Risk Factors and Incidence of Syphilis in HIV-infected persons, the HIV Outpatient Study, 1999-2015

RM Novak[1], A Ghanem[1], R Hart[2], D Ward[3], C Armon[2], and K Buchacz[4] for the HIV Outpatient Study (HOPS)

[1]University of Illinois College of Medicine, Chicago, IL; [2]Cerner Corporation, Kansas City, MO; [3]Dupont Circle Physicians Group, Washington, DC; [4]Centers for Disease Control and Prevention, Atlanta, GA

Richard M. Novak, MD
Professor of Medicine
University of Illinois
College of Medicine
rmnovak@uic.edu

#864

BACKGROUND

- The incidence of syphilis has been increasing, especially among gay, bisexual and other men who have sex with men (MSM) for at least a decade in the United States (U.S.).[1, 2, 3, 4]
- Syphilis testing for HIV-infected patients who are sexually active is recommended at least annually.[5]
- We assessed incidence, temporal trends and associated risk factors for newly diagnosed syphilis infections among HIV-infected patients in care during a 16 year period.

METHODS

- We analyzed data from the HIV Outpatient Study (HOPS) cohort participants seen at ten U.S. HIV clinical practice sites from January 1, 1999 to June 30, 2015.
- New syphilis cases were defined based on a combination of established laboratory parameters as well as clinical diagnoses.
- We assessed incidence rates of syphilis by patient sociodemographic, clinical and behavioral characteristics, and performed multivariable Poisson regression analyses of incident syphilis infection rates using propensity score adjustment for the probability for having >1 syphilis test.

RESULTS

- We studied 6,888 HIV-infected participants, among whom 641 had one or more new syphilis diagnoses during a median follow-up of 5.2 years (interquartile range: 2.0 to 10.8).
- Most study participants were male (78%) and aged 31-50 years (Table 1) and 57% of participants were MSM, 36% heterosexuals, and 6% other/unknown risk. 10% were persons who inject drugs (PWID).
- There were a total of 799 syphilis diagnoses among 641 participants, for an overall incidence of 1.8 per 100 person-years (95% Confidence Interval 1.7-2.0).
- Rates of diagnosed syphilis were highest in the most recent years and followed a similar pattern as increasing syphilis testing rates (Figure 1).
- MSM participants as well as those followed in earlier time periods had the longest time to first syphilis test compared to other HIV transmission risk groups or later time periods, respectively (Figure 2).
- The crude incidence rate of syphilis was higher among MSM than heterosexual males and females (2.6 vs. 1.0 and 0.4, P<0.001), was higher among participants aged 18-30 years than over 50 years (3.0 vs. 0.8, P<0.001), and was elevated among non-Hispanic blacks vs. white and Hispanic/Latino participants (Figure 3).
- In multivariable analyses, the independent risk factors for syphilis included (all P<0.001): younger age, being non-Hispanic Black, having MSM HIV risk, and being followed in later time periods (Table 2).

Table 1: Baseline characteristics of HOPS participants by incident syphilis outcome, HIV Outpatient Study (n=6,888)

