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Syphilis Testing and Diagnosis Among People With Human Immunodeficiency Virus (HIV) Engaged in Care at 4 US Clinical Sites, 2014-2018

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Background. Despite rising rates of syphilis among people with human immunodeficiency virus (HIV; PWH) in the United States, there is no optimal syphilis screening frequency or prioritization.

Methods. We reviewed records of all PWH in care between 1 January 2014 and 16 November 2018 from 4 sites in the Centers for AIDS Research Network of Integrated Clinical Systems Cohort (CNICS; N = 8455). We calculated rates of syphilis testing and incident syphilis and used Cox proportional hazards models modified for recurrent events to examine demographic and clinical predictors of testing and diagnosis.

Results. Participants contributed 29 568 person-years of follow-up. The rate of syphilis testing was 118 tests per 100 person-years (95% confidence interval [CI]: 117–119). The rate of incident syphilis was 4.7 cases per 100 person-years (95% CI: 4.5–5.0). Syphilis diagnosis rates were highest among younger cisgender men who have sex with men and transgender women, Hispanic individuals, people who inject drugs, and those with detectable HIV RNA, rectal infections, and hepatitis C.

Conclusions. We identified PWH who may benefit from more frequent syphilis testing and interventions for syphilis prevention.

Keywords. people living with HIV; syphilis testing; syphilis incidence.

Since the early 2000s, the incidence of syphilis has been rising among gay, bisexual, and other men who have sex with men (MSM) in the United States, and more recently among women and people who inject drugs (PWID) [1–4]. Syphilis is more common in people with human immunodeficiency virus (HIV; PWH) and new cases of syphilis have increased over time among PWH engaged in care [3, 4]. Syphilis is associated with incident HIV infection, and PWH who are not virally suppressed experience a higher incidence of new and recurrent syphilis compared with those PWH who are not virally suppressed [4]. People with HIV who face barriers to regular clinic visits and antiretroviral medication adherence may also be less likely to use condoms consistently [5, 6]. In addition, some studies have found that HIV RNA levels increase during primary and secondary syphilis, which may increase the risk of onward HIV transmission [7, 8]. Syphilis is also associated with a higher incidence of sexually transmitted hepatitis C virus (HCV) infection among MSM with HIV. Syphilis may be a marker of individuals at higher risk of HCV acquisition and/or cause mucosal disruption and inflammation that facilitates HCV transmission [9].

The Centers for Disease Control and Prevention (CDC) currently recommends annual screening for syphilis among PWH and every 3–6 months among MSM at higher risk [10]. While syphilis testing among PWH in care has increased over time [3], up to one-third of sexually active MSM living with HIV have not been screened for syphilis in the prior year [11]. More frequent screening is not recommended for women with HIV, but a recent study found syphilis to be common among women living with HIV engaged in care, particularly among Black women, women who inject drugs, and women with HCV [12].

In the context of increasing syphilis diagnoses among PWH, there is an urgent need for studies to identify predictors of syphilis testing and incident cases and inform screening recommendations and delivery of behavioral and biomedical syphilis prevention [13–16]. We examined rates of syphilis testing and incident cases in a multisite clinical cohort of PWH engaged in care and sought to identify sociodemographic and clinical characteristics associated with syphilis testing and diagnosis.

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METHODS

Data Source

The Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) is a dynamic prospective observational cohort study of adult PWH in routine clinical care at 8 academic institutions across the United States [17]. Methods of data collection have been previously reported [17]. Briefly, comprehensive clinical data collected through electronic medical records and other institutional data systems undergo rigorous data-quality assessment and are harmonized in a central data repository that is updated quarterly. CNICS research has been approved by institutional review boards at each site.

We studied all PWH receiving care with at least 1 year of follow-up beginning on or after 1 January 2014 through 16 November 2018 at 4 CNICS sites with relevant data available at the time of analysis: Fenway Community Health Center/Harvard Medical School, Boston, Massachusetts; Johns Hopkins University, Baltimore, Maryland; University of Washington, Seattle, Washington; and University of California–San Diego, San Diego, California. Participant follow-up time was divided into 3-month intervals to reduce bias introduced by participants with very frequent visits (median: 13; range: 2–48) and to mirror intervals for clinic visits and syphilis testing and follow-up [10]. The observation period ended with the earliest of occurrence of death, last date of voluntary CNICS participation, or 16 November 2018.

Outcomes

Syphilis Testing

We defined syphilis testing as any non-treponemal or treponemal test performed on serum within a given 3-month follow-up interval.

Incident Syphilis

We defined a case of incident syphilis as having 1 of the 4 following criteria within a given 3-month follow-up interval:

1. A rapid plasma reagin (RPR) titer of 1:16 or greater at a patient's first 3-month follow-up interval during the study period
2. A reactive RPR with a titer of 1:4 or greater after a nonreactive RPR in a patient with a history of a reactive RPR during the study period
3. A reactive RPR with a titer of 1:1 or greater after a nonreactive RPR in a patient without a history of a reactive RPR during the study period
4. A 4-fold or greater increase in RPR titer from 1 follow-up interval to the next follow-up interval

These criteria were chosen because they were found to have a sensitivity of 78% and a specificity of 99% for an incident syphilis case when compared with detailed medical chart review [18]. For criterion 1, we explored the impact of reducing the RPR titer cutoff to 1:8 or greater, which did not increase the sensitivity of the criteria. The addition of a reactive treponemal test to criteria 2 and 3 also did not improve the sensitivity of the criteria. Clinic-administered antibiotic treatment information (eg, intramuscular benzathine penicillin G) was not always available for incorporation into the criteria.

