Risk Factors and Incidence of Syphilis in HIV Outpatients (HOPS 1999-2015)

BY
ABDELHAMID GHANEM
M.B.CH.B University Of Sebha, 2008

THESIS

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Defense Committee:

Jack Zwanziger, Chair & Advisor
Richard Novak, Infectious Diseases
Maximo Brito, Infectious Diseases

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LIST OF ABBREVIATIONS

AIDS: Acquired Immunodeficiency Syndrome

CDC: Centers for Disease Control and Prevention

CI: Confidence Interval

HAART: Highly Active Antiretroviral Therapy

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HOPS: HIV Outpatients Study

HRH: High Risk Heterosexual

IQR: Interquartile Range

IDU: Injecting Drug Use

IVDU: Intravenous Drug Use

LP: Lumber Puncture

MSM: Men who have Sex with Men

RPR: Rapid Plasma Reagin

STIs: Sexually Transmitted Infections

VL: Viral Load

US: United States

SUMMARY

A cohort study to investigate the incidence, associated risk factors and trends for new and current cases of syphilis in Human Immunodeficiency Virus (HIV) infected patients who are enrolled to HIV Outpatients Study (HOPS) using descriptive, univarate and multivariate analysis. All the patients in the HOPS database over the past 15 years were included in the analysis.

Socio-demographic variables were age, sex at birth, race/ethnicity, HIV acquisition risk group, heterosexual males and females, males and females who injecting drug use (IDU) and other, employment at consent and health insurance coverage information were included in the study. We studied 6888 HIV-infected participants, among whom 641 had one or more new syphilis diagnoses during a median follow-up of 5.2 years {interquartile ranges (IQRs): 2.0 - 10.8}.

We found that high-risk groups (young men who have sex with men, non-Hispanic ethnicity, being employed and having private insurance coverage) had a higher rate of syphilis in HOPS. Future studies that follow HOPS patients for longer period of time are needed to determine whether these results can be replicated.

I. GENERAL BACKGROUND

A. Rationale and Background

The incidence of syphilis has been increasing in the United States (US), especially among men who have sex with men (MSM) for last decade in the US[3-4]. It may be more common place among HIV-infected MSM, an indicator of unprotected sexual contact and associated with incident HIV infection[6-8]. Annual screening for syphilis among HIV-infected persons is the standard of care, but several studies suggest more frequent testing is both cost effective and more efficient at identifying infections[9-11]. Would more frequent screening in a targeted subgroup that is particularly at risk identify more cases? Based on centers for disease control and prevention (CDC) sexually transmitted infections (STIs) guidelines annual screening is recommended for sexually active MSM and every 3 to 6 months for those who are at high-risk[2].

One study of prophylactic long-term antibiotics suggests this may be an effective approach to reducing the risk of syphilis[10]. If either approaches are to be implemented, identifying and characterizing those at greatest risk for incident new and recurrent syphilis may lead to more targeted management and prevention. Syphilis, either new or recurrent incident cases may be a marker of poor adherence to therapy and may identify individuals more likely to transmit their HIV infections[13-16]. Other studies suggest that longer duration of HIV treatment is associated with a greater risk of incident syphilis[17]. Poor control of HIV may also be associated with higher treatment failures for syphilis, although this is controversial[18-20].

Whether syphilis impacts control of HIV infection is less clear[22-23]. Understanding the current risk behaviors associated with new incident and recurrent cases of syphilis may better define who

should be screened and at what frequency. While the current STI treatment guidelines recommend a number of therapeutic approaches for syphilis, only penicillin therapy has been proven to be effective in RCTs[24-29]. The intensity of penicillin therapy is also controversial among clinicians[30-33]. A comparison of outcomes for treated syphilis cases would be informative.

When if ever is a lumber puncture (LP) a necessary part of syphilis management in asymptomatic HIV-infected patients? There is a wealth of conflicting literature on this subject[34-36]. Does syphilis ever relapse in HIV patients, or are these so-called relapses actually recurrent infections? Understanding if there are any predictors of recurrent infection and whether immunologic status can be a marker of recurrence may shed light on this.

B. Syphilis

Syphilis is a genital ulcerative disease caused by the bacterium *Treponema Pallidum*, is associated with significant complications if left untreated and can facilitate the transmission and acquisition of HIV infection[1]. According to a CDC report, in 2014, a total of 19,999 cases of syphilis were reported in the United States, yielding a rate of 6.3 cases per 100,000 population. This rate represents a 15% increase compared with 2013 (5.5 cases per 100,000 population), and a 40% increase compared with 2010 (4.5 cases per 100,000 population)[2]. In addition, 61% were MSM. About 798 cases of syphilis were reported in Illinois and it was ranked 9 among 50 states with a rate of 6.2 cases per 100,000 population compared to the U.S. rate of 5.5[2].

The rate of reported syphilis cases among men was much higher than the rate among women and men account for a large majority (90.8%) of syphilis cases in which the gender is known. The

MSM's continued to account for the majority of syphilis cases in 2014. The CDC reported that syphilis cases reached their lowest prevalence in 2000 and 2001, but has increased almost every year since then. This increase was largely attributable to an increase among men, and in particular among MSM. However, during 2013–2014, rates increased among both men and women in every region of the country, although MSM continued to account for the majority of syphilis cases in 2014. Nationally, the highest rates syphilis in 2014 were observed among men aged 20–24 years and 25–29 years and among black men[2].

C. HIV Out-patient Study (HOPS)

HOPS is an ongoing prospective observational cohort study, that was initiated in 1993 by the US Centers for Disease Control and Prevention (CDC), and is currently expected to continue collecting and analyzing longitudinal data on HIV infected outpatients. It is the longest running and only remaining US government sponsored multi-site prospective cohort of a diverse spectrum of people living with HIV infection and receiving routine clinical care in the United States. Study sites are 12 clinics (7 university clinics, 3 public clinics, and 2 private clinics) in 10 US cities that provide care for HIV infected patients. These include, Tampa, FL; Washington, DC; Denver, CO (three sites); Chicago, IL (two sites); Stonybrook, NY; and Philadelphia, PA. All HOPS clinicians have extensive experience treating HIV infected people

II. OBJECTIVE AND HYPOTHESES OF STUDY

A. Primary Objectives

The primary objectives of this study were firstly to estimate the incidence of first and subsequent syphilis diagnoses among HIV-infected patients in the HOPS and to identify risk factors for new incident syphilis cases among HIV-infected patients in the HOPS. As we had full access to syphilis test results and treatment regimens, we hypothesize that rates of syphilis would be elevated in MSM compared with other risk groups, and will also be higher among persons who are younger and of black race/ethnicity. Secondly, to identify the trends in new syphilis cases over time in the HOPS during 1999-2015 and associated risk factors "age, race, gender, risk behavior, insurance coverage, substance use, co-morbidities including co-infections such as hepatitis, other STIs, control of HIV infection {CD4, Viral loads (VL)}", we hypothesize that overall the rates of syphilis may or may not remain level, but that they may increase over time in certain subgroups; for example, young MSM will show higher rates of new and recurrent infections.

- Number/percentage of patients enrolled in the HOPS with a history of syphilis; we expect higher prevalence among MSM group compared with other risk groups.
- Treatment outcomes in terms of cured vs relapsed; we expect failure of therapy to be rare, but associated with poorly controlled HIV infection
- Predictors of cure: symptoms, Rapid Plasma Reagin (RPR) titer, choice of treatment, CD4 count
- Syphilis and response to HIV treatment; we expect to see no effect of syphilis on response to HIV therapy, but may be a marker of non-adherence

- Association of testing frequency and new cases, may not be able to eliminate selection bias, but expect there to be an association between testing frequency and diagnosis
- Association if any of prevalent syphilis and Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) as well as incident syphilis and incident HCV, our expectation, there will be higher prevalence among HIV patients
- Incidence of syphilis among HOPS participants concurrently on antibiotic prophylaxis of other infections compared to those not on antibiotics.
- Usefulness of LP in selecting treatment; we expect LP to contribute only rarely to a diagnosis of neurosyphilis, and only in persons with symptoms consistent with neurosyphilis

B. <u>Secondary Objectives</u>

The secondary objectives of this study were to evaluate the use of laboratory-based definitions for their potential in monitoring rates of new syphilis diagnoses in terms of the following:

1. Treatment outcomes: cured vs relapsed
2. Usefulness of LP in selecting treatment
3. Syphilis and response to HIV treatment

III. METHODS

A. Data Source

The HIV Outpatient Study (HOPS) is an ongoing, prospective, observational cohort study of HIV-infected adults (age 18 and older) seen at HIV specialty clinics since 1993. As an open cohort, HOPS has continued enrollments of new patients, as some patients transfer to care at other locations, are lost to follow-up, or die.

B. Ethical Considerations

Participants signed an informed consent, and the HOPS protocol was reviewed and approved by the institutional review boards of the CDC (Atlanta, GA) and each local site.

C. Study Design

It is a multi-site prospective cohort of a diverse spectrum of people living with HIV infection and receiving routine clinical care in the United States.

D. Analysis

- Descriptive statistics:
    - To describe the socio-demographic and HIV-related characteristics of patients included in the study stratified by HIV transmission category as well as by whether or not they ultimately became infected with incident syphilis during follow-up.
    - Socio-demographic variables were age (including participants aged 18 and older), sex at birth, race/ethnicity (including non-Hispanic black, non-Hispanic white, Hispanic, and persons of other race/ethnicity), HIV acquisition risk group (including men who have sex with men [MSM], heterosexual males and females, males and females who inject drugs [IDU] and other), employment at consent (including full

time, part time, unemployed, retired and other) and health insurance coverage (including private, public, self-pay and other).

- Characteristics of patients at the time of incident syphilis—among those who had incident syphilis at least once during follow-up, look at clinical and HIV-related variables included year of HIV diagnosis, history of Acquired Immunodeficiency Syndrome (AIDS) diagnosis by immunologic or clinical criteria, antiretroviral (ARV) exposure status, and most recent CD4 count within last 6 months, most recent viral load and other concurrent STDs (including gonorrhea, chlamydia, HBV, and HCV).

- Univariate analyses:
  - Incident syphilis screening rates and incident syphilis rates overall and stratified by HIV transmission group
    - Adjusted for insurance, HCV, HBV, use of antibiotic prophylaxis and site
  - Trends in incident syphilis rates by year
  - Treatment outcomes—among patients with incident syphilis and who were treated within 90 days of diagnosis
- Multivariable analyses.

E. Study Population

All the patients in the HOPS database with a diagnosis of HIV over the past 15 years were included in the analysis. The 12 clinics participating in HOPS included in this analysis comprise public, private and university-based sites and are located in different US cities.

F. Outcome

- Primary:

1. Incident cases of syphilis including prior cases, new cases and recurrent new cases; risks for prior, new and recurrent cases
2. Trends in new syphilis cases over time in the HOPS during 1999-2015 and associated risk factors "age, race, gender, risk behavior, insurance (public, private, other/unknown), substance use, co-morbidities including co-infections such as hepatitis, other STIs, control of HIV infection (CD4, VL)"

- Secondary:
  1. Number of treatment failures (less than 4 fold decline in titer after treatment).
  2. Association if any with testing frequency and diagnosis

G. Observation time

- Start of observation time: January 1st, 1999
- End of observation time: June 30th, 2015

H. Data Collection

Information was abstracted from medical records for each visit, entered electronically by trained staff, compiled centrally, and reviewed and edited before being analyzed. Abstracted information included demographic characteristics; risk factors for HIV infection, symptoms, diagnosed diseases (both definitive and presumptive), prescribed medications including dose and duration, laboratory values (including CD4 counts and plasma HIV-1 RNA viral loads), mortality, and hospitalization records (primarily from discharge summaries).

Summaries of descriptive data were performed using SAS version 9.3: we report un-weighted frequencies and weighted percentages with 95% confidence intervals (CIs) to characterize all self-

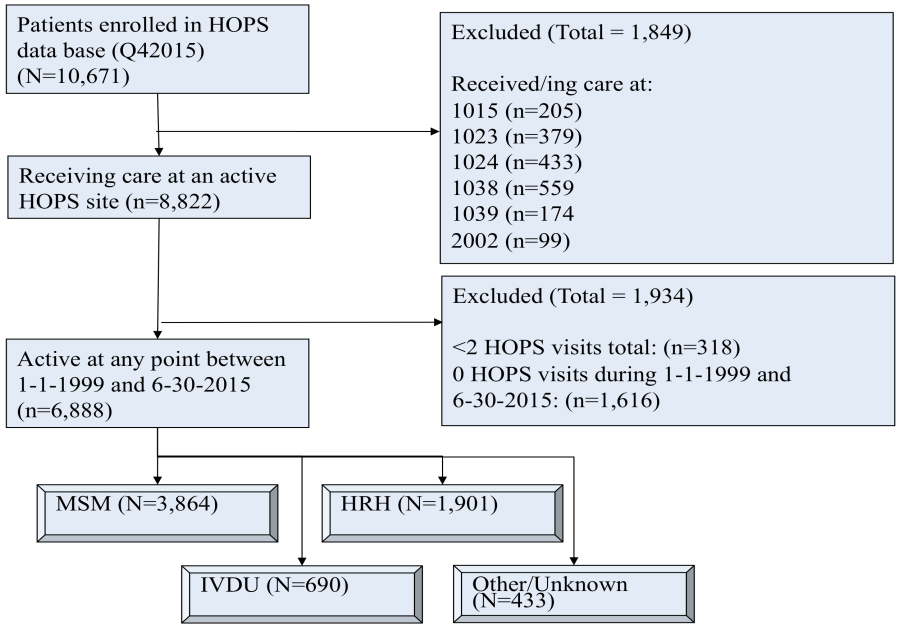
reported and clinical characteristics; the weighted estimates are designed to represent the population of adults with HIV infection receiving medical care in the US from January 1st, 1999 to mid 2015. For continuous variables, we report medians and interquartile ranges (IQRs).

