10.7)	14 (1.8)	—
Outreach, n (%)	32 (2.1)	32 (4.6)	—	—
Other, n (%)	54 (3.5)	34 (4.8)	20 (2.5)	—

*Variable not completely ascertained in partner services or SSuN interviews: MSM status (n = 1522), sex partners during critical period (n = 1225), diagnosis provider (n = 1510).

† The critical period is defined as 3 months for gonorrhea diagnoses and 3, 6, and 12 months for primary, secondary, and early latent syphilis, respectively.

(Fig. 2A). Among MSM with a repeat syphilis diagnosis or gonorrhea diagnosis, more than 1 in 8 syphilis or gonorrhea diagnoses were followed by an HIV diagnosis within 2 years (Fig. 2B).

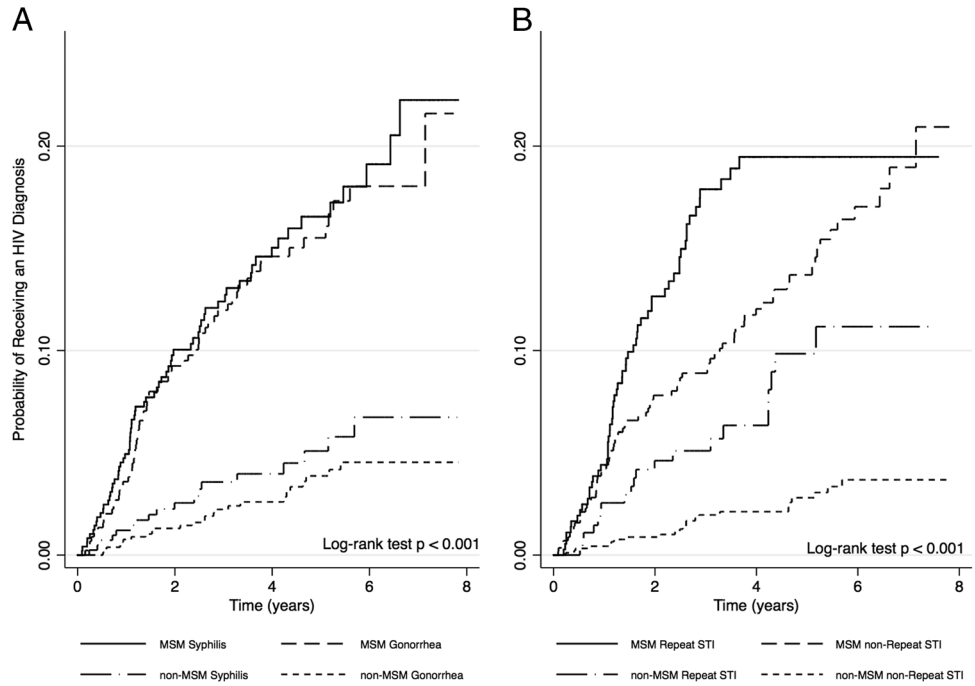


Figure 2. Cumulative risk of HIV diagnosis among men after a syphilis or gonorrhea diagnosis by (A) syphilis or gonorrhea diagnosis and MSM status and (B) repeat syphilis or gonorrhea and MSM status, Baltimore City, 2009–2015.

TABLE 2. Incidence of an HIV Diagnosis Among MSM Compared With Non-MSM Stratified by Syphilis Diagnoses (N = 898) and Gonorrhea Diagnoses (N = 1243), Baltimore City, 2009–2015

Characteristics	No. STI Diagnoses	Years at Risk	No. HIV Diagnoses	HIV Incidence per 100 Diagnosis-Years	HIV IRR	95% CI
Syphilis						
MSM status						
MSM	485	1719	69	4.01	3.62*	(2.15–6.08)
Non-MSM	413	1623	18	1.11		
Gonorrhea						
MSM status						
MSM	380	1795	65	3.62	4.94*	(3.11–7.83)
Non-MSM	761	3408	25	0.73		

*$P < 0.001$.