Covariates

Sociodemographic Characteristics

We examined age in years (18–29, 30–39, 40–49, 50–59, and 60 years and older), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, American Indian/Alaska Native, another race or multiracial), sex-gender (cisgender man, cisgender woman, transgender man, transgender woman), CDC HIV transmission risk (heterosexual, injection drug use [IDU], MSM and MSM who use injection drugs (MSM/IDU), other/unknown), clinical site (Boston, MA; Baltimore, MD; San Diego, CA; Seattle, WA), and year of cohort entry (1995–2001, 2002–2007, 2008–2013, 2014–2018). Age was modeled as a time-varying covariate while all other sociodemographic characteristics did not vary with time. Of note, the MSM and MSM/IDU risk categories include transgender women who have sex with men.

Clinical Characteristics

We examined time-varying covariates of HIV RNA (<200 copies/mL, ≥200 copies/mL); *Neisseria gonorrhoeae* (GC) and/or *Chlamydia trachomatis* (CT) nucleic acid amplification testing (NAAT) of any anatomic site (yes, no); HCV enzyme-linked immunoassay (EIA) testing (yes, no); prior syphilis diagnosis (yes, no); positive rectal, pharyngeal, and urogenital GC NAAT (yes, no for each); positive rectal, pharyngeal, and urogenital CT NAAT (yes, no for each); and positive HCV EIA (yes, no).

Statistical Analysis

Using survival analysis methods modified for recurrent events [19], we calculated rates of syphilis testing and diagnosis with 95% confidence intervals (CIs) overall and stratified by baseline sociodemographic characteristics, including age, race/ethnicity, sex-gender, and HIV transmission risk. Because there were only 5 participants contributing 17.5 person-years of follow-up who identified as transgender men, we only estimated aggregate rates of syphilis testing and incident syphilis.

Using Cox proportional hazards regression modified for recurrent events [19] and robust standard error estimation, we calculated crude and adjusted hazard ratios (aHRs) and 95% CIs comparing rates of syphilis testing and incident syphilis by sociodemographic and clinical characteristics. We examined bivariable testing and diagnosis models including each covariate of interest. We modeled time-varying covariates differently for testing and diagnosis models. In testing models, we

Table 1. Baseline Characteristics of People With HIV Engaged in Care: 4 US CNICS Sites, 2014–2018

Characteristics	No. (%)
Age,y	
16–29	859 (10.1)
30–39	1617 (19.1)
40–49	2482 (29.4)
50–59	2617 (31.0)
60 and older	880 (10.4)
Race/ethnicity	
American Indian/Alaska Native	87 (1.0)
Asian/Pacific Islander	266 (3.1)
Black	2444 (28.9)
Hispanic	1537 (18.2)
White	3954 (46.8)
Another race, multiracial	167 (2.0)
Gender	
Cisgender man	6991 (82.7)
Cisgender woman	1355 (16.0)
Transgender man	5 (0.06)
Transgender woman	104 (1.2)
HIV transmission risk	
Heterosexual	1783 (21.1)
IDU	751 (8.9)
MSM	4947 (58.5)
MSM/IDU	630 (7.4)
Other/unknown	344 (4.1)
Site	
Boston, MA	1334 (15.8)
Baltimore, MD	1899 (22.5)
San Diego, CA	2923 (34.6)
Seattle, WA	2299 (27.2)
Year of cohort entry	
1995–2001	1409 (16.7)
2002–2007	2071 (24.5)
2008–2013	2969 (35.1)
2014–2018	2006 (23.7)

N = 8455.

Abbreviations: CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men.

assessed whether GC/CT and HCV testing increased syphilis testing in the same interval (ie, concurrent sexually transmitted infection [STI]/HCV testing) and whether a detectable HIV RNA and STI/HCV diagnosis in the prior interval increased syphilis testing in the subsequent interval. In diagnosis models, we assessed whether a detectable HIV RNA and new diagnoses of HCV and site-specific GC/CT increased the risk of incident syphilis in the same interval. Finally, we assessed whether incident syphilis in the prior 3-month interval increased the risk of syphilis diagnosis in the subsequent interval.

Covariates from bivariable models with a global Wald test $P < .25$ were included in the multivariable models. The testing model was stratified by clinical site and total follow-up time and the diagnosis model was stratified by clinical site and total number of syphilis tests. For multivariable models, we defined statistical significance as $P < .05$. Log-log plots and comparisons of Kaplan-Meier observed survival curves and Cox predicted curves did not reveal violations of the proportional hazards assumption. We used STATA 16.0 (StataCorp, College Station, TX).