IV. RESULTS

A. Prospective Analysis

This analysis included 10,671 participants enrolled in the HOPS database who were diagnosed with HIV infection. We excluded 3783 for the following reasons: 1849 patients were excluded because they received care at inactive sites, 318 had <2 HOPS total visits and 1,616 had 0 HOPS visits between January 1st, 1999, and June 30th, 2015. (Figure 1)

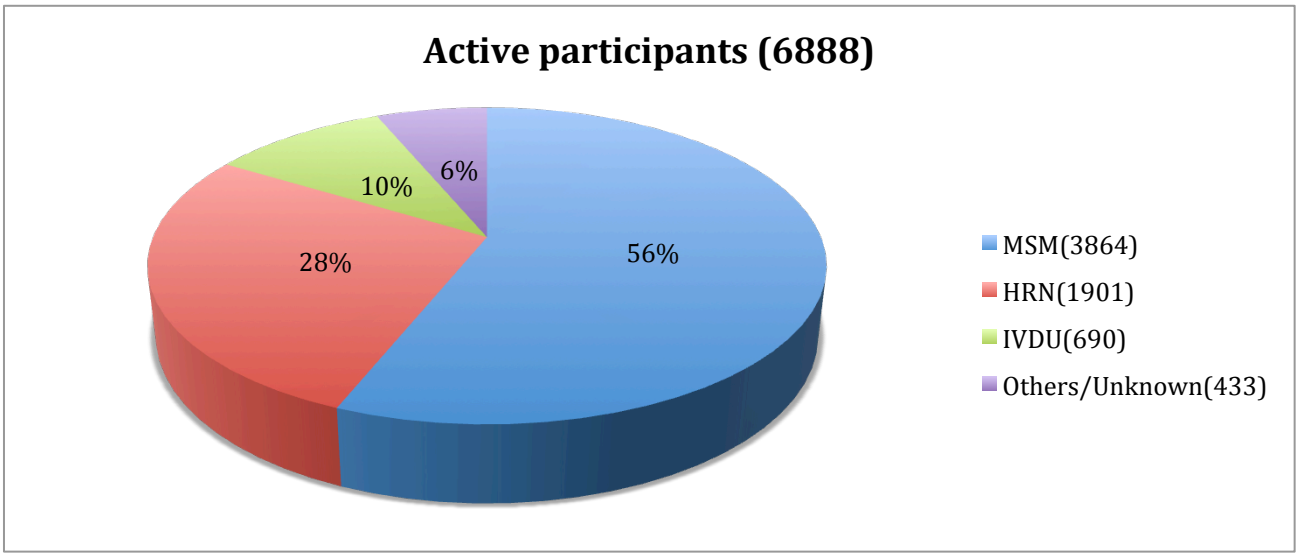
Figure 1: Eligible and excluded participants



Among the 6,888 eligible participants included in this analysis who were active at some point between January 1st, 1999 and June 30th, 2015 were alive at the end of the study period, most were

MSM 3,864 (56%) and heterosexual 1,901 (28%), but HOPS had fewer participants with Intravenous Drug Use (IVDU) as a risk factor for their HIV acquisition 690 (10%). (Figure 2)

Figure 2: Percentages of eligible participants



B. Socio-demographic, Behavioral and Clinical Characteristics of HOPS

We included 6888 HOPS participants in the primary analysis. After the HOPS database was weighted, we identified a lower percentage of HOPS participants with ages above 50 years (N=919, 13.3%) and 18-30 years (N=1160, 16.8%), and a higher percentage aged 31-40 years (N=2605, 37.8%) and 41-50 years (N=2204,32%)(Figure 3). A higher percentage of HOPS participants were male (N=5375,78%)(Figure 4). Moreover, the majority of HOPS participants were identified as non-Hispanic (N=5788, 84%), a higher percentage were non-Hispanic white

(49.3%) and non-Hispanic black (34.7%), a lower percentage were Hispanic (N=847,12.3%) and unknown ethnicity (N=253, 3.7%)(Figure 5). In addition, a higher percentage of participants were full time employees (N=3121, 45.3%) comparing to unemployed (N=2,597, 37.7%)(Figure 6). Also, a higher percentage of HOPS participants had private insurance coverage (N=3,596, 52.2%) compared to those with public insurance coverage (N=2,624, 38.1%)(Figure 7). Clinically, slightly over half of HOPS participants were diagnosed before 2002 (N=3,884, 56.4%), and almost half of them had a most recent CD4 count ≥ 350 cells/mm^3 (N=3276, 47.6%) and/or had AIDS (N=3,348, 48.6%). All results were significant with p-value of <0.001. Further demographic and behavioral factors for HOPS participants are described in Table 1.