HIV Incidence Rates After a Syphilis or Gonorrhea Diagnosis

Overall, the HIV incidence rate was 2.11 per 100 diagnosis-years. Individuals who identified as MSM had 3.62 (95% CI, 2.15–6.08) and 4.94 (95% CI, 3.11–7.83) times higher HIV incidence rates compared to non-MSM after a syphilis and gonorrhea diagnosis, respectively (Table 2).

Younger age (<25 years) was associated with higher HIV incidence among MSM diagnosed with gonorrhea (IRR, 2.66; 95% CI, 1.45–4.90) and non-MSM diagnosed with syphilis (IRR, 3.45; 95% CI, 1.36–8.74) but not in any other subgroup. A repeat diagnosis was associated with higher HIV incidence among MSM diagnosed with syphilis (IRR, 2.66; 95% CI, 1.45–4.90) and non-MSM diagnosed with gonorrhea (IRR, 5.36; 95% CI, 2.37–12.14) (Table 3). Of these 16 gonorrhea diagnoses were associated with a later HIV diagnosis, 14 were followed by another gonorrhea diagnosis, and 2 were followed by a syphilis diagnosis.

HIV Incidence Among the General Population of MSM and Non-MSM

In this analysis, 6.8% (n = 104) of males (13.5% of MSM and 2.5% of non-MSM) were diagnosed with HIV during a median follow-up time of 1.9 years (25th, 75th percentiles: 7.2 months, 3.6 years). To contextualize these findings to the general population, we calculated a parallel measure of HIV incidence among MSM and non-MSM from 2009 to 2016 in Baltimore City. Grey et al[27] estimate that 8.98% of males older than 18 years in Baltimore City were MSM in 2009.[27] We applied this proportion to the 2008 Census population of males older than 18 years in Baltimore City.[28] Using Baltimore City surveillance data from 2009,[29] we subtracted

TABLE 3. Incidence of an HIV Diagnosis Stratified by Syphilis or Gonorrhea Diagnosis and MSM Status, Baltimore City, 2009–2015 (N = 2150)

Characteristics	No. Syphilis or Gonorrhea Diagnoses	Years at Risk	No. HIV Diagnoses	HIV Incidence per 100 Person-years	HIV IRR	95% CI
MSM with syphilis						
Age, y						
<25	164	653	31	4.75	1.33	(0.83–2.14)
≥25	321	1066	38	3.56		
>1 Syphilis or gonorrhea diagnosis						
Yes	148	448	26	5.80	1.71*	(1.05–2.79)
No	337	1271	43	3.38		
MSM with Gonorrhea						
Age, y						
<25	258	1077	52	4.83	2.66*	(1.45–4.90)
≥25	187	718	13	1.81		
>1 syphilis or gonorrhea diagnosis						
Yes	214	726	33	4.54	1.52	(0.93–2.47)
No	231	1068	32	3.00		
Non-MSM with syphilis						
Age, y						
<25	115	432	10	2.32	3.45*	(1.36–8.74)
≥25	298	1191	8	0.67		
>1 Syphilis or gonorrhea diagnosis						
Yes	48	167	4	2.40	2.49	(0.82–7.58)
No	365	1456	14	0.96		
Non-MSM with gonorrhea						
Age, y						
<25	422	1838	8	0.44	0.40	(0.17–0.93)
≥25	364	1570	17	1.08		
>1 syphilis or gonorrhea diagnosis						
Yes	226	848	16	1.89	5.36†	(2.37–12.14)
No	560	2560	9	0.35		

*$P < 0.05$.
†$P < 0.001$.

the number of prevalent cases of HIV among MSM and non-MSM in 2008 from the total number of MSM and non-MSM from the 2008 Census population to define the at risk population of MSM and non-MSM in 2009. We then calculated the number of incident HIV diagnoses among MSM and non-MSM from 2009 to 2016 using 2016 Baltimore city surveillance data.[30] We then divided the number of incident HIV diagnoses by the estimated number of HIV-negative MSM and non-MSM from 2009. Using these estimates, we calculated that 9.54% of MSM and 0.91% of non-MSM were diagnosed with HIV from 2009 to 2016 in Baltimore City.