RESULTS

During the study period, 8455 participants contributed 29 567.5 person-years of follow-up time (median: 4 years; range: 1–5 years). Ten percent of participants were aged 16–29 years, 28.9% were non-Hispanic Black, and 18.1% were Hispanic (Table 1). Sixteen percent were cisgender women and 1.2% were transgender women. Men who have sex with men comprised 58.5% of the sample, and 58.8% entered the cohort after 2007.

Over the entire duration of follow-up, 30 (0.3%), 1600 (18.9%), and 4803 (56.8%) participants were tested at least every 3, 6, and 12 months, respectively. Among 5577 MSM and MSM/IDU, 26 (0.5%), 1427 (25.6%), and 3789 (67.9%) participants were tested at least every 3, 6, and 12 months, respectively.

Rate of Syphilis Testing by Sociodemographic Characteristics

There were 34 989 total syphilis tests for a rate of 118 tests per 100 person-years (95% CI: 117, 119). Among cisgender men, the rate of syphilis testing was lowest among PWID aged 60 years and older and highest among MSM aged 16–29 years (Table 2). Among cisgender women, the rate of syphilis testing was lowest among American Indian/Alaska Native heterosexuals and highest among American Indians/Alaska Natives with unknown/other risk. Among transgender women, the rate of syphilis testing was lowest among those 60 years of age and older who have sex with men and who inject drugs and highest among those 30–39 years of age who have sex with men and who inject drugs.

Rate of Incident Syphilis by Sociodemographic Characteristics

There were 1406 incident syphilis cases, resulting in a rate of 4.7 cases per 100 person-years (95% CI: 4.5–5.0). Of the 1406 syphilis cases, 852 (60.6%) represented first diagnoses and 554 (39.4%) represented recurrent diagnoses during the study period. Two hundred fifty cases (17.7%), 136 cases (9.7%), 490 cases (34.8%) and 530 cases (37.7%) were based on criterion 1, 2, 3, and 4, respectively.

Among cisgender men, MSM/IDU 16–29 years of age experienced the highest rate of incident syphilis (Table 2). Hispanic women who inject drugs experienced the highest rate of incident syphilis among cisgender women. Among transgender women, those aged 30–39 years who have sex with men and inject drugs experienced the highest rate of incident syphilis followed by those who identify as Hispanic.

Sociodemographic and Clinical Predictors of Syphilis Testing

Compared with PWH aged 40–49 years, PWH aged 16–29 years had a higher rate of testing while PWH aged 50–59

Table 2. Syphilis Testing and Diagnosis Rates Stratified by HIV Transmission Risk, Gender, Age, and Race/Ethnicity Among People With HIV: 4 US CNICS Sites, 2014–2018