Figure 3: Eligible participants stratified by age

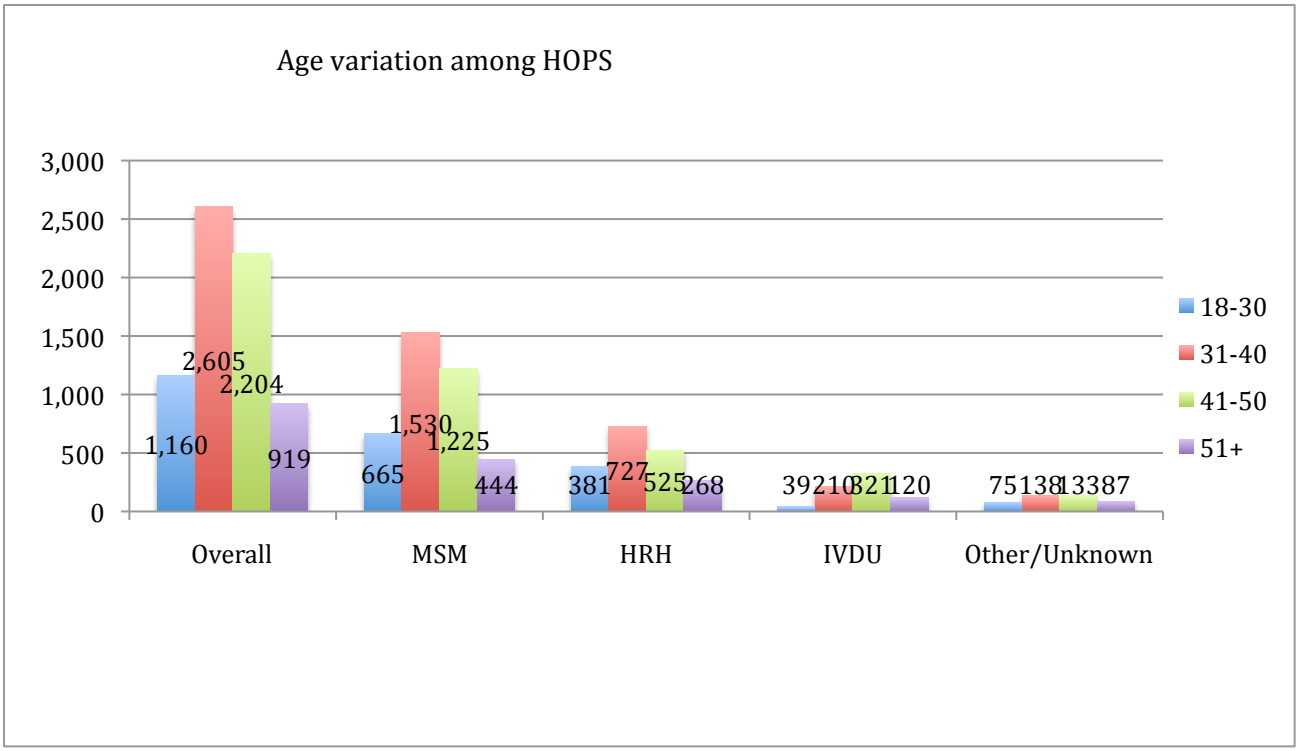


Figure 4: Eligible participants stratified by gender

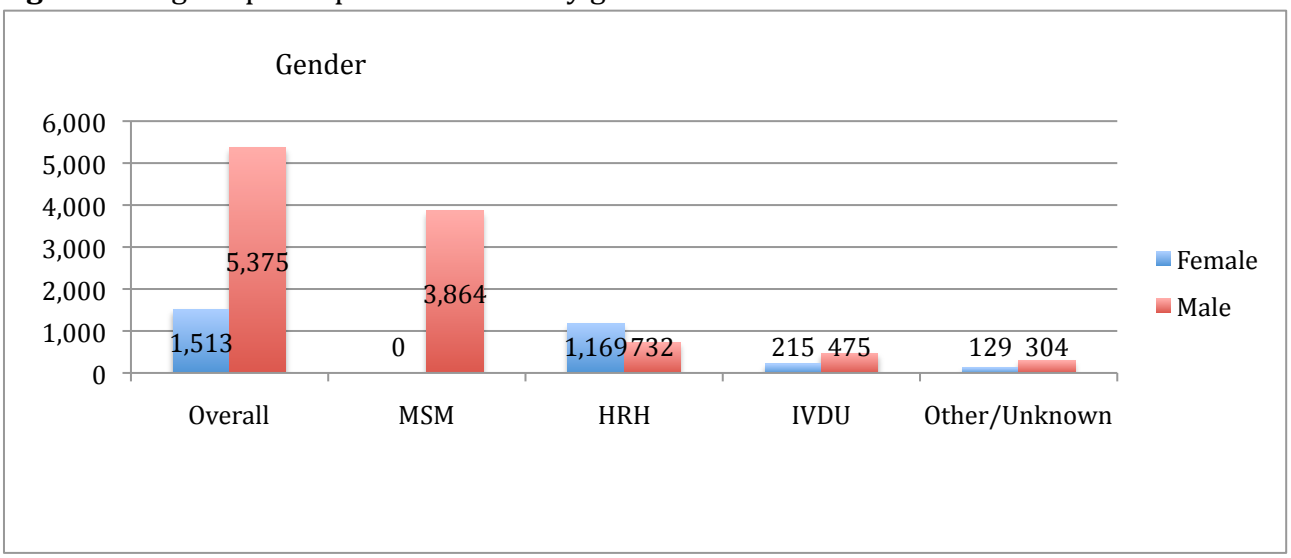


Figure 5: Eligible participants stratified by ethnicity

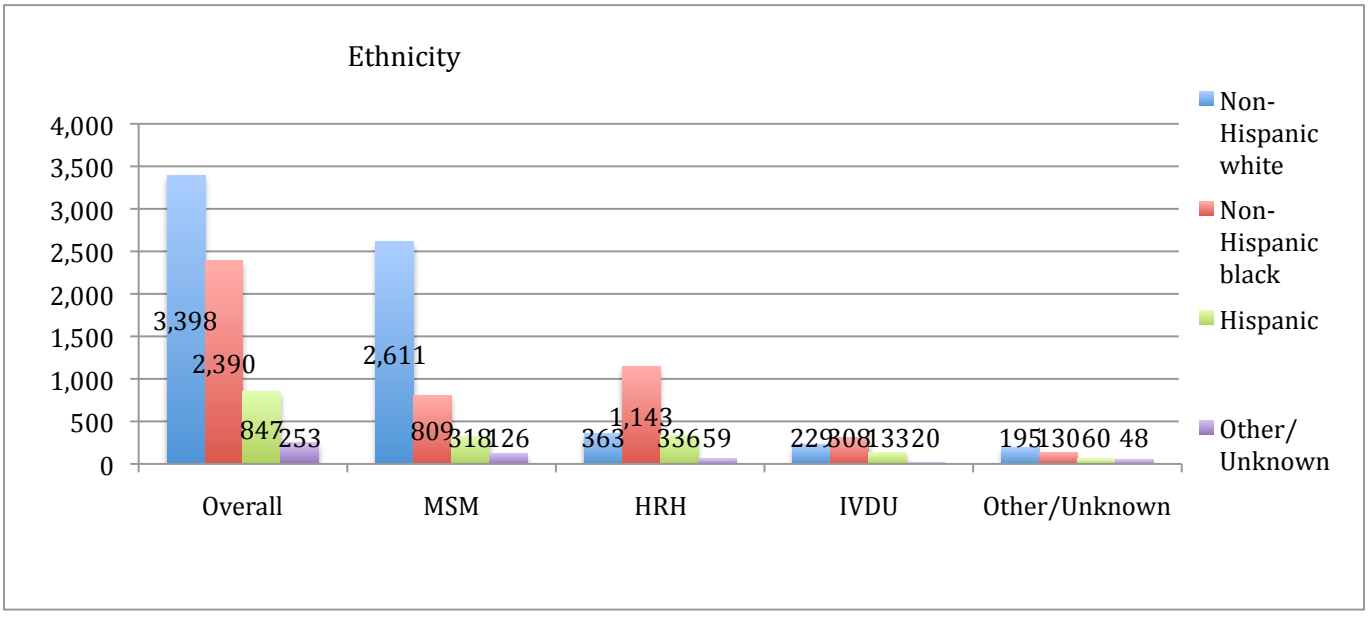


Figure 6: Eligible participants stratified by employment status

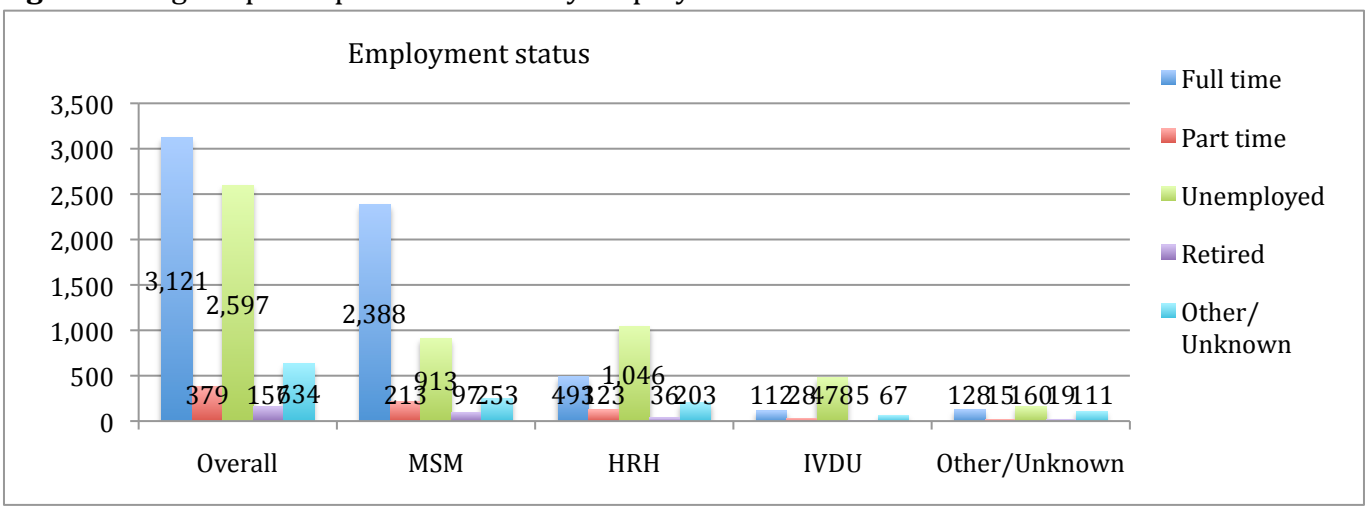


Figure 7: Eligible participants stratified by insurance coverage

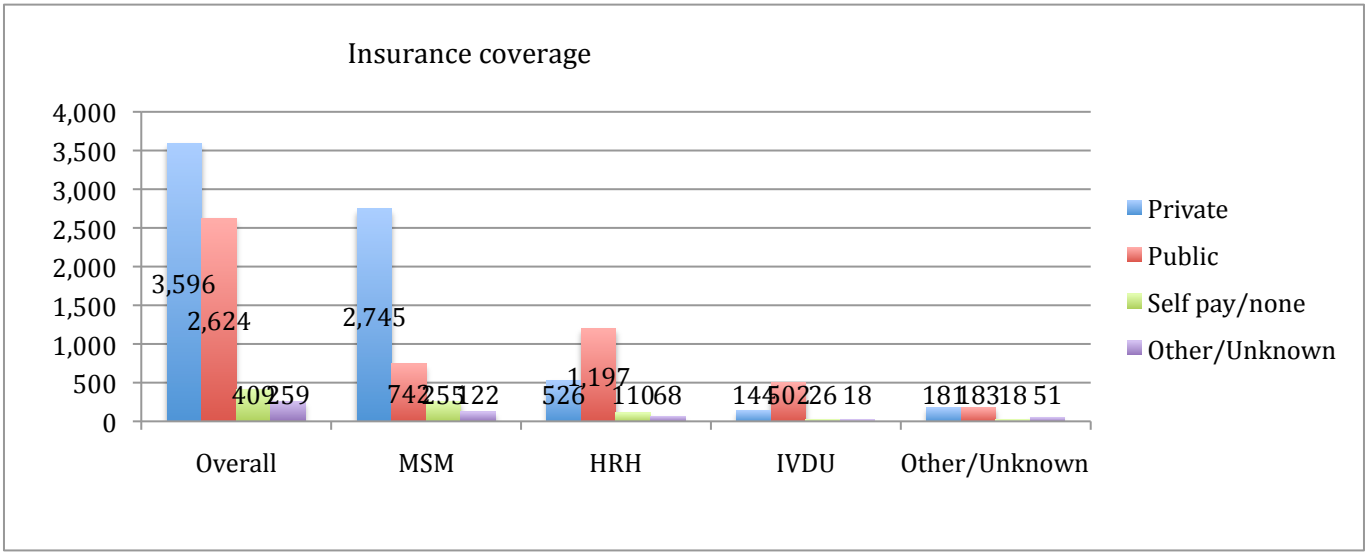


TABLE I

PROFILE OF CHARACTERISTICS: ALL VARIABLES ARE TAKEN AT THE INDEX DATE OF ACTIVE PATIENTS IN THE HOPS FROM 1-1-1999 TO 6-30-2015 (N=6,888)

Characteristics at index date[a] (No., % or median, IQR)	**HIV risk category**										**P value[c]**
	Overall		**MSM**		**HRH**		**IVDU**		**Other/ Unknown**		
	(n=6,888)		**(n=3,864)**		**(n=1,901)**		**(n=690)**		**(n=433)**		
Age at index date (years)	N	%	N	%	N	%	N	%	n	%	<0.001
18-30	1,160	(16.8)	665	(17.2)	381	(20.0)	39	(5.7)	75	(17.3)	
31-40	2,605	(37.8)	1,530	(39.6)	727	(38.2)	210	(30.4)	138	(31.9)	
41-50	2,204	(32.0)	1,225	(31.7)	525	(27.6)	321	(46.5)	133	(30.7)	
51+	919	(13.3)	444	(11.5)	268	(14.1)	120	(17.4)	87	(20.1)	
Sex at birth, n (%)											<0.001
Female	1,513	(22.0)	0	(0.0)	1,169	(61.5)	215	(31.2)	129	(29.8)	
Male	5,375	(78.0)	3,864	(100.0)	732	(38.5)	475	(68.8)	304	(70.2)	
Race/ethnicity, n (%)											<0.001
Non-Hispanic white	3,398	(49.3)	2,611	(67.6)	363	(19.1)	229	(33.2)	195	(45.0)	
Non-Hispanic black	2,390	(34.7)	809	(20.9)	1,143	(60.1)	308	(44.6)	130	(30.0)	
Hispanic	847	(12.3)	318	(8.2)	336	(17.7)	133	(19.3)	60	(13.9)	
Other/Unknown	253	(3.7)	126	(3.3)	59	(3.1)	20	(2.9)	48	(11.1)	
Employment at consent, n (%)											<0.001
Full time	3,121	(45.3)	2,388	(61.8)	493	(25.9)	112	(16.2)	128	(29.6)	
Part time	379	(5.5)	213	(5.5)	123	(6.5)	28	(4.1)	15	(3.5)	
Unemployed	2,597	(37.7)	913	(23.6)	1,046	(55.0)	478	(69.3)	160	(37.0)	
Retired	157	(2.3)	97	(2.5)	36	(1.9)	5	(0.7)	19	(4.4)	
Other/Unknown	634	(9.2)	253	(6.5)	203	(10.7)	67	(9.7)	111	(25.6)	
Insurance, n (%)											<0.001
Private	3,596	(52.2)	2,745	(71.0)	526	(27.7)	144	(20.9)	181	(41.8)	
Public	2,624	(38.1)	742	(19.2)	1,197	(63.0)	502	(72.8)	183	(42.3)	
Self pay/none	409	(5.9)	255	(6.6)	110	(5.8)	26	(3.8)	18	(4.2)	
Other/Unknown	259	(3.8)	122	(3.2)	68	(3.6)	18	(2.6)	51	(11.8)	
AIDS status, n (%)	3,348	(48.6)	1,756	(45.4)	957	(50.3)	409	(59.3)	226	(52.2)	<0.001
BMI (kg/m^2), n (%)											<0.001
< 18.5	218	(3.2)	90	(2.3)	85	(4.5)	26	(3.8)	17	(3.9)	
18.5-24.9	3,245	(47.1)	2,021	(52.3)	740	(38.9)	312	(45.2)	172	(39.7)	
25-29.9	2,058	(29.9)	1,243	(32.2)	487	(25.6)	198	(28.7)	130	(30.0)	
≥ 30	1,039	(15.1)	352	(9.1)	504	(26.5)	104	(15.1)	79	(18.2)	
Unknown	328	(4.8)	158	(4.1)	85	(4.5)	50	(7.2)	35	(8.1)	
Chronic HBV Infection, n (%)	398	(5.8)	224	(5.8)	72	(3.8)	77	(11.2)	25	(5.8)	<0.001
Chronic HCV Infection, n (%)	876	(12.7)	162	(4.2)	221	(11.6)	422	(61.2)	71	(16.4)	<0.001
Calendar period of index date, n (%)											<0.001
1999-2002	3,884	(56.4)	2,198	(56.9)	975	(51.3)	497	(72.0)	214	(49.4)	
2003-2006	1,326	(19.3)	738	(19.1)	374	(19.7)	111	(16.1)	103	(23.8)	
2007-2010	1,021	(14.8)	571	(14.8)	308	(16.2)	55	(8.0)	87	(20.1)	
2011-2015	657	(9.5)	357	(9.2)	244	(12.8)	27	(3.9)	29	(6.7)	

TABLE I

PROFILE OF CHARACTERISTICS: ALL VARIABLES ARE TAKEN AT THE INDEX DATE OF ACTIVE PATIENTS IN THE HOPS FROM 1-1-1999 TO 6-30-2015 (N=6,888) (Continued)

Characteristics at index date[a] (No., % or median, IQR)	**HIV risk category**										**P value[c]**
	Overall		**MSM**		**HRH**		**IVDU**		**Other/ Unknown**		
	(n=6,888)		**(n=3,864)**		**(n=1,901)**		**(n=690)**		**(n=433)**		
CD4 at index date[b]	N	%	N	%	N	%	N	%	N	%	<0.001
< 50	588	(8.5)	239	(6.2)	240	(12.6)	55	(8.0)	54	(12.5)	
50-199	1,016	(14.8)	500	(12.9)	290	(15.3)	153	(22.2)	73	(16.9)	
200-349	1,272	(18.5)	725	(18.8)	360	(18.9)	112	(16.2)	75	(17.3)	
350-499	1,182	(17.2)	729	(18.9)	270	(14.2)	104	(15.1)	79	(18.2)	
500+	2,094	(30.4)	1,358	(35.1)	482	(25.4)	160	(23.2)	94	(21.7)	
Unknown	736	(10.7)	313	(8.1)	259	(13.6)	106	(15.4)	58	(13.4)	
Median CD4 at index date (IQR)	6,152	371 (191, 581)	3,551	408 (229, 607)	1,642	318 (139, 545)	584	308 (141, 531)	375	324 (116, 503)	<0.001
Median years HIV+ (IQR)	6,888	4.5 (0.5, 9.4)	3,864	4.8 (0.6, 10.0)	1,901	2.7 (0.2, 6.5)	690	7.0 (3.0, 10.5)	433	5.6 (1.2, 10.5)	<0.001
Median years AIDS defined (IQR)	3,348	2.3 (0.2, 5.0)	1,756	2.9 (0.4, 5.5)	957	0.8 (0.1, 3.4)	409	3.0 (0.6, 5.4)	226	2.4 (0.1, 5.2)	<0.001
Antibiotic prophylaxis[d]	767	(11.1)	435	(11.3)	166	(8.7)	116	(16.8)	50	(11.5)	<0.001
Syphilis prior to index date, n (%)	34	(0.5)	26	(0.7)	4	(0.2)	4	(0.6)	0	(0.0)	0.040
Site, n (%)											<0.001
IDRI	543	(7.9)	229	(5.9)	211	(11.1)	49	(7.1)	54	(12.5)	
Dupont	913	(13.3)	877	(22.7)	24	(1.3)	4	(0.6)	8	(1.8)	
DIDC (1021 & 1025)	1,146	(16.6)	955	(24.7)	87	(4.6)	52	(7.5)	52	(12.0)	
NU	1,295	(18.8)	776	(20.1)	266	(14.0)	82	(11.9)	171	(39.5)	
Stonybrook	620	(9.0)	201	(5.2)	245	(12.9)	145	(21.0)	29	(6.7)	
Temple	1,477	(21.4)	278	(7.2)	874	(46.0)	267	(38.7)	58	(13.4)	
National Jewish	328	(4.8)	260	(6.7)	20	(1.1)	12	(1.7)	36	(8.3)	
APEX	78	(1.1)	66	(1.7)	9	(0.5)	3	(0.4)	0	(0.0)	
UIC	488	(7.1)	222	(5.7)	165	(8.7)	76	(11.0)	25	(5.8)	

[a] Index date is the later of first HOPS visit or 01-01-1999.

[b] Closest value to index from values documented 6 months prior thru 3 months post index date.

[c] Kruskall-Wallis tests for continuous variables, chi-square test for categorical variables

[d] Antibiotic prophylaxis includes azithromycin and/or bactrim given as prophylaxis prior to the index date

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HRH, heterosexuals; IQR, interquartile range; IVDU, intravenous drug users; MSM, males who have sex with males range; IVDU, intravenous drug users; MSM, males who have sex with males.