Characteristics at index date* (No., % or median, IQR)	Overall (n=6,888)	Incident Syphilis: No incident syphilis (n=6,247)	Incident Syphilis: Incident Syphilis (n=641)	P-value‡
Age at index date (years), n (%)				<0.001
18-30	1,160 (16.8)	1,003 (16.1)	157 (24.5)	
31-40	2,605 (37.8)	2,333 (37.3)	272 (42.4)	
41-50	2,204 (32.0)	2,031 (32.5)	173 (27.0)	
51+	919 (13.3)	880 (14.1)	39 (6.1)	
Sex at birth, n (%)				<0.001
F	1,513 (22.0)	1,479 (23.7)	34 (5.3)	
M	5,375 (78.0)	4,768 (76.3)	607 (94.7)	
Race/ethnicity, n (%)				0.10
Non-Hispanic white	3,398 (49.3)	3,079 (49.3)	319 (49.8)	
Non-Hispanic black	2,390 (34.7)	2,154 (34.5)	236 (36.8)	
Hispanic	847 (12.3)	787 (12.6)	60 (9.4)	
Other/Unknown	253 (3.7)	227 (3.6)	26 (4.1)	
HIV Transmission Risk Category, n (%)				<0.001
MSM	3,953 (57.4)	3,422 (54.8)	531 (82.8)	
Heterosexual Males	1,118 (16.2)	1,063 (17.0)	55 (8.6)	
Heterosexual Females	1,384 (20.1)	1,350 (21.6)	34 (5.3)	
Other/Unknown	433 (6.3)	412 (6.6)	21 (3.3)	
PWID, n (%)	690 (10.0)	666 (10.7)	24 (3.7)	<0.001
Insurance, n (%)				<0.001
Private	3,596 (52.2)	3,189 (51.0)	407 (63.5)	
Public	2,624 (38.1)	2,483 (39.7)	141 (22.0)	
Self pay/none	409 (5.9)	341 (5.5)	68 (10.6)	
Other/Unknown	259 (3.8)	234 (3.7)	25 (3.9)	
AIDS status, n (%)	3,348 (48.6)	3,093 (49.5)	255 (39.8)	<0.001
Chronic HBV Infection, n (%)	398 (5.8)	345 (5.5)	53 (8.3)	0.005
Chronic HCV Infection, n (%)	876 (12.7)	832 (13.3)	44 (6.9)	<0.001
Calendar period of index date, n (%)				<0.001
1999-2002	3,884 (56.4)	3,598 (57.6)	286 (44.6)	
2003-2006	1,326 (19.3)	1,176 (18.8)	150 (23.4)	
2007-2010	1,021 (14.8)	880 (14.1)	141 (22.0)	
2011-2015	657 (9.5)	593 (9.5)	64 (10.0)	
CD4 at index date†, n (%)				<0.001
< 50	588 (8.5)	552 (8.8)	36 (5.6)	
50-199	1,016 (14.8)	937 (15.0)	79 (12.3)	
200-349	1,272 (18.5)	1,156 (18.5)	116 (18.1)	
350-499	1,182 (17.2)	1,046 (16.7)	136 (21.2)	
500+	2,094 (30.4)	1,870 (29.9)	224 (34.9)	
Unknown	736 (10.7)	686 (11.0)	50 (7.8)	
ART exposure, n (%)				<0.001
Experienced	4,442 (64.5)	4,082 (65.3)	360 (56.2)	
Naïve	2,118 (30.7)	1,849 (29.6)	269 (42.0)	
Unknown	328 (4.8)	316 (5.1)	12 (1.9)	
Antibiotic prophylaxis prior to index date, n (%)#	767 (11.1)	727 (11.6)	40 (6.2)	<0.001
Antibiotic prophylaxis prior to end of study, n (%)#	2,187 (31.8)	2,005 (32.1)	182 (28.4)	0.055
Site Type, n (%)				0.044
Private	3,008 (43.7)	2,704 (43.3)	304 (47.4)	
Public (Academic)	3,880 (56.3)	3,543 (56.7)	337 (52.6)	

* Index date is the later of first HOPS visit or 01-01-1999.
† Closest value to index from values documented 6 months prior thru 3 months post index date.
‡ Kruskall-Wallis tests for continuous variables, chi-square test for categorical variables
# Antibiotic prophylaxis includes azithromycin and/or bactrim given as prophylaxis
Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MSM, men who have sex with men; PWID, persons who inject drugs

Table 2: Univariate and Multivariable analyses of factors associated with incident syphilis, HIV Outpatient Study (n=6,888)

Independent variables	Univariate RR (95% CI)	P-value	Multivariable aRR (95% CI)	P-value
Age group				
18-30	1.69 (1.36, 2.09)	<0.001	1.33 (1.10, 1.61)	0.003
31-40	Referent		Referent	
41-50	0.82 (0.66, 1.01)	0.058	0.80 (0.67, 0.95)	0.011
51+	0.41 (0.29, 0.58)	<0.001	0.43 (0.31, 0.60)	<0.001
Female sex	0.17 (0.12, 0.24)	<0.001		
Race/ethnicity				
non-Hispanic White	Referent		Referent	
non-Hispanic Black	1.30 (1.08, 1.57)	0.005	1.62 (1.37, 1.91)	<0.001
Hispanic	0.78 (0.58, 1.05)	0.097	0.86 (0.66, 1.13)	0.28
Other/Unknown	1.28 (0.84, 1.97)	0.25	1.44 (0.99, 2.09)	0.054
HIV transmission risk group				
MSM	2.63 (1.97, 3.50)	<0.001	3.11 (2.38, 4.06)	<0.001
Het Males	Referent		Referent	
Het Females	0.41 (0.27, 0.64)	<0.001	0.35 (0.23, 0.52)	<0.001
Other/Unknown	0.92 (0.54, 1.57)	0.76	0.87 (0.54, 1.38)	0.55
PWID	0.31 (0.21, 0.47)	<0.001		
Payor				
Private	Referent			
Public	0.57 (0.46, 0.70)	<0.001		
Self pay/none	1.87 (1.40, 2.50)	<0.001		
Other/Unknown	0.90 (0.59, 1.37)	0.61		
CD4 at index date				
<200	0.71 (0.56, 0.90)	0.005		
200-349	0.81 (0.63, 1.03)	0.088		
350-499	1.12 (0.89, 1.43)	0.34		
500+	Referent			
Unknown	0.54 (0.39, 0.74)	<0.001		
Given antibiotic prophylaxis#	0.39 (0.28, 0.54)	<0.001		
Site Type				
Private	1.14 (0.96, 1.35)	0.13		
Public (Academic)	Referent			
Calendar period of index date				
1999	Referent			
2000-2004	1.81 (1.44, 2.26)	<0.001	1.48 (1.22, 1.80)	<0.001
2005-2009	3.49 (2.80, 4.34)	<0.001	2.08 (1.57, 2.74)	<0.001
2010-2015	5.57 (4.11, 7.56)	<0.001	4.19 (3.15, 5.58)	<0.001