	HIV Transmission Risk				
	Heterosexual	IDU	MSM	MSM/IDU	Unknown/Other
Rate of syphilis testing per 100 person-years (95% CI); overall rate: 118 tests per 100 person-years (95% CI: 117, 119)					
Cisgender men					
Age, y					
16–29	147 (119, 181)	146 (93, 229)	185 (178, 193)	164 (142, 189)	161 (136, 192)
30–39	104 (93, 116)	115 (92, 144)	161 (157, 165)	150 (138, 161)	135 (117, 156)
40–49	93 (87, 100)	95 (84, 107)	145 (142, 149)	124 (116, 133)	115 (99, 134)
50–59	85 (80, 91)	78 (72, 84)	125 (122, 128)	107 (100, 115)	101 (89, 114)
60 and older	79 (71, 87)	62 (55, 69)	108 (103, 112)	103 (90, 118)	84 (69, 102)
Race/ethnicity					
American Indian/Alaska Native	104 (71, 153)	117 (83, 166)	142 (123, 164)	134 (102, 177)	125 (52, 300)
Asian/Pacific Islander	79 (59, 102)	103 (66, 159)	143 (134, 152)	91 (65, 128)	105 (72, 153)
Black	81 (77, 86)	67 (62, 73)	133 (128, 137)	113 (102, 126)	93 (82, 105)
Hispanic	113 (105, 123)	109 (91, 131)	162 (158, 167)	142 (128, 156)	158 (140, 179)
White	90 (83, 97)	88 (80, 97)	132 (130, 135)	123 (118, 129)	111 (99, 124)
Another race, multiracial	97 (68, 138)	65 (29, 144)	157 (145, 170)	100 (59, 169)	78 (46, 131)
Cisgender women					
Age, y					
16–29	96 (82, 112)	92 (52, 162)	…	…	99 (82, 120)
30–39	77 (70, 84)	75 (60, 94)	…	…	101 (80, 129)
40–49	70 (65, 75)	76 (66, 87)	…	…	77 (55, 107)
50–59	64 (59, 68)	61 (54, 70)	…	…	56 (42, 74)
60 and older	54 (47, 61)	60 (50, 72)	…	…	63 (46, 85)
Race/ethnicity					
American Indian/Alaska Native	45 (28, 71)	66 (40, 109)	…	…	154 (64, 370)
Asian/Pacific Islander	73 (55, 98)	89 (33, 237)	…	…	106 (70, 161)
Black	63 (59, 66)	66 (60, 73)	…	…	69 (58, 82)
Hispanic	90 (82, 99)	79 (54, 115)	…	…	109 (87, 137)
White	70 (63, 75)	64 (56, 73)	…	…	70 (55, 89)
Another race, multiracial	81 (55, 117)	102 (62, 166)	…	…	108 (51, 226)
Transgender women					
Age, y					
16–29	…	…	169 (131, 218)	107 (40, 284)	…
30–39	…	…	162 (133, 197)	190 (123, 295)	…
40–49	…	…	150 (125, 179)	144 (99, 208)	…
50–59	…	…	124 (102, 150)	143 (96, 214)	…
60 and older	…	…	85 (55, 132)	22 (3, 158)	…
Race/ethnicity					
American Indian/Alaska Native	…	…	160 (95, 270)	no obs	…
Asian/Pacific Islander	…	…	133 (84, 212)	no obs	…
Black	…	…	140 (114, 172)	118 (69, 203)	…
Hispanic	…	…	137 (118, 160)	161 (119, 219)	…
White	…	…	149 (124, 181)	122 (80, 186)	…
Another race, multiracial	…	…	143 (77, 266)	no obs	…
Rate of incident syphilis per 100 person-years (95% CI); overall rate: 4.7 syphilis cases per 100 person-years (95% CI: 4.5, 5.0)					
Cisgender men					
Age, y					
16–29	0	0	10.4 (8.8, 12.3)	11.6 (6.7, 20.0)	10.2 (5.1, 20.5)
30–39	2.1 (1.0, 4.5)	1.5 (.2, 10.5)	11.0 (9.9, 12.2)	10.9 (8.2, 14.4)	8.6 (4.9, 15.2)
40–49	1.1 (.6, 2.1)	2.6 (1.2, 5.4)	7.6 (6.8, 8.4)	5.6 (4.0, 7.8)	3.5 (1.5, 8.5)
50–59	.9 (.5, 1.7)	.9 (.4, 1.9)	4.7 (4.2, 5.3)	2.7 (1.8, 4.3)	1.6 (.6, 4.3)
60 and older	.2 (.02, 1.3)	0	3.0 (2.3, 3.7)	1.5 (.5, 4.6)	2.4 (.8, 7.5)
Race/ethnicity					
American Indian/Alaska Native	0	0	4.6 (2.0, 10.2)	5.3 (1.3, 21.0)	0
Asian/Pacific Islander	1.5 (.2, 10.4)	5.1 (.7, 36.4)	8.3 (6.3, 10.7)	11.3 (4.1, 29.4)	3.9 (.5, 27.6)
Black	.4 (.2, 0.9)	.2 (.05, .8)	5.3 (4.4, 6.2)	3.2 (1.7, 5.9)	3.2 (1.6, 6.4)

Table 2. Continued

	HIV Transmission Risk				
	Heterosexual	IDU	MSM	MSM/IDU	Unknown/Other
Hispanic	2.0 (1.1, 3.7)	1.8 (.4, 7.3)	9.7 (8.7, 10.8)	9.0 (6.0, 13.3)	8.2 (4.8, 14.1)
White	1.3 (.6, 2.5)	2.0 (1.1, 3.7)	6.2 (5.7, 6.7)	5.4 (4.3, 6.7)	3.3 (1.7, 6.4)
Another race, multiracial	3.2 (.4, 22.9)	0	8.1 (5.7, 11.4)	7.1 (1.0, 50.7)	5.5 (.7, 39.4)
Cisgender women					
Age, y					
16–29	0	0	…	…	.9 (.1, 6.6)
30–39	.2 (.02, 1.1)	2.0 (.5, 8.1)	…	…	0
40–49	.09 (.01, .7)	.4 (.05, 2.8)	…	…	0
50–59	.3 (.09, .8)	.2 (.3, 1.7)	…	…	0
60 and older	0	.5 (.07, 3.5)	…	…	0
Race/ethnicity					
American Indian/Alaska Native	0	0	…	…	0
Asian/Pacific Islander	0	0	…	…	0
Black	.05 (.01, .3)	.4 (.09, 1.5)	…	…	0
Hispanic	.6 (.2, 1.8)	5.8 (1.5, 23.3)	…	…	0
White	.1 (.02, 1.0)	.3 (.04, 2.0)	…	…	1.1 (0.1, 7.5)
Another race, multiracial	0	0	…	…	0
Transgender women					
Age, y					
16–29	…	…	8.6 (2.8, 26.6)	0	…
30–39	…	…	7.9 (3.3, 19.1)	19.0 (4.8, 76.2)	…
40–49	…	…	7.5 (3.4, 16.8)	0	…
50–59	…	…	6.0 (2.5, 14.5)	6.0 (.8, 42.4)	…
60 and older	…	…	0	0	…
Race/ethnicity					
American Indian/Alaska Native	…	…	0	no obs	…
Asian/Pacific Islander	…	…	0	no obs	…
Black	…	…	4.6 (1.5, 14.2)	9.1 (1.3, 64.5)	…
Hispanic	…	…	11.8 (7.0, 19.9)	7.7 (1.9, 30.8)	…
White	…	…	2.8 (.7, 11.3)	0	…
Another race, multiracial	…	…	0	no obs	…

The ellipses " …" indicate <20 observations in the data among those with the combination of gender and HIV transmission risk.