C. Incidence of syphilis in the HOPS

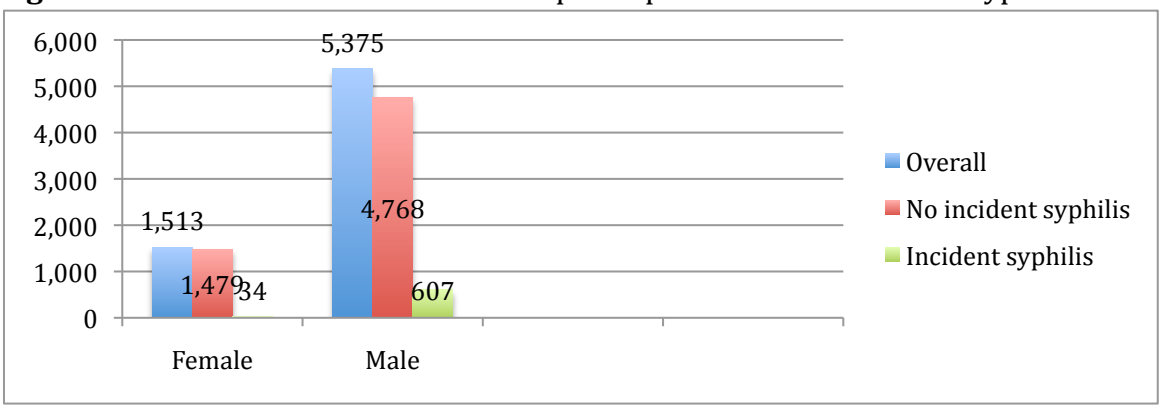
A total of 6888 HIV-infected participants with more than one outpatient encounter were included in this prospective observational cohort study from January 1st, 1999 through June 30th, 2015. Of these, 641 (9.3%) HOPS participants were diagnosed with Syphilis. During the observational period, there were 799 cases of incident syphilis among 641 patients out of the total 6,888 participants included. Of these 641 participants, 528 patients had 1 case of incident syphilis, 81 had 2 infections, 22 had 3 infections, 8 had 4 infections, 1 had 5 infections and 1 had 6 infections. The 641 patients eligible for the cohort analyses contributed 45,185 person-years of follow-up time during the study period, with a median of 5.2 [IQR, 2.0–10.8].

Risk factors for incidence of syphilis were younger age, male gender, non-Hispanic ethnicity, history of hepatitis, and gonorrhea. Using the highly active antiretroviral therapy (HAART) was not associated with disease. HIV specific factors include CD4 cell count, Viral RNA level, and AIDS defining illnesses weren't associated with incident of syphilis. Employment at the time of consent, insurance (public vs. private), AIDS status, BMI, chronic HBV infection, chronic HCV infection, calendar period of index date, CD4, antibiotic prophylaxis, prior history of syphilis and sites were included in the analysis as well. There were significant differences between those with syphilis and without syphilis in age, gender, ethnicity, employment at consent, insurance, AIDS status, chronic HBV infection, chronic HCV infection, calendar period of index date and sites. (Table 2)

1. Gender Effect

We examined the gender relationship to the Syphilis cases. Of 641 participants, 607 (94.7%) participants were male (p value <0.001). (Figure 8)

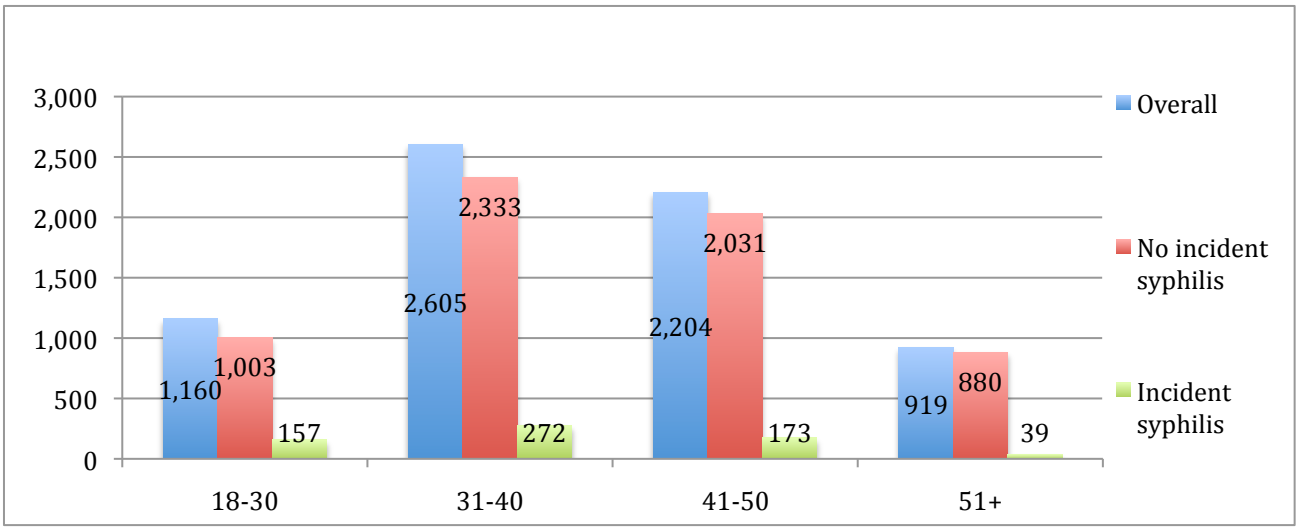
Figure 8: Gender variations in the HOPS participants with and without syphilis



2. Age Variation

Of 641 participants, 157 (24.5%) were aged between18-30, 272 (42.4%) were aged between 31-40, 173 (27.0%) were between 41-50 and 39 (6.1%) were above 50 with p value <0.001. (Figure 9)

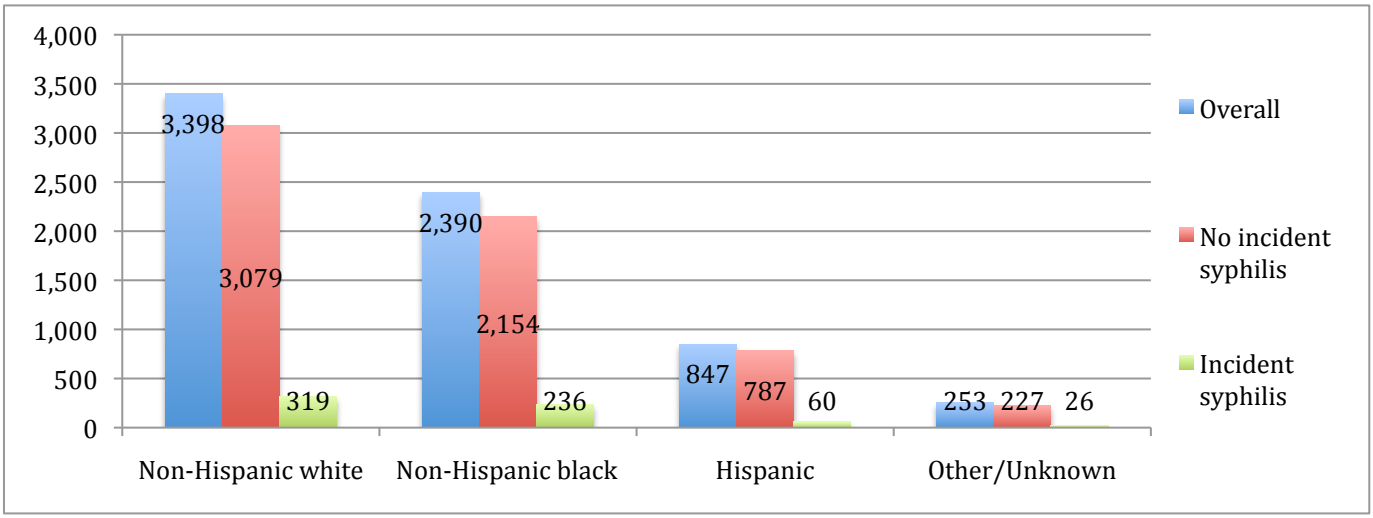
Figure 9: Age variation in the HOPS participants



3. Racial differences

We found that there were racial differences in the number of syphilis cases in the HOPS: of 641 participants, 319 (49.8%) were non-Hispanic white, 236 (36.8%) were non-Hispanic black, 60 (9.4%) were Hispanic and 26 (4.1%) were unknown. We found that the incident cases of syphilis among HOPS was not significantly related to race. It was high among non-Hispanics at 555 (86.6%) comparing to 60 (9.4%) Hispanics with p value 0.10. (Figure 10)

Figure 10: Racial differences in syphilis events



4. Occupational and Insurance effect

Of 641 participants, 375 (58.5%) were employed full time and 165 (25.7%) were unemployed; 407 (63.5%) had private insurance coverage, while 141 (22%) had public insurance ($p<0.001$). (Figures 11-12)

Figure 11: Occupational variation in the HOPS participants

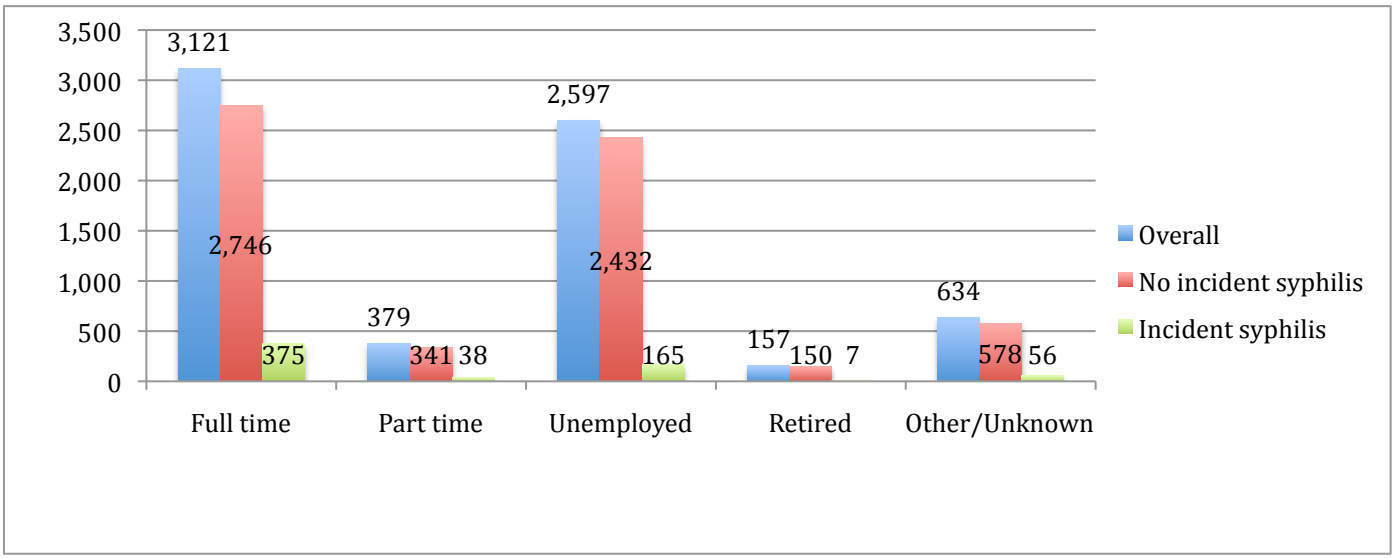
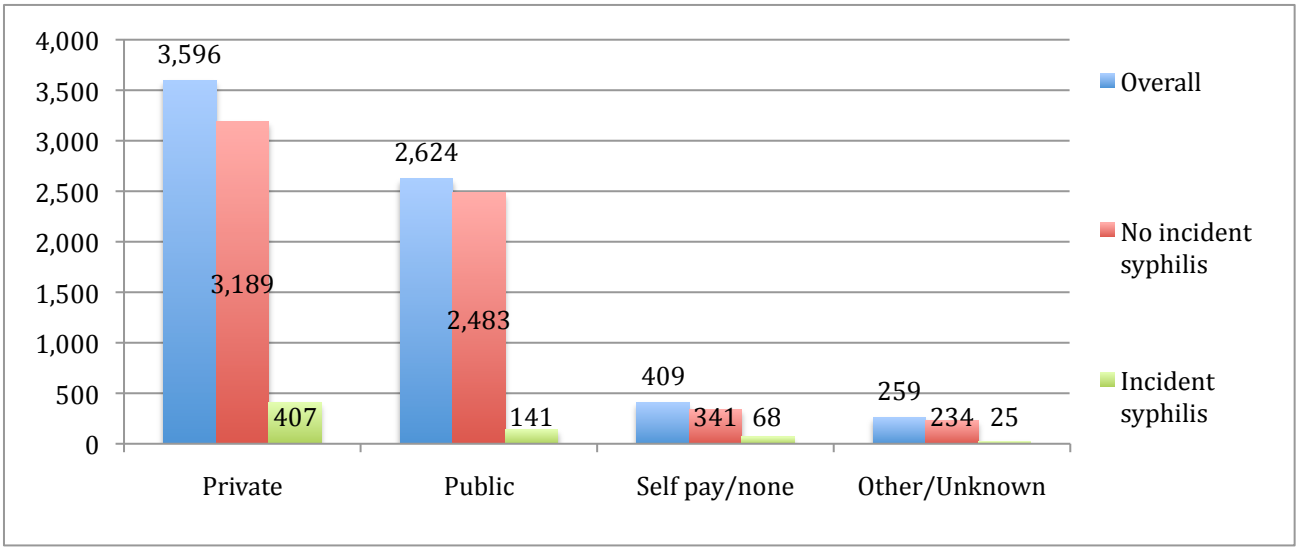