DISCUSSION

We determined the risk of an HIV diagnosis after a syphilis diagnosis and separately, gonorrhea diagnosis among males from 2009 to 2016 in Baltimore City using public health surveillance data. Among these males overall, who were 86.9% black and 38.8% MSM, HIV incidence was 13.5% among MSM and 2.5% among non-MSM, startling statistics highlighting racial and sexual minority disparities. Compared with estimates of HIV incidence among all MSM and non-MSM, these incidence estimates suggest elevated risk of HIV among both MSM and non-MSM with a prior syphilis diagnosis or gonorrhea diagnosis.

We found that approximately 1 in 10 and 1 in 50 syphilis or gonorrhea diagnoses were followed by an HIV diagnosis within 2 years among MSM and non-MSM males, respectively. Identifying as MSM (compared with non-MSM) was associated with a 3.62- and 4.94-fold increase in HIV risk after a syphilis and gonorrhea infection, respectively. Younger age (<25) was associated with a 2.66- and 3.45-fold increase in HIV risk among MSM with gonorrhea and non-MSM with syphilis, respectively. A repeat syphilis and gonorrhea diagnosis was associated with a 1.71- and 5.36-fold increase in HIV risk among MSM with syphilis and non-MSM with gonorrhea, respectively.

These results support conclusions from previous studies that MSM diagnosed with syphilis or gonorrhea are at high-risk for HIV. Less is known among non-MSM males; a few studies have assessed the risk of HIV associated with a syphilis, gonorrhea, or chlamydia diagnosis after a syphilis diagnosis in males including non-MSM,[21–23] but did not independently assess the risk of an HIV diagnosis after a gonorrhea diagnosis or assess the relative risk of a repeat diagnosis for MSM and non-MSM separately. Additionally, prior studies have used either the first or last STI diagnosis to classify an individual. This diagnosis-level analysis conducted herein more accurately reflects the risk after a specific diagnosis.

There are several limitations to this study. First, the diagnosis date does not represent the date of a syphilis, gonorrhea, or HIV infection and may have resulted in an underestimation of time at risk for a syphilis or gonorrhea diagnosis and overestimation of the time at risk for an HIV diagnosis. The diagnosis date, however, represents an actionable date that health care providers and public health officials use to assess an individual's risk. Second, it is possible that people acquired HIV during follow-up but did not have an HIV diagnosis reported. This might have occurred if an individual went undiagnosed or was diagnosed with HIV after moving outside of the city. This may have underestimated our HIV incidence. Finally, we were underpowered to assess the significance of additional covariates such as the number of sex partners during the critical period or the site of gonorrhea infection.

These findings add to the body of evidence that syphilis and gonorrhea diagnoses are objective biomarkers of HIV risk that do not require additional risk assessment that can be difficult to ascertain in high volume clinic settings. This analysis suggests that health care providers should offer PrEP to any MSM client diagnosed with a syphilis (ie, primary, secondary, or early latent) or gonorrhea diagnosis, and health care providers should encourage STI testing at every interaction with the health care system among sexually active MSM and non-MSM males in high-prevalence areas. The short time to an HIV diagnosis among MSM diagnosed with syphilis or gonorrhea suggests immediate PrEP initiation is critical. It is important to note that this analysis also provides guidance for health care providers in identifying non-MSM male clients at higher risk for HIV. Although HIV incidence was lower among non-MSM compared with MSM, non-MSM with a previous gonorrhea diagnosis at the time of a syphilis diagnosis or gonorrhea diagnosis represent a high-risk subgroup that should be targeted for enhanced HIV prevention strategies, such as PrEP.

These results also demonstrate the value of using surveillance data of standard morbidity reporting to guide prevention strategies and suggest that public health officials should follow-up with MSM with any syphilis or gonorrhea diagnosis and non-MSM males with a previous gonorrhea diagnosis at time of a syphilis or gonorrhea diagnosis for PrEP referral.

Although every city has its unique transmission network, these results may be generalizable to urban settings with concentrated epidemics similar to Baltimore City. Further research on the role of repeat infections is needed to better understand the relationship between the timing, diagnosis, and number of prior STIs on HIV acquisition. Continued investigation on how to best motivate uptake and sustain adherence to PrEP among different high-risk subgroups will be key in maximizing the public health impact of PrEP.

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