* Antibiotic prophylaxis includes azithromycin and/or bactrim given as prophylaxis prior to the later of first HOPS visit or 01-01-1999.

Abbreviations: aRR, adjusted rate ratio; MSM, men who have sex with men; PWID, people who inject drugs; RR, rate ratio.

Figure 1: Syphilis incidence and testing rates (with 95% confidence interval bars) by year, the HIV Outpatient Study (n=6,888)

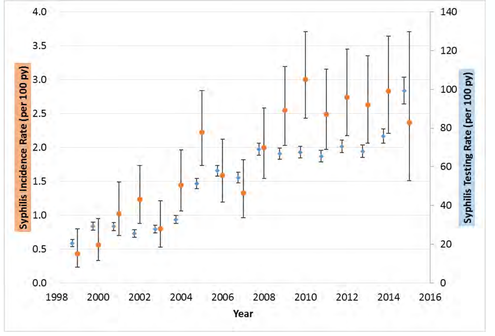


Figure 2: Kaplan-Meier graph of years to first syphilis test by HIV transmission risk category and calendar period, the HIV Outpatient Study (n=6,888)

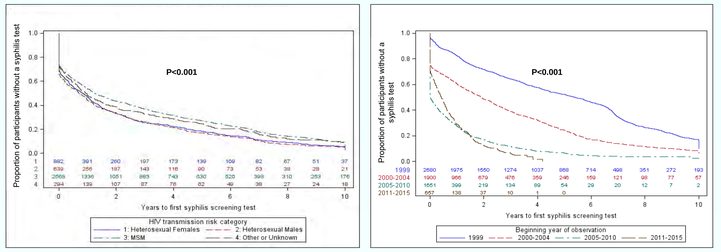
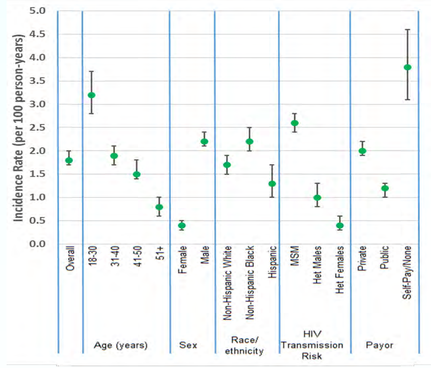


Figure 3: Syphilis incidence rates (with 95% confidence interval bars) among active HOPS participants, the HIV Outpatient Study (n=6,888)



LIMITATIONS

- Both syphilis testing and syphilis incidence increased over time, likely due to increased recognition of risk. Trends in syphilis incidence may reflect in part improved screening and detection of asymptomatic syphilis cases.

CONCLUSIONS

- The steady increases in the syphilis incidence rate through 2015, particularly among HIV-infected patients who are younger, non-Hispanic, and MSM, reflect ongoing sexual risk.
- There is a need for ongoing syphilis testing and comprehensive sexual risk reduction interventions in this population.

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Centers for Disease Control and Prevention (CDC), Atlanta, GA; Harlen Hays, Rachel Hart, Thilakavathy Subramanian, Carl Armon, Bonnie Dean, Stacey Purinton, Dana Franklin, Cheryl Akridge, Nabil Rayeed, Cerner Corporation, Kansas City, MO; Frank J. Palella, Saira Jahangir, Conor Daniel Flaherty, Patricia Bustamante, Feinberg School of Medicine, Northwestern University, Chicago, IL; John Hammer, Kenneth S. Greenberg, Barbara Widick, Rosa Franklin, Rose Medical Center, Denver, CO; Bienvenido G. Yangco, Kalliope Chagaris, Infectious Disease Research Institute, Tampa, FL; Douglas J. Ward, Troy Thomas, Cheryl Stewart, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley, Dania Beadle, Princess Davenport, Lewis Katz School of Medicine at Temple University, Philadelphia, PA; Richard M. Novak, Andrea Wendrow, University of Illinois at Chicago, Chicago, IL; Benjamin Young, Mia Scott, Barbara Widick, Billie Thomas, APEX Family Medicine, Denver, CO.

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