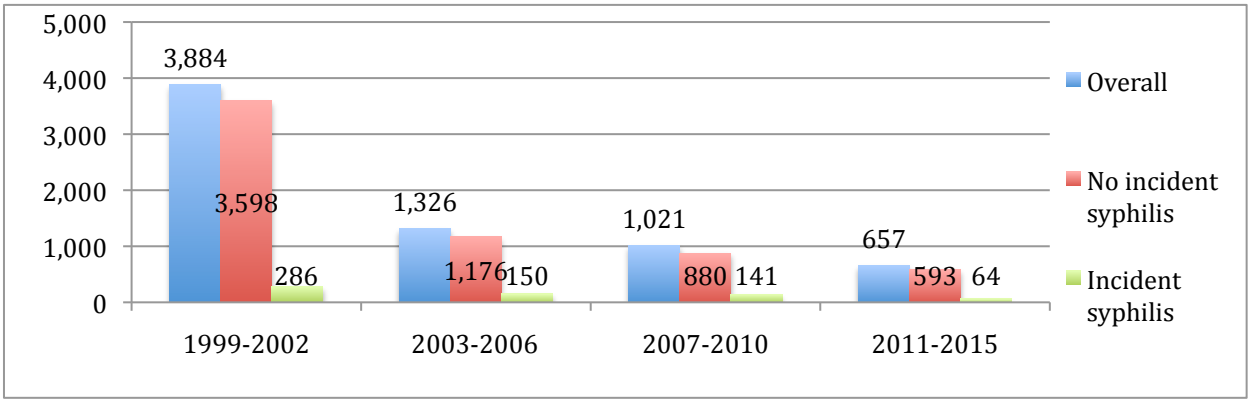
Figure 12: Differences of insurance in the HOPS participants



5. Calendar Period

Of 641 participants, 286 (44.6%) were diagnosed during 1999-2002. Interestingly, the total number of cases per period was 150 (23.4%) during the period of 2003-2006 and remained similar during 2007-2010 at 141 (22%)(Figure 13). This simply reflects fewer patients were followed in the HOPS in the more recent intervals.

Figure 13: Variation of syphilis cases stratified by the diagnosed year



6. Sites

Of 641 participants, the highest number of syphilis cases were at Dupont at 151 (23.6%) and NU at 118 (18.4%), followed by Temple at 102 (15.9%), DIDC (1021 & 1025) 97 (15.1%) and finally by UIC at 82 (12.8%) (Figure 14)

Figure 14: Variation of syphilis cases in different HOPS sites

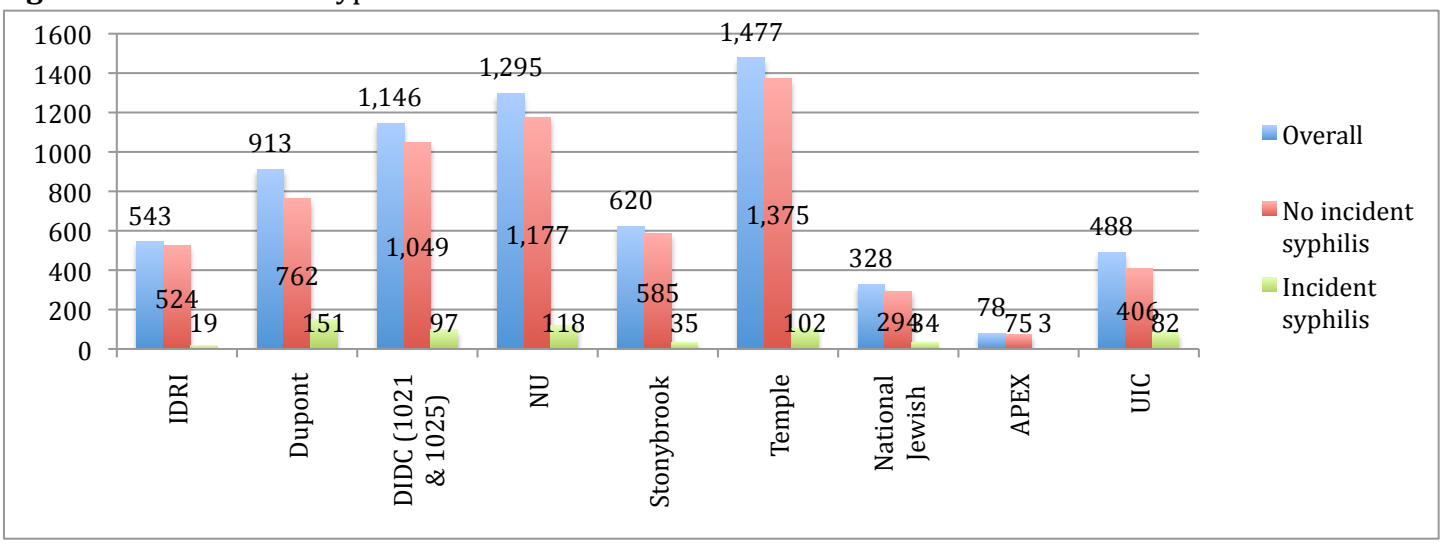


TABLE II

COMPARING CHARACTERISTICS OF PARTICIPANTS WITH AND WITHOUT INCIDENT SYPHILIS

Characteristics at index date* (No., % or median, IQR)	**Incident Syphilis**						**p value‡**
	Overall		**No incident syphilis**		**Incident Syphilis**		
	(n=6,888)		**(n=6,247)**		**(n=641)**		
Age at index date (years),	N	%	N	%	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)	
Employment at consent, n (%)							<0.001
Full time	3,121	(45.3)	2,746	(44.0)	375	(58.5)	
Part time	379	(5.5)	341	(5.5)	38	(5.9)	
Unemployed	2,597	(37.7)	2,432	(38.9)	165	(25.7)	
Retired	157	(2.3)	150	(2.4)	7	(1.1)	
Other/Unknown	634	(9.2)	578	(9.3)	56	(8.7)	
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
BMI (kg/m^2), n (%)							<0.001
< 18.5	218	(3.2)	203	(3.2)	15	(2.3)	
18.5-24.9	3,245	(47.1)	2,904	(46.5)	341	(53.2)	
25-29.9	2,058	(29.9)	1,850	(29.6)	208	(32.4)	
≥ 30	1,039	(15.1)	977	(15.6)	62	(9.7)	
Unknown	328	(4.8)	313	(5.0)	15	(2.3)	
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)	

TABLE II

COMPARING CHARACTERISTICS OF PARTICIPANTS WITH AND WITHOUT INCIDENT SYPHILIS (Continued)

Characteristics at index date[a] (No., % or median, IQR)	**Incident Syphilis**						**p value[c]**
	Overall		**No incident syphilis**		**Incident Syphilis**		
	(n=6,888)		**(n=6,247)**		**(n=641)**		
CD4 at index date[b], n (%)	N	%	N	%	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)	
Median CD4 at index date (IQR)	6,152	371 (191, 581)	5,561	366 (185, 580)	591	411 (250, 587)	<0.001
Median years HIV+ (IQR)	6,888	4.5 (0.5, 9.4)	6,247	4.7 (0.6, 9.5)	641	2.3 (0.2, 6.7)	<0.001
Median years AIDS defined (IQR)	3,348	2.3 (0.2, 5.0)	3,093	2.4 (0.2, 5.1)	255	1.3 (0.04, 3.6)	<0.001
Antibiotic prophylaxis, n (%)[d]	767	(11.1)	727	(11.6)	40	(6.2)	<0.001
Syphilis prior to index date, n (%)	34	(0.5)	31	(0.5)	3	(0.5)	1.000
Site, n (%)							<0.001
IDRI	543	(7.9)	524	(8.4)	19	(3.0)	
Dupont	913	(13.3)	762	(12.2)	151	(23.6)	
DIDC (1021 & 1025)	1,146	(16.6)	1,049	(16.8)	97	(15.1)	
NU	1,295	(18.8)	1,177	(18.8)	118	(18.4)	
Stonybrook	620	(9.0)	585	(9.4)	35	(5.5)	
Temple	1,477	(21.4)	1,375	(22.0)	102	(15.9)	
National Jewish	328	(4.8)	294	(4.7)	34	(5.3)	
APEX	78	(1.1)	75	(1.2)	3	(0.5)	
UIC	488	(7.1)	406	(6.5)	82	(12.8)	

[a] Index date is the later of first HOPS visit or 01-01-1999.
[b] Closest value to index from values documented 6 months prior thru 3 months post index date.
[c] Kruskall-Wallis tests for continuous variables, chi-square test for categorical variables
[d] Antibiotic prophylaxis includes Azithromycin and/or Bactrim given as prophylaxis prior to the index date
Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HRH, heterosexuals; IQR, interquartile range; IVDU, intravenous drug users; MSM, males who have sex with males

By adjusting the high-risk group, we identified that of 641 participants 526 (82%) were MSM compared to 115 (18%) in other risk groups. Overall, the highest percentage of syphilis was associated with high CD4+ cell counts and low viral loads. Of 641 participants, 542 (65.3%) had their most recent CD4 cell count ≥ 350, and 383 (59.8%) had their most recent viral load test 0-199. Among MSM, the majority of participants had their most recent CD4 cell count over 200. The number of persons with chronic HCV was lower among MSM at 44 (8.4%) compared to other risk groups (30, 26.1%, p value <0.001). (Table 3). It is significant however that MSM with higher viral loads are also getting syphilis, suggesting they are having unsafe sex and risking HIV transmission.

TABLE III

COMPARING SYPHILIS PERCENTAGES OF MSM TO OTHER RISK GROUPS

			HIV risk category				p value[b]
	Overall (n=641)		MSM (n=526)		Other (n=115)		
CD4 closest to syphilis case[a], n (%)	n	%	n	%	n	%	0.008
<50	10	(1.6)	5	(1.0)	5	(4.3)	
50-199	63	(9.8)	47	(8.9)	16	(13.9)	
200-349	123	(19.2)	101	(19.2)	22	(19.1)	
350-499	154	(24.0)	126	(24.0)	28	(24.3)	
≥500	265	(41.3)	229	(43.5)	36	(31.3)	
Unknown	26	(4.1)	18	(3.4)	8	(7.0)	
Viral load closest to syphilis case*, n (%)							0.021
0-199	383	(59.8)	327	(62.2)	56	(48.7)	
200-999	55	(8.6)	38	(7.2)	17	(14.8)	
1,000-99,999	131	(20.4)	103	(19.6)	28	(24.3)	
≥100,000	35	(5.5)	30	(5.7)	5	(4.3)	
Unknown	37	(5.8)	28	(5.3)	9	(7.8)	
Gonorrhea prior to syphilis case, n (%)	77	(12.0)	70	(13.3)	7	(6.1)	0.031
Chlamydia prior to syphilis case, n (%)	53	(8.3)	44	(8.4)	9	(7.8)	0.85
Chronic HBV prior to syphilis case, n (%)	75	(11.7)	54	(10.3)	21	(18.3)	0.016
Chronic HCV prior to syphilis case, n (%)	74	(11.5)	44	(8.4)	30	(26.1)	<0.001

[a] Within 6 months prior and 1 month after syphilis case. For patients with multiple cases of incident syphilis, the earliest is taken.

[b] P-values are derived from chi-square tests and Fisher's exact tests

D. <u>Syphilis Incidence Rates Among Active HOPS Patients and associated risk factors</u>

During the study period, 799 syphilis events were reported over a total of 45,185 person-years (PYs) of follow-up time during the study period, resulting in an incidence rate of 1.8 per 100 P-Ys (95% confidence interval (CI): 1.65 -1.9) with P-value <0.001 (Table 4). However, in our analysis, MSM appeared to be positively associated with increased syphilis incidence at 2.6 per 100 P-Ys (95% CI: 2.4 - 2.75), compared with 0.7 (95% CI: 0.5 -0.8) in High Risk Heterosexual (HRH), 0.6 per 100 P-Ys (95% CI: 0.4 – 0.9) in IVDU and 0.9 (95% CI: 0.6-1.3) in unknown risk group. This was significantly higher (P = <0.001) (Figure 16).

In the multivariable analysis of risk factor assessment for syphilis incidence, HOPS participants aged 18-30 years old had the highest syphilis incidence at 3.0 per 100 PYs (95% CI: 2.6 -3.5) compared to participants aged over 50 years old at 0.7 per 100 PYs (95% CI: 0.6 -1.0) (Figure 17). Syphilis incidence rates were 2.1 per 100 PYs (95% CI: 1.9 -2.4) in non-Hispanic black participants, 1.6 per 100 PYs (95% CI: 1.5 -1.8) in non-Hispanic white compared to Hispanic participants at 1.3 per 100 PYs (95% CI: 1.0 -1.6) (Figure 18). There was diversity of the incidence rates among MSM based on the different HOPS sites (Figure 19).

In a similar multivariate analysis for syphilis incidence, participants who had been seen in the most recent time period, 2011-2015 had a higher risk of contracting syphilis with an incidence of 5.4 per 100 P-Ys CI (4.3-6.7). In contrast, the incidence rate was lowest in those seen in the early time period at 1.1 per 100 PYs (CI 1.0-1.25) (Figure 20). Moreover, the incidence rate increased in each calendar year (Figure 21).