Abbreviations: CI, confidence interval; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; no obs, no observations.

years and 60 years and older had a lower testing rate (Table 3). Hispanic PWH experienced a higher testing rate than non-Hispanic White PWH and cisgender women had a lower testing rate compared with cisgender men. Compared with those with heterosexual transmission risk, MSM, MSM/IDU, and those with other/unknown transmission risk, but not PWID, had a higher rate of syphilis testing. People with HIV who entered the CNICS cohort between 2014 and 2018 had a higher rate of testing than those who entered the cohort between 1995 and 2001 (adjusted for chronological age in the multivariable model).

The rate of syphilis testing was lower after intervals in which PWH had a detectable HIV RNA compared with after intervals in which PWH had an undetectable HIV RNA. The rate of syphilis testing was higher during intervals in which PWH tested for GC/CT compared with during intervals in which GC/CT testing did not occur. Rates of syphilis testing were higher after intervals in which PWH had a syphilis diagnosis, a positive GC NAAT, or a positive CT NAAT compared with after intervals without a syphilis diagnosis or positive GC or CT NAAT.

Sociodemographic and Clinical Predictors of Incident Syphilis

Compared with PWH aged 40–49 years, PWH aged 30–39 years had a higher rate of incident syphilis and PWH aged 50–59 years and 60 years and older had a lower rate of incident syphilis (Table 4). Hispanic PWH had a higher rate of incident syphilis than White PWH. Cisgender women had a lower rate of incident syphilis compared with cisgender men. Compared with those with heterosexual transmission risk, those with all other transmission risk had a higher rate of rate of incident syphilis; however, the aHR for PWID was not statistically significant. Compared with PWH who entered the CNICS cohort in 1995–2001, PWH who entered the cohort after 2001 experienced a higher rate of incident syphilis.

Table 3. Rates of Syphilis Testing by Sociodemographic and Clinical Characteristics and Bivariable and Multivariable Syphilis Testing Models: 4 US CNICS Sites, 2014–2018

Characteristics	Syphilis Tests	Person-Years	Syphilis Tests per 100 Person-Years (95% CI)	Crude HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*
Sociodemographic characteristics							
Age, y							
16–29	3228	1924.75	168 (162, 173)	1.35 (1.29, 1.42)	<.001	1.12 (1.07, 1.18)	<.001
30–39	7313	5140.25	142 (139, 146)	1.15 (1.12, 1.20)	<.001	1.01 (0.98, 1.04)	.458
40–49	9565	7757.75	123 (121, 126)	Ref		Ref	
50–59	10 934	10 327	106 (104, 108)	.86 (.83, .89)	<.001	.93 (.90, .96)	<.001
60 and older	3949	4417.75	89 (87, 92)	.72 (.68, .76)	<.001	.87 (.83, .91)	<.001
Race/ethnicity							
American Indian/Alaska Native	352	300.5	117 (105, 130)	.96 (.82, 1.12)	.594	1.08 (.96, 1.22)	.185
Asian/Pacific Islander	1166	912.5	128 (121, 135)	1.05 (.97, 1.14)	.256	.96 (.89, 1.03)	.291
Black	7889	8593	92 (90, 94)	.75 (.73, .78)	<.001	1.01 (.98, 1.05)	.521
Hispanic	7925	5407.25	146 (143, 150)	1.19 (1.15, 1.24)	<.001	1.05 (1.02, 1.08)	.003
White	16 907	13 820.75	122 (120, 124)	Ref		Ref	
Another race, multiracial	750	533.5	141 (131, 151)	1.14 (1.05, 1.24)	.001	.96 (.89, 1.04)	.347
Gender							
Cisgender man	31 175	24 422	128 (126, 129)	Ref		Ref	
Cisgender woman	3282	4767.75	69 (66, 71)	.54 (.52, .57)	<.001	.76 (.72, .80)	<.001
Transgender man	31	17.5	177 (125, 252)	1.40 (.79, 2.46)	.249	1.31 (.63, 2.71)	.467
Transgender woman	501	360.25	139 (127, 152)	1.08 (.98, 1.20)	.130	.96 (.87, 1.06)	.424
HIV transmission risk							
Heterosexual	4873	6244	78 (76, 80)	Ref		Ref	
IDU	1930	2618.25	74 (70, 77)	.94 (.89, 1.01)	.077	1.03 (.97, 1.09)	.351
MSM	24 362	17 433	140 (138, 141)	1.76 (1.71, 1.84)	<.001	1.25 (1.19, 1.30)	<.001
MSM/IDU	2689	2167.5	124 (119, 129)	1.50 (1.50, 1.69)	<.001	1.28 (1.20, 1.36)	<.001
Other/unknown	1135	1104.75	103 (97, 109)	1.31 (1.20, 1.43)	<.001	1.08 (1.00, 1.16)	.046
Year of cohort entry							
1995–2001	5011	5294.75	95 (92, 97)	Ref		Ref	
2002–2007	8693	7805.75	111 (109, 114)	1.17 (1.12, 1.23)	<.001	1.03 (.99, 1.07)	.198
2008–2013	13 440	10 946.5	123 (121, 125)	1.29 (1.23, 1.35)	<.001	1.02 (.98, 1.06)	.383
2014–2018	7845	5520.5	142 (139, 145)	1.51 (1.44, 1.59)	<.001	1.05 (1.00, 1.10)	.040
Time-varying HIV RNA							
HIV RNA >200 copies/mL, prior interval							
No	27 102	24 346.5	111 (110, 113)	Ref		Ref	
Yes	3179	3107.25	102 (99, 106)	.95 (.92, .99)	.011	.96 (.93, .99)	.021
Time-varying STI and HCV testing							
GC/CT NAAT (any anatomic site), current interval							
No	13 131	17 389.25	75 (74, 77)	Ref		Ref	
Yes	21 858	12 178.25	179 (177, 182)	2.34 (2.28, 2.40)	<.001	2.00 (1.95, 2.06)	<.001
HCV EIA, current interval							
No	24 666	23 278.5	106 (105, 107)	Ref		Ref	
Yes	10 323	6289	164 (161, 167)	1.49 (1.46, 1.52)	<.001	1.02 (1.00, 1.05)	.078
Time-varying STI and HCV diagnoses							
Syphilis diagnosis, prior interval							
No	29 249	26 914.25	109 (107, 110)	Ref		Ref	
Yes	1032	539.5	191 (180, 203)	1.75 (1.66, 1.84)	<.001	1.26 (1.20, 1.33)	<.001
GC NAAT positive (any anatomic site), prior interval							
No	29 031	6806.5	108 (107, 110)	Ref		Ref	
Yes	1250	647.25	193 (182, 204)	1.77 (1.69, 1.85)	<.001	1.13 (1.07, 1.18)	<.001
CT NAAT positive (any anatomic site), prior interval							
No	29 005	26 763.75	108 (107, 110)	Ref		Ref	
Yes	1267	690	185 (175, 195)	1.71 (1.63, 1.79)	<.001	1.08 (1.03, 1.14)	.001
HCV EIA positive, prior interval							
No	29 966	27 148	110 (109, 112)	Ref		[b]	
Yes	315	305.75	103 (92, 115)	.95 (.86, 1.05)	.337	[b]	