TABLE IV

INCIDENCE RATES OF SYPHILIS AND ASSOCIATED RISK FACTORS AMONG ACTIVE HOPS PATIENTS, 1999-2015 **(N=6,888)**

	No.	Total Cases	Incidence Rate per person-years (PYs)	95% confidence interval	Person-Years (PYs)
Overall	**(6,888)**	**799**	**1.768**	**1.649-1.894**	**45185**
HIV Risk Category					
MSM	(3,864)	667	2.554	2.366 - 2.753	26115.25
HRH	(1,901)	81	0.6757	0.5401 - 0.8355	11987.22
IVDU	(690)	26	0.6009	0.4009 - 0.8678	4327.07
Other/Unknown	(433)	25	0.9072	0.6001 - 1.32	2755.61
Age at index date (years)					
18-30	(1,160)	195	3.047	2.641 - 3.498	6400.55
31-40	(2,605)	343	1.838	1.651 - 2.04	18664.16
41-50	(2,204)	218	1.502	1.312 - 1.712	14514.11
51+	(919)	43	0.767	0.5621 - 1.024	5606.31
Race/ethnicity					
Non-Hispanic white	(3,398)	403	1.647	1.492 -1.813	24474.56
Non-Hispanic black	(2,390)	298	2.121	1.89 -2.372	14049.4
Hispanic	(847)	67	1.292	1.009 -1.631	5185.17
Other/Unknown	(253)	31	2.1	1.452 -2.945	1476.01
Calendar period of index date					
1999-2002	(3,884)	356	1.129	1.016 - 1.251	31533.46
2003-2006	(1,326)	201	2.539	2.206 - 2.909	7915.37
2007-2010	(1,021)	169	3.858	3.308 - 4.473	4381.06
2011-2015	(657)	73	5.386	4.253 - 6.734	1355.24
Site					
IDRI	(543)		0.8131	0.5302 – 1.247	
Dupont	(913)		2.607	2.26 – 3.006	
DIDC (1021 & 1025)	(1,146)		1.886	1.582 – 2.249	
NU	(1,295)		1.494	1.266 – 1.764	
Stonybrook	(620)		0.8909	0.6652 – 1.193	
Temple	(1,477)		1.586	1.321 – 1.905	
National Jewish	(328)		1.315	0.9718 – 1.779	
APEX	(78)		0.8047	0,2595 – 2.495	
UIC	(488)		3.386	2.832 – 4.05	

Figure 15: Overall syphilis incidence rates among active HOPS patients

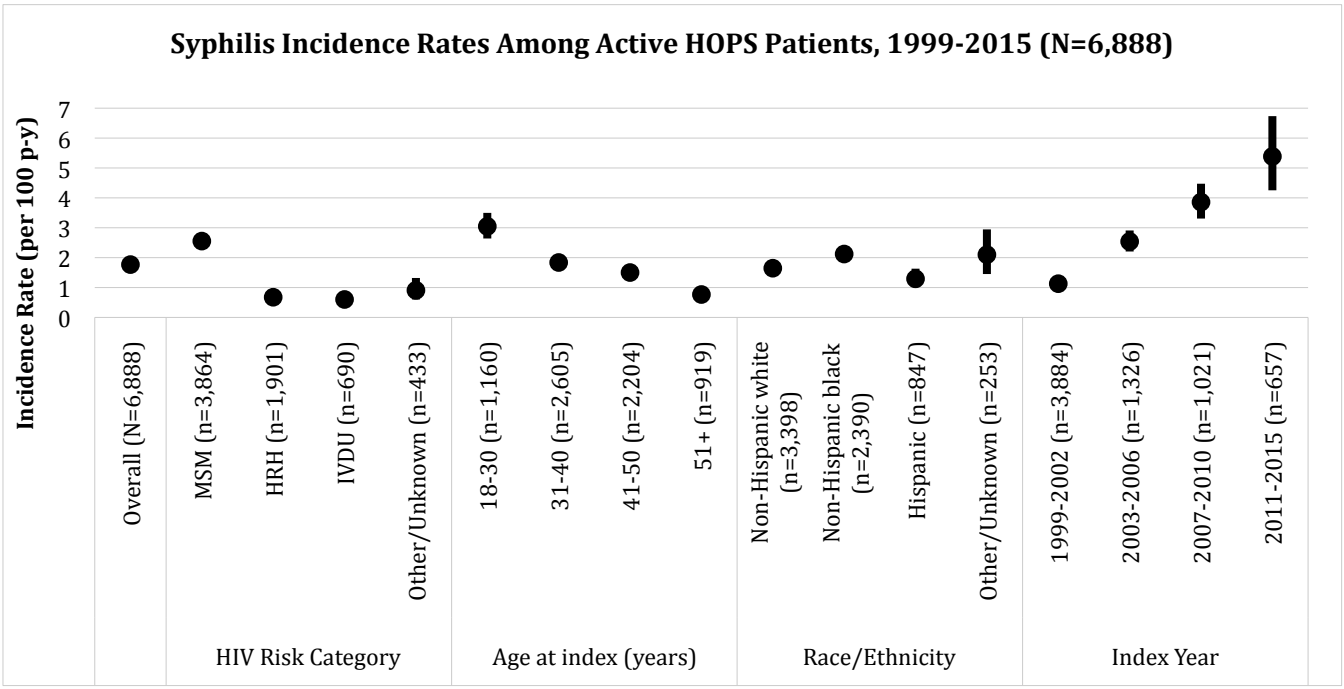


Figure 16: Syphilis incidence rates among active HOPS patients stratified by HIV Risk groups

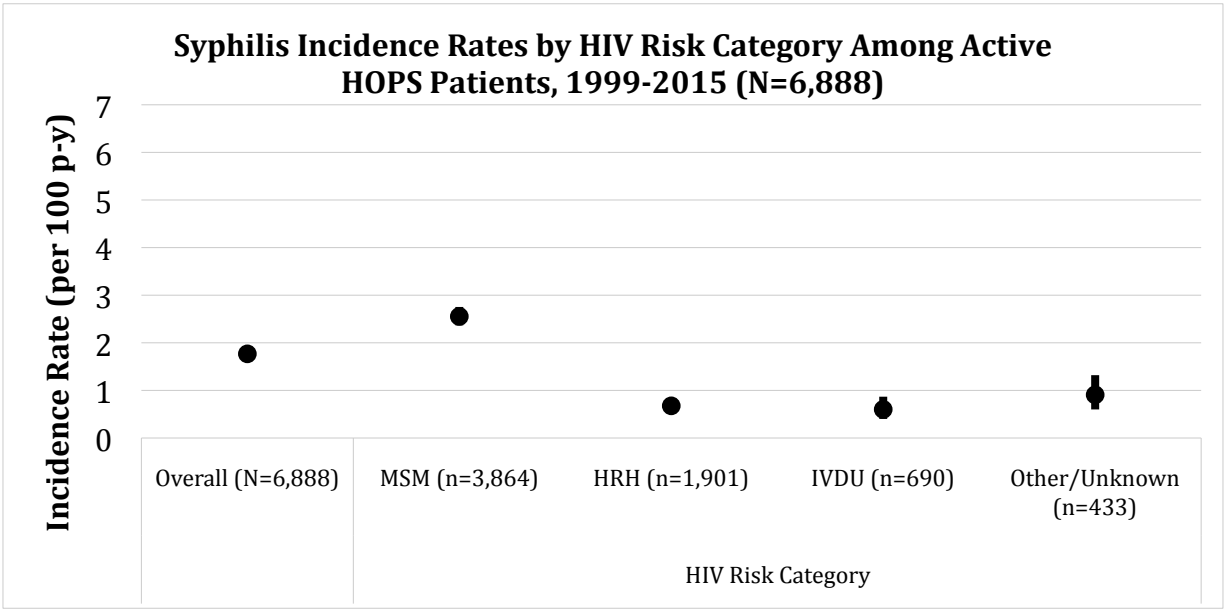


Figure 17: Syphilis incidence rates among active HOPS patients stratified by participant's ages

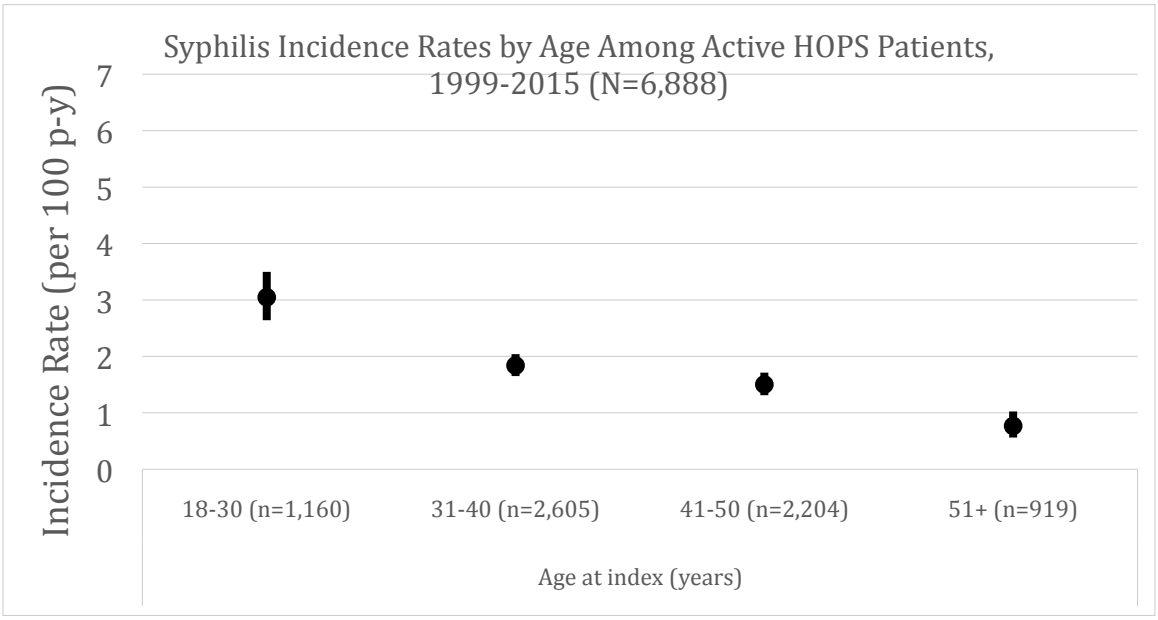


Figure 18: Syphilis incidence rates among active HOPS patients stratified by ethnicity

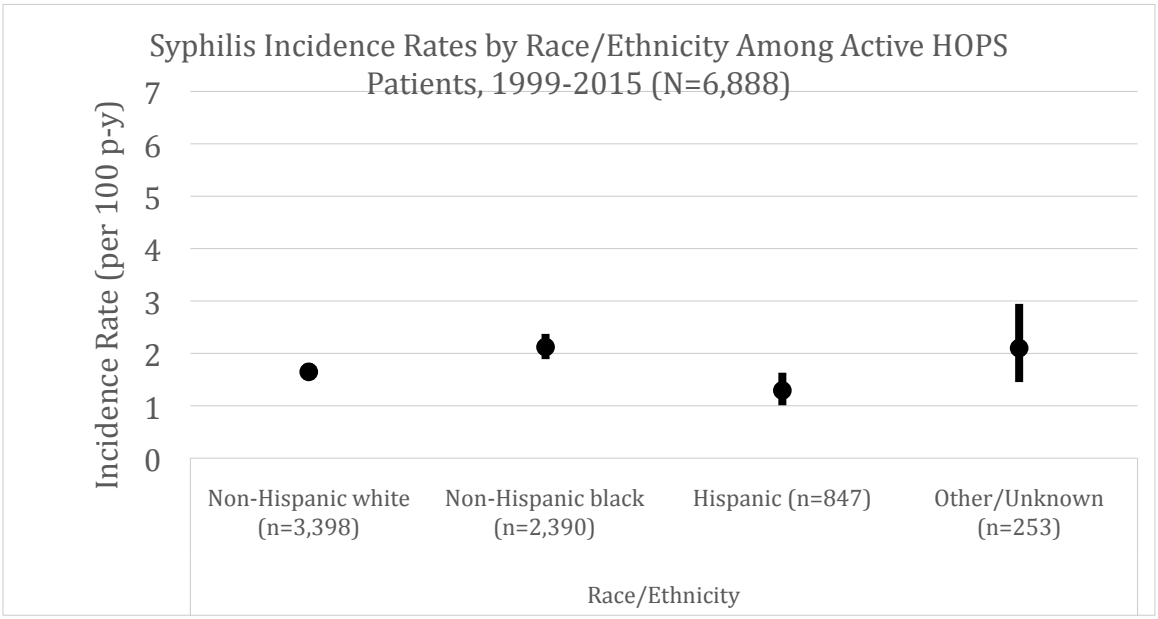


Figure 19: Syphilis incidence rates among active HOPS patients stratified by HOPS sites

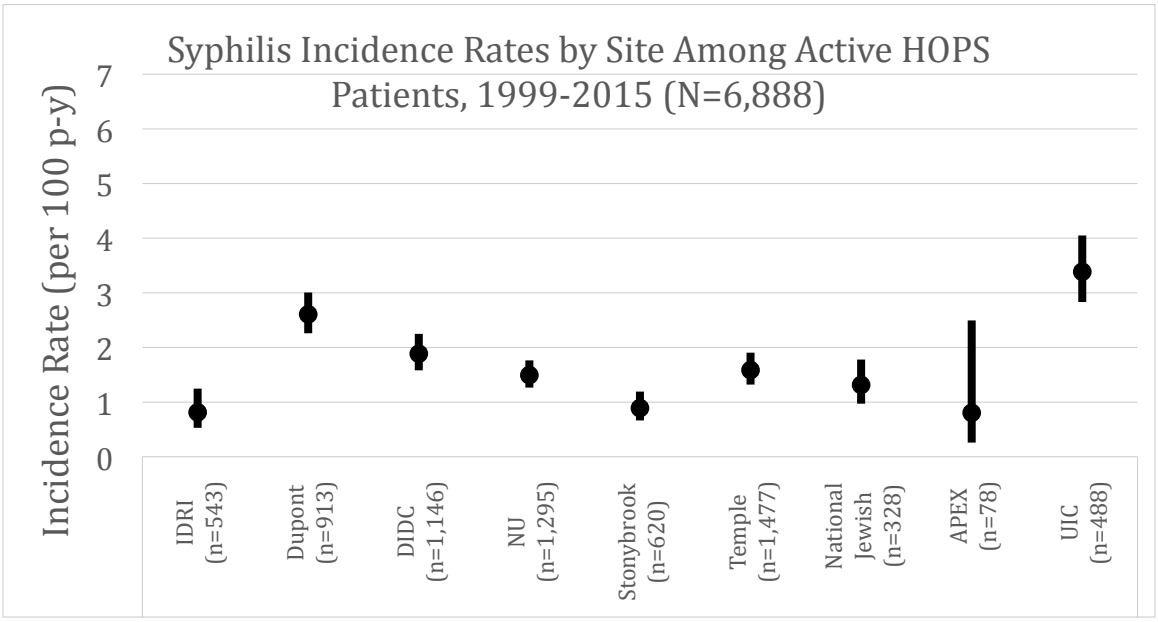


Figure 20: Syphilis incidence rates among active HOPS patients stratified by index year

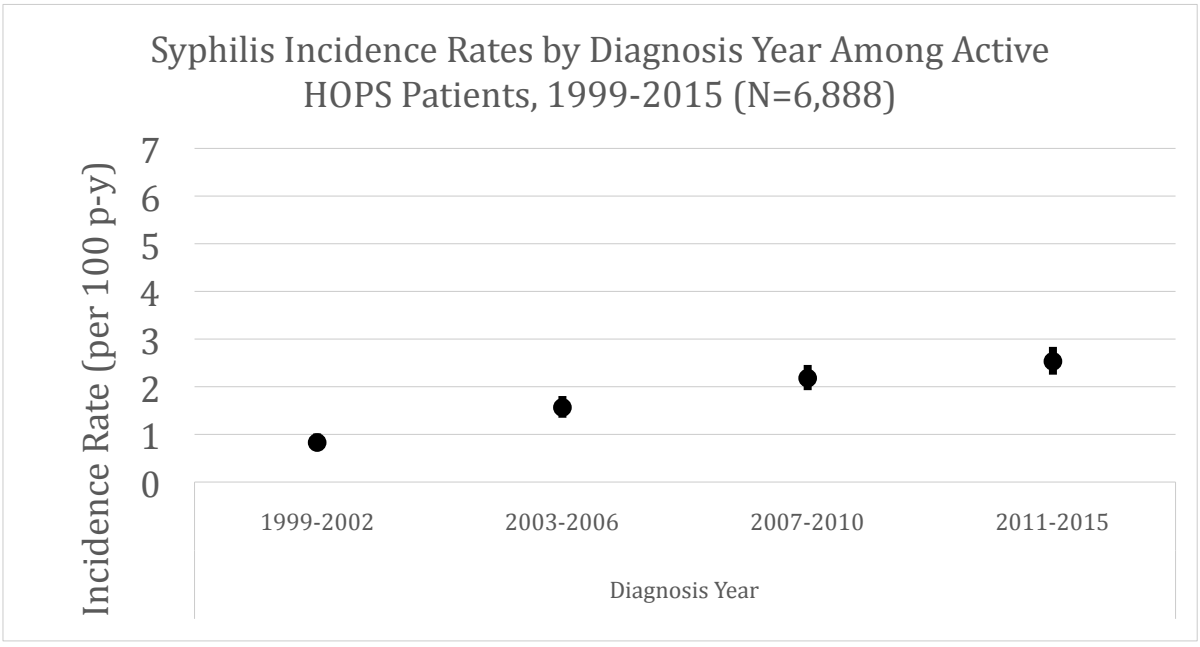
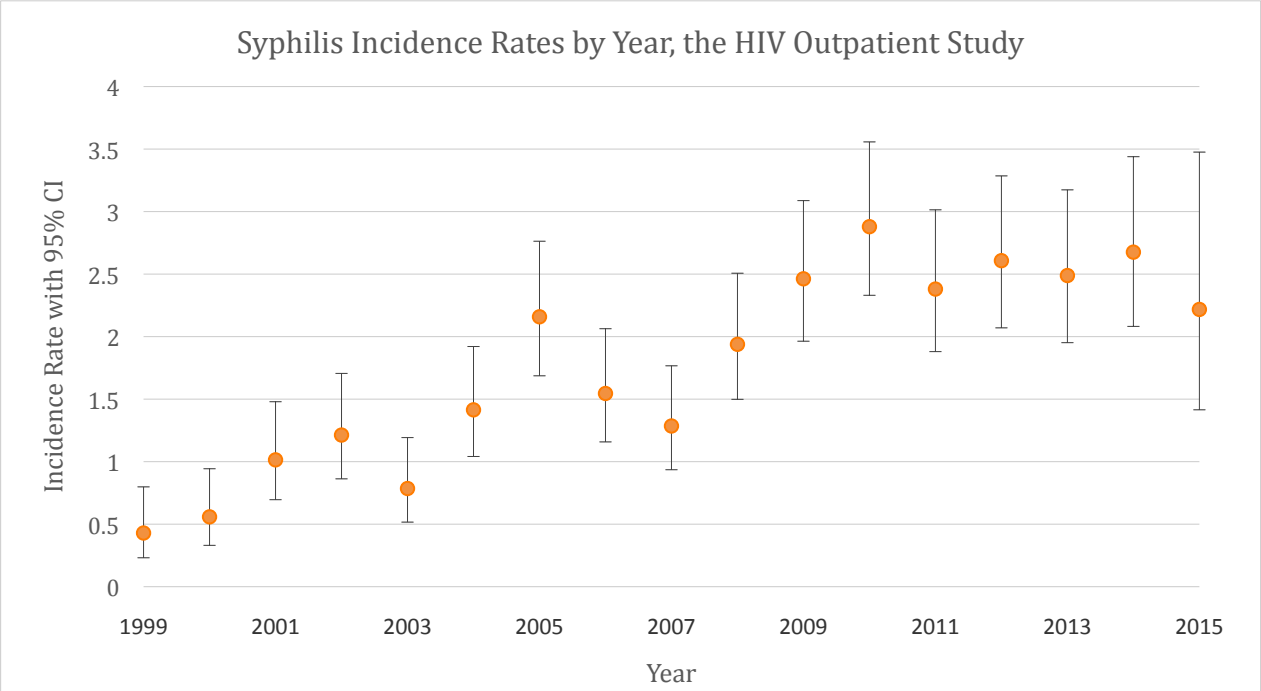


Figure 21: Syphilis incidence rates among active HOPS patients stratified by calendar year



We examined the screening rates among HOPS participants and stratified them by different HIV transmission categories. Overall rates were 54.1 per 100 PYs (95% CI: 53.4-54.8). It was 53.3 (95% CI: 52.4-54.1) in MSM, 56.7 (95% CI: 55.3-58.0) in heterosexuals, 55.5 (95% CI 53.3-57.8) in IV drug users and 48.3 (95% CI: 45.8-51.0) in those with unknown risk factors. In addition, we studied the relationship of syphilis incidence and insurance coverage and stratified by HIV transmission categories, we did find that the incidence rate of syphilis in MSM was 2.4 (95% CI: 2.2-2.6) among those who had private insurance compared to 2.5 (95% CI: 2.1-3.0) in those with public insurance and 5.2 (95% CI: 4.2-6.5) in Self-pay patients. The incidence rate among MSM with HCV was 2.5 (95% CI: 2.3-2.7) compared to 3.6 (95% CI: 2.7-4.7) in non-HCV MSM. Moreover,

the rates among MSM with Hepatitis B virus infection was 2.5 (95% CI: 2.4-2.8) compared to non-HBV MSM at 2.7 (95% CI: 1.8-4.0). Finally, we identified that the incidence rates among MSM varied based on the different HOPS sites (Figure19). It was highest at UIC 6.7 (95% CI: 5.5-8.1), then followed by Temple at 5.4 (95% CI: 4.2-7.0), Dupont at 2.7 (95% CI: 2.3-3.1), DIDC at 2.1 (95% CI: 1.8-2.5), Northwestern at 2.1 (95% CI: 1.8-2.6), StonyBrook at 1.8 (95% CI: 1.2-2.5), IDRI at 1.6 (95% CI: 1.0-2.7), National Jewish at 1.5 (95% CI: 1.1-2.0) and APEX at 1.1 (0.3-3.3). (Table 5, Figure19)

TABLE V

UNADJUSTED TESTING RATES AND INCIDENCE RATES BY HIV TRANSMISSION CATEGORY

	HIV transmission group				
	Overall (n=6,888)	**MSM (n=3,864)**	**HRH (n=1,901)**	**IVDU (n=690)**	**Other/Unknown (n=433)**
Testing rate per 100 person-years (95% CI)					
Overall	54.1 (53.4-54.8)	53.3 (52.4-54.1)	56.7 (55.3-58.0)	55.5 (53.3-57.8)	48.3 (45.8-51.0)
Insurance					
Private	48.8 (47.9-49.6)	49.2 (48.2-50.1)	48.9 (46.8-51.1)	52.2 (47.9-56.9)	40.1 (36.8-43.7)
Public	60.5 (59.3-61.7)	63.7 (61.3-66.2)	61.3 (59.5-63.1)	54.8 (52.2-57.5)	58.6 (54.0-63.6)
Self-pay	71.4 (68.2-74.8)	75.9 (71.6-80.4)	63.1 (57.5-69.3)	78.2 (67.3-90.9)	48.4 (36.6-64.0)
Other/Unknown/None	51.8 (48.3-55.5)	58.1 (52.6-64.1)	40.2 (34.2-47.1)	61.0 (46.5-80.0)	49.8 (43.3-57.3)
History of Chronic HCV					
No	53.6 (52.9-54.3)	52.8 (51.9-53.7)	56.2 (54.8-57.6)	54.3 (52.0-56.7)	47.9 (45.3-50.7)
Yes	61.9 (59.1-64.9)	60.4 (56.7-64.4)	68.3 (61.2-76.3)	63.1 (57.0-69.8)	54.4 (44.5-66.4)
History of Chronic HBV					
No	53.7 (52.9-54.4)	52.9 (52.1-53.9)	56.1 (54.8-57.6)	50.8 (47.5-54.3)	51.7 (48.8-54.7)
Yes	57.4 (55.3-59.5)	61.6 (56.7-66.9)	61.5 (57.2-66.2)	58.4 (55.6-61.4)	30.4 (25.6-36.0)
Antibiotic prophylaxis[a]					
No	57.0 (56.2-57.7)	56.5 (55.5-57.5)	58.6 (57.1-60.1)	58.1 (55.7-60.7)	52.2 (49.4-55.2)
Yes	35.8 (34.3-37.3)	33.5 (31.7-35.4)	41.8 (38.5-45.3)	42.6 (38.1-47.6)	22.4 (18.0-27.9)

TABLE V
UNADJUSTED TESTING RATES AND INCIDENCE RATES BY HIV TRANSMISSION CATEGORY.
(Continued)