Abbreviations: CI, confidence interval; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; CT, *Chlamydia trachomatis*; EIA, enzyme-linked immunoassay; GC, *Neisseria gonorrhoeae*; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug use; MSM, men who have sex with men; NAAT, nucleic acid amplification test; Ref, referent; STI, sexually transmitted infection.

[a]Adjusted models are stratified by clinic site and total follow-up time contributed by each participant.

[b]Not included in the multivariable regression model ($P > .25$).

The rate of incident syphilis was higher during intervals in which PWH had a detectable HIV RNA compared with during intervals in which PWH had an undetectable HIV RNA. The rates of incident syphilis were higher during intervals in which PWH had a positive rectal GC NAAT, a positive rectal CT NAAT, and a positive urogenital CT NAAT compared with during intervals in which PWH did not experience these positive NAATs. Finally, the rate of incident syphilis was higher during an interval in which PWH had a positive HCV EIA compared with during intervals without a positive HCV EIA. In a multivariable model restricted to only MSM (excluding MSM/IDU), the rate of incident syphilis was higher during intervals in which PWH had a positive HCV EIA compared with during intervals without a positive HCV EIA (aHR: 1.84; 95% CI: 1.12, 3.03; $P < .001$).

DISCUSSION

Our estimates of the rate of syphilis testing and incident syphilis among PWH were higher than those previously reported among PWH engaged in care but are consistent with increasing testing and diagnosis rates over the past 2 decades [3]. Similar to prior studies, rates of syphilis testing were higher among younger PWH, cisgender men, and transgender women who have sex with men. We observed the highest rate of incident syphilis among younger MSM and transgender women who have sex with men and inject drugs, particularly among those who identify as Hispanic. These high rates of incident syphilis are likely influenced by the complex, reinforcing interactions between multiple factors, including but not limited to transphobia, homophobia, racism, and stigma related to HIV status, sexual behavior, and substance use [20–23].

Despite an association between detectable HIV RNA and an incident syphilis diagnosis, PWH with a detectable HIV RNA level at a prior visit experienced a lower syphilis testing rate than those with an undetectable HIV RNA level. Such a mismatch in screening and diagnosis may potentiate forward HIV and syphilis transmission. While syphilis may increase HIV RNA levels [7, 8], this mismatch more likely reflects barriers to syphilis screening among PWH who also face challenges in achieving durable viral suppression due to substance use, social and economic disadvantage, and discrimination based on race/ethnicity, sexual orientation, and gender identity [2, 12, 20, 22–24]. These same factors may affect condom use, sex partner selection, and conversations about STI testing with potential sex partners [5, 6]. We also observed a mismatch in screening and diagnosis rates among PWID. While PWID were not more likely to be tested for syphilis than heterosexuals, they were diagnosed with syphilis twice as frequently. This finding is consistent with an increase in syphilis cases among PWID in the United States, particularly among cisgender women [2, 12]. In our data, Hispanic cisgender women who inject drugs experienced high rates of syphilis diagnosis. This finding emphasizes the importance of integrating syphilis testing into harm-reduction and substance-use-disorder treatment programs that serve PWH.