	Overall (n=6,888)	MSM (n=3,864)	HRH (n=1,901)	IVDU (n=690)	Other/Unknown (n=433)
Site					
IDRI	43.3 (40.9-45.9)	42.0 (38.2-46.3)	44.2 (40.4-48.3)	37.8 (31.4-45.4)	52.5 (43.7-63.1)
Dupont	27.2 (26.1-28.5)	28.0 (26.8-29.3)	4.9 (2.4-9.8)	4.9 (1.2-19.7)	8.6 (3.2-23.0)
DIDC	60.8 (58.9-62.7)	63.5 (61.4-65.6)	43.7 (38.2-49.9)	53.4 (44.8-63.7)	40.8 (33.7-49.5)
Northwestern	38.9 (37.6-40.1)	44.7 (42.9-46.5)	27.1 (25.0-29.5)	29.9 (25.6-34.9)	36.1 (32.9-39.5)
StonyBrook	71.9 (69.6-74.3)	77.3 (73.1-81.7)	67.7 (64.3-71.3)	70.9 (66.2-76.0)	79.0 (67.2-93.0)
Temple	67.3 (65.4-69.2)	85.4 (80.0-91.1)	66.9 (64.6-69.3)	54.1 (50.3-58.2)	65.9 (57.4-75.7)
National Jewish	59.5 (56.9-62.3)	60.3 (57.4-63.4)	49.4 (40.9-59.7)	64.8 (52.0-80.7)	57.7 (49.6-67.3)
APEX	81.0 (72.4-90.7)	83.2 (73.1-94.6)	108.5 (83.3-141.4)	36.0 (22.1-58.8)	NA
UIC	84.5 (81.5-87.6)	106.0 (100.9-111.3)	71.0 (66.4-75.8)	64.7 (58.6-71.4)	69.5 (59.2-81.6)
Incidence rate per 100 person-years (95% CI)					
Overall	1.8 (1.6-1.9)	2.6 (2.4-2.8)	0.7 (0.5-0.8)	0.6 (0.4-0.9)	0.9 (0.6-1.3)
Insurance					
Private	2.0 (1.8-2.1)	2.4 (2.2-2.6)	0.7 (0.4-1.0)	0.5 (0.2-1.2)	0.9 (0.5-1.6)
Public	1.1 (1.0-1.3)	2.5 (2.1-3.0)	0.6 (0.4-0.8)	0.6 (0.3-0.9)	0.8 (0.4-1.6)
Self-pay	3.6 (2.9-4.4)	5.2 (4.2-6.5)	1.4 (0.8-2.7)	1.4 (0.4-4.3)	NA
Other/Unknown/None	1.8 (1.2-2.6)	2.6 (1.7-4.2)	0.8 (0.3-2.5)	1.2 (0.2-8.3)	1.3 (0.5-3.0)
History of Chronic HCV					
Yes	1.7 (1.6-1.8)	2.5 (2.3-2.7)	0.6 (0.5-0.8)	0.6 (0.4-1.0)	0.7 (0.5-1.2)
No	2.6 (2.1-3.3)	3.6 (2.7-4.7)	1.9 (1.0-3.7)	0.3 (0.1-1.4)	3.4 (1.5-7.6)
History of Chronic HBV					
Yes	1.9 (1.7-2.0)	2.5 (2.4-2.8)	0.7 (0.5-0.8)	0.6 (0.3-1.1)	1.0 (0.7-1.5)
No	1.0 (0.8-1.3)	2.7 (1.8-4.0)	0.9 (0.5-1.6)	0.6 (0.4-1.0)	0.2 (0.0-1.6)
Antibiotic prophylaxis[#]					
No	1.9 (1.8-2.1)	2.8 (2.6-3.1)	0.7 (0.5-0.8)	0.6 (0.4-0.9)	0.9 (0.6-1.4)
Yes	0.8 (0.6-1.0)	0.8 (0.6-1.2)	0.7 (0.4-1.4)	0.5 (0.2-1.5)	0.8 (0.3-2.6)
Site					<0.001
IDRI	0.8 (0.5-1.2)	1.6 (1.0-2.7)	0.3 (0.1-0.8)	0.7 (0.2-2.7)	NA
Dupont	2.6 (2.3-3.0)	2.7 (2.3-3.1)	NA	NA	NA
DIDC	1.9 (1.6-2.2)	2.1 (1.8-2.5)	0.6 (0.2-1.9)	0.9 (0.2-3.4)	0.4 (0.1-2.8)
Northwestern	1.5 (1.3-1.8)	2.1 (1.8-2.6)	0.4 (0.2-0.8)	0.6 (0.2-1.7)	0.8 (0.4-1.5)
StonyBrook	0.9 (0.7-1.2)	1.8 (1.2-2.5)	0.4 (0.2-0.7)	0.4 (0.2-1.1)	2.2 (0.8-5.8)
Temple	1.6 (1.3-1.9)	5.4 (4.2-7.0)	1.0 (0.7-1.3)	0.8 (0.4-1.4)	1.0 (0.3-3.0)
National Jewish	1.3 (1.0-1.8)	1.5 (1.1-2.0)	NA	NA	1.4 (0.5-3.7)
APEX	0.8 (0.3-2.5)	1.1 (0.3-3.3)	NA	NA	NA
UIC	3.4 (2.8-4.0)	6.7 (5.5-8.1)	1.1 (0.7-1.9)	0.7 (0.2-1.8)	1.4 (0.5-4.3)

[a] Antibiotic prophylaxis includes azithromycin and/or bactrim given as prophylaxis prior to the index date
P vales <0.001

E. <u>Risk factors associated with incident syphilis</u>

In the univarate model, the risk factors for incidence of syphilis were among those who aged 18-30, males who has sex with men, non-Hispanic black ethnicity, who were full time employed and have Self-pay or no insurance coverage.

In the final multivariate model, the risk factors for incident syphilis were age (younger age: HR 1.51; 95% CI 1.25-1.83) with P-value <0.001, ethnicity (Non-Hispanic black: HR 1.74; 95% CI 1.46-2.08, HIV risk category: MSM: HR 4.27; 95% CI 3.41-5.35, Employment at consent (Full time: HR 1.16; 95% CI 0.95-1.41 with P-value 0.14, Insurance (Private HR 1.00; 95% CI 0.81-1.24 with P-value 0.99, AIDS status (HR 0.83; 95% CI 0.71-0.98) with P-value 0.030, history of hepatitis B (HR 1.51; 95% CI 1.14-2.01) with P-value 0.005, history of hepatitis C (HR 1.13; 95% CI 0.82-1.57) with P-value 0.44 and Calendar period of index date (2003-2006 HR 2.07; 95% CI 1.68-2.54; 2007-2010: HR 3.39; 95% CI 2.72-4.23; 2011-2015: HR 4.13; 95% CI 3.04-5.59; referent 1999-2002 with P-value <0.001) (Table 6).

In conclusion, in multivariate analysis of the incidence of syphilis and associated risk factors, we found that the incidence was significantly associated with age, race, HIV risk categories, Aids status, HBV and calendar years. However, it wasn't significant associated with the employment status at the time of consent, insurance coverage categories and Chronic HCV infection compared to significance of univariate analysis.

TABLE VI

MULTIVARIABLE ANALYSES OF THE SYPHILIS INCIDENCE AND ASSOCIATED RISK FACTORS

Risk factors	Univariate		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at index date (years)				
18-30	Referent		1.51 (1.25-1.83)	< 0.001
31-40	0.62 (0.51-0.75)	< 0.001		
41-50	0.49 (0.39-0.61)	< 0.001		
51+	0.28 (0.19-0.39)	< 0.001		
Sex at birth				
F	Referent			
M	5.38 (3.81-7.60)	< 0.001		
Race/ethnicity				
Non-Hispanic white	Referent			
Non-Hispanic black	1.25 (1.06-1.48)	0.009	1.74 (1.46-2.08)	< 0.001
Hispanic	0.85 (0.64-1.12)	0.24		
Other/Unknown	1.27 (0.85-1.89)	0.25		
HIV risk category				
IVDU	0.97 (0.61-1.53)	0.88		
MSM	3.68 (2.87-4.72)	< 0.001	4.27 (3.41-5.35)	< 0.001
Heterosexual	Referent			
Other/Unknown HIV risk	1.28 (0.79-2.09)	0.32		
Employment at consent				
Full time	Referent		1.16 (0.95-1.41)	0.14
Part time	0.86 (0.62-1.20)	0.37		
Unemployed	0.61 (0.51-0.74)	< 0.001		
Retired	0.35 (0.17-0.74)	0.006		
Other/Unknown	0.92 (0.70-1.22)	0.58		
Insurance				
Private	Referent		1.00 (0.81-1.24)	0.99
Public	0.56 (0.46-0.68)	< 0.001		
Self pay/None	1.73 (1.34-2.24)	< 0.001		
Other/Unknown	0.97 (0.65-1.45)	0.89		
AIDS status	0.69 (0.59-0.81)	< 0.001	0.83 (0.71-0.98)	0.030
HBV Infection at index date	1.44 (1.09-1.91)	0.011	1.51 (1.14-2.01)	0.005
HCV Infection at index date	0.54 (0.40-0.74)	< 0.001	1.13 (0.82-1.57)	0.44
Calendar period of index date				
1999-2002	Referent			
2003-2006	2.14 (1.75-2.63)	< 0.001	2.07 (1.68-2.54)	< 0.001
2007-2010	3.59 (2.89-4.46)	< 0.001	3.39 (2.72-4.23)	< 0.001
2011-2015	4.62 (3.45-6.18)	< 0.001	4.13 (3.04-5.59)	< 0.001
CD4 at index date				
< 50	0.72 (0.51-1.03)	0.07		
50-199	0.80 (0.62-1.03)	0.09		
200-349	0.89 (0.71-1.11)	0.30		
350-499	1.11 (0.90-1.37)	0.34		
500+	Referent			
Unknown	0.64 (0.47-0.87)	0.004		

TABLE VI

MULTIVARIABLE ANALYSES OF THE SYPHILIS INCIDENCE AND ASSOCIATED RISK FACTORS (Continued)

Risk factors	Univariate		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Syphilis prior to index date	0.74 (0.24-2.29)	0.60		
Site				
IDRI	0.46 (0.28-0.76)	0.002		
Dupont	1.54 (1.19-1.98)	0.001		
DIDC (1021 & 1025)	Referent			
NU	0.84 (0.65-1.10)	0.22		
Stonybrook	0.49 (0.33-0.72)	< 0.001		
Temple	0.92 (0.70-1.21)	0.54		
National Jewish	0.79 (0.53-1.16)	0.22		
APEX	0.51 (0.16-1.59)	0.24		
UIC	1.68 (1.25-2.25)	< 0.001		

V. DISCUSSION

In a group of 6888 HOPS patients in the United States studied over a 15-year period, we examined the relationship of HIV risk factors and HIV transmission groups to incidence rates of syphilis in the HOPS. We found that participants in the HOPS differed by some demographic and clinical characteristics. We found that HIV-positive MSM had a higher syphilis incidence rate. Interestingly, other risk factors that showed significant associations with the incidence of syphilis were age, ethnicity, and insurance coverage. In examining the risk factors for HIV infection, young men who have sex with men, non-Hispanic ethnicity, being employed and having private insurance coverage predicted higher percentage of syphilis. Based on our analysis, we found that in addition to HIV risk factors, a lower CD4+ cell count was not significantly related to the incidence of syphilis. Moreover, the socioeconomic status of patients can explain that most participants are employed and self pay patients; this could be a marker that wealthy people may engage in different sexual behaviors and social networks or alternatively may be explained by confounding.

There have been several definitions of syphilis over time; however, syphilis is not a clinical diagnosis only as was considered before but it is a combination of clinical, laboratory and treatment. We defined syphilis based on these different methods because this is the data we had: how syphilis was entered into the database differs by site, and we are looking back at it years after it was collected so we can't change how syphilis was defined by the clinician: we had to come up with a definition that took into account all the data we have in the database. Results of association between HIV risk factors and incidence of syphilis are mixed. For example, one study found that incidence of syphilis was associated with a lower CD4+ cell count in specific age group [35-36];

however, we found that men with CD4 cell counts ≥ 350 had high syphilis diagnosis rates. Moreover, we found that MSM with low viral load have the highest percentage rate of syphilis compared to other groups.

Future research should explore underlying causes of re-infection. Hypothesized explanations include ongoing risk behaviors, perhaps due to beliefs that syphilis is a minor health problem. Nevertheless, in our cohort, 94.7 % of new syphilis diagnoses were among men based on the laboratory and treatment evidence. Syphilis diagnoses were most common among young men at a rate of 3.0 per 100 person-years for those between age of 18 and 30. Declining risk with age is a common feature of STI epidemiology among HIV-positive and general populations as well. Targeting syphilis control interventions only to young men, however, may miss a substantial number of new cases. Although diagnoses were three times less likely among men over the age of 50, they still occurred at a rate of 0.8 per 100 person-years.

The potential mechanisms linking HIV risk factors and incidence of syphilis are uncertain. One possible explanation, untreated HIV infections along with changing in sexual behaviors especially for individuals who persistently practice unprotected sex with unknown infected partners, has been significantly associated with a high incidence rate. Another possible explanation of the positive relationship between HIV risk factors and incident syphilis may be due to lack of education regarding this disease, and/or limited access to the health care system and treatment programs especially among the poor. The rate of new incident cases of syphilis has been increasing over the last decade. The rates were high among HIV-positive MSM in HOPS patients compared to other HIV positive males.

In fact, the rates we documented in the cohort are under-estimates since there were not active screening programs. From that data, it is clear that the rate of incidence is highly correlated with the testing rate. For example, in terms of insurance coverage, it appears that the incidence rate and screening rate was highest in those with no insurance. When evaluating the effect of the HIV risk groups, MSM was the most consistent predictor of a high incidence of syphilis.

In our results, Hepatitis B virus and Hepatitis C infections were included. Among MSM, the incidence of syphilis was not significantly associated with HCV or HBV because the syphilis rates were lower in persons with hepatitis (HCV or HBV) than those without it. In contrast, among IV drug users, the incidence of syphilis was significantly associated with HCV but it was not significantly related to HBV infections: the incidence rates were similar in positive and negative Hepatitis B infection. It is possible this is because IV drug use was the main force driving HCV infection. It possible that needle use is the cause of syphilis in IVDs but they also exchange sex for drugs. Thus, there should be equal amounts of syphilis in men and women IVDS.

The association of incidence of syphilis with CD4 counts and viral load have been extensively studied. The results were contradictory, in our data; we found that the incidence of syphilis is associated with CD4 cell counts ≥ 350 and low viral load men. In contrast, another study found that incidence of syphilis was correlated with a brief decrease in the CD4 cell count as well as an increase in VL, which implies that syphilis may increase the risk of HIV transmission[39]. However, there are many other factors that are associated with CD4 count; like drug interaction and resistance, patient's adherence and other chronic medical conditions.

Antibiotics prophylaxis was included in this analysis. The relationship of antibiotics prophylaxis among MSM to incidence of syphilis was significantly related. We found that MSM with antibiotics prophylaxis have a lower incidence rate. Using antibiotics for a long time because of other infections leads to unplanned prophylaxis against syphilis. The association between antibiotic prophylaxis and