Rates of incident syphilis were higher among PWH who were diagnosed with rectal GC or CT during the same 3-month interval. This finding has several implications. First, rectal inflammation caused by GC or CT infection may facilitate *Treponema pallidum* infection. Second, rectal chancres, which are often missed on clinical examination, may facilitate GC and/or CT infection of the rectal mucosa. Third, those who practice receptive anal sex may be at higher risk for syphilis compared with those who have only insertive anal sex. Fourth, those with rectal GC or CT should be routinely screened for syphilis to assess for coinfection. Finally, rectal *T. pallidum* NAAT may augment serologic syphilis screening among PWH, and among MSM in particular [25]. There are limitations to modeling site-specific GC/CT. Since we do not know the exact timing of *T. pallidum* infection in relation to GC or CT infection, we cannot draw conclusions about the directionality of this association.

Rates of incident syphilis were higher among PWH with a positive HCV EIA during the same 3-month interval. We observed this association for the entire sample and among MSM excluding MSM/IDU. Syphilis chancres may facilitate HCV transmission and/or syphilis may increase HCV RNA levels in blood and the rectal mucosa, leading to a greater probability of sexual HCV transmission [26]. Recent syphilis was associated with HCV infection among MSM living with HIV [9]. Therefore, HCV screening should be part of routine STI screening, especially among PWH with syphilis [27].

This work has important limitations. First, not all syphilis testing and diagnosis occurs within the context of HIV care. Baltimore, Maryland; San Diego, California; and Seattle, Washington, have robust local public health sexual health clinics where CNICS participants access STI testing. As syphilis testing and diagnosis outside HIV care are not necessarily captured in CNICS data, our data likely underestimate syphilis testing and diagnosis rates; matching CNICS records with public health STI surveillance data may provide more accurate rates of syphilis diagnosis and allow for evaluation of partner services, treatment, and follow-up data that may provide insight into recurrent diagnoses. Furthermore, the Baltimore, Maryland, site serves the majority (1428/2444, 58.4%) of Black PWH in our cohort; thus, this bias in syphilis testing and diagnosis rates may be particularly exaggerated among Black PWH in our sample. Possibly as a result, and in contrast to other studies, we did not find a higher rate of syphilis diagnosis among Black PWH compared with other races and ethnicities. Second, the sensitivity of the criteria used to define a syphilis diagnosis was only 78%, indicating missing syphilis diagnoses. Therefore, our estimates likely represent lower bounds of syphilis testing and diagnosis rates among PWH in this cohort. Third, the present analyses did not incorporate

Table 4. Rates of Incident Syphilis by Sociodemographic and Clinical Characteristics and Bivariable and Multivariable Syphilis Diagnosis Models: 4 US CNICS Sites, 2014–20188

Characteristics	Syphilis Diagnoses	Person-Years	Syphilis Diagnoses per 100 Person-Years (95% CI)	Crude HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*
Sociodemographic characteristics							
Age, y							
16–29	164	1924.75	8.5 (7.3, 9.9)	1.62 (1.32, 1.99)	<.001	1.10 (.88, 1.39)	.389
30–39	439	5140.25	8.5 (7.8, 9.4)	1.64 (1.41, 1.90)	<.001	1.33 (1.14, 1.55)	<.001
40–49	404	7757.75	5.2 (4.7, 5.7)	Ref		Ref	
50–59	324	10 327	3.1 (2.8, 3.5)	.60 (.51, .71)	<.001	.81 (.69, .96)	.014
60 and older	75	4417.75	1.7 (1.3, 2.1)	.32 (.24, .43)	<.001	.56 (.42, .76)	<.001
Race/ethnicity							
American Indian/ Alaska Native	8	300.5	2.7 (1.3, 5.3)	.52 (.24, 1.11)	.090	.56 (.26, 1.18)	.129
Asian/Pacific Islander	62	912.5	6.8 (5.3, 8.7)	1.32 (.98, 1.77)	.067	.93 (.68, 1.29)	.686
Black	172	8593	2.0 (1.7, 2.3)	.39 (.32, .47)	<.001	1.01 (.83, 1.22)	.912
Hispanic	416	5407.25	7.7 (7.0, 8.5)	1.49 (1.30, 1.70)	<.001	1.15 (1.00, 1.33)	.052
White	713	13 820.75	5.2 (4.8, 5.5)	Ref		Ref	
Another race, multiracial	35	533.5	6.6 (4.7, 9.1)	1.26 (.88, 1.81)	.208	.80 (.54, 1.20)	.283
Gender							
Cisgender man	1373	24 422	5.6 (5.3, 5.9)	Ref		Ref	
Cisgender woman	11	4767.75	0.2 (0.1, 0.4)	.04 (.02, .07)	<.001	.27 (.13, .54)	<.001
Transgender man	0	17.5	0	NA		NA	
Transgender woman	22	360.25	6.1 (4.0, 9.3)	1.08 (.71, 1.79)	.736	.86 (.56, 1.33)	.505
HIV transmission risk							
Heterosexual	32	6244	0.5 (0.4, 0.7)	Ref		Ref	
IDU	20	2618.25	0.8 (0.5, 1.2)	1.49 (.81, 2.76)	.202	2.01 (.99, 3.58)	.055
MSM	1199	17 433	6.9 (6.5, 7.3)	13.3 (9.22, 19.3)	<.001	2.50 (1.67, 3.74)	<.001
MSM/IDU	122	2167.5	5.6 (4.7, 6.7)	11.0 (7.27, 16.5)	<.001	2.39 (1.53, 3.74)	<.001
Other/unknown	33	1104.75	3.0 (2.1, 4.2)	5.78 (3.32, 10.1)	<.001	2.00 (1.14, 3.49)	.015
Year of cohort entry							
1995–2001	111	5294.75	2.1 (1.7, 2.5)	Ref		Ref	
2002–2007	329	7805.75	4.2 (3.8, 4.7)	2.00 (1.57, 2.55)	<.001	1.29 (1.01, 1.65)	.043
2008–2013	591	10 946.5	5.4 (5.0, 5.8)	2.56 (2.05, 3.21)	<.001	1.25 (1.00, 1.58)	.054
2014–2018	375	5520.5	6.8 (6.1, 7.5)	3.22 (2.55, 4.07)	<.001	1.64 (1.28, 2.10)	<.001
Time-varying HIV RNA							
HIV RNA >200 copies/mL, current interval							
No	1181	25 942	4.5 (4.3, 4.8)	Ref		Ref	
Yes	225	3625.5	6.2 (5.4, 7.1)	1.27 (1.09, 1.47)	.002	1.53 (1.29, 1.80)	<.001
Time-varying STI and HCV diagnoses							
Rectal GC NAAT positive, current interval							
No	1320	29 185.5	4.5 (4.3, 4.8)	Ref		Ref	
Yes	86	382	22.5 (18.2, 27.8)	4.95 (4.01, 6.10)	<.001	1.66 (1.26, 2.18)	<.001
Rectal CT NAAT positive, current interval							
No	1313	29 059.25	4.5 (4.3, 4.8)	Ref		Ref	
Yes	93	508.25	18.3 (14.9, 22.4)	3.97 (3.20, 4.92)	<.001	1.47 (1.14, 1.90)	.003
Pharyngeal GC NAAT positive, current interval							
No	1342	29 252.25	4.6 (4.3, 4.8)	Ref		Ref	
Yes	64	315.25	20.3 (15.9, 25.9)	4.45 (3.49, 5.68)	<.001	1.35 (.99, 1.84)	.057
Pharyngeal CT NAAT positive, current interval							
No	1383	29 452.25	4.7 (4.4, 4.9)	Ref		Ref	
Yes	23	115.25	20.0 (13.3, 30.0)	4.31 (2.82, 6.57)	<.001	1.33 (.79, 2.26)	.285
Urogenital GC NAAT positive, current interval							
No	1374	29 365.5	4.7 (4.4, 4.9)	Ref		Ref	
Yes	32	202	15.8 (11.2, 22.4)	3.37 (2.42, 4.69)	<.001	1.15 (.80, 1.66)	.451
Urogenital CT NAAT positive, current interval							
No	1365	29 329.25	4.6 (4.4, 4.9)	Ref		Ref	
Yes	41	238.25	17.2 (12.7, 23.4)	3.61 (2.67, 4.89)	<.001	1.56 (1.11, 2.18)	.010

Table 4. Continued

Characteristics	Syphilis Diagnoses	Person-Years	Syphilis Diagnoses per 100 Person-Years (95% CI)	Crude HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*
HCV EIA positive, current interval							
No	1372	29 211.75	4.7 (4.4, 5.0)	Ref		Ref	
Yes	34	355.75	9.6 (6.8, 13.4)	1.92 (1.37, 2.68)	<.001	1.75 (1.12, 2.74)	.014
Syphilis diagnosis, prior interval							
No	1143	26 914.25	4.2 (4.0, 4.5)	Ref		Ref	
Yes	51	539.5	9.4 (7.2, 12.4)	2.22 (1.68, 2.92)	<.001	.87 (.66, 1.16)	.344

Abbreviations: CI, confidence interval; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; CT, *Chlamydia trachomatis*; EIA, enzyme-linked immunoassay; GC, *Neisseria gonorrhoeae*; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, injection drug use; MSM, men who have sex with men; NAAT, nucleic acid amplification test; Ref, referent; STI, sexually transmitted infection.

[a]Adjusted models are stratified by clinic site and total number of syphilis tests contributed by each participant.

sexual and substance-use behaviors; future work will incorporate these data to further tailor syphilis testing recommendations. Finally, our results may not be generalizable outside well-resourced academic medical practices.

Rates of incident syphilis are high among PWH in care. Younger cisgender men and transgender women who have sex with men, PWID, Hispanic PWH, and those with detectable HIV RNA, rectal infections, and HCV are more likely to experience a syphilis diagnosis and should thus be prioritized for syphilis testing and behavioral and biomedical interventions for STI prevention [13–16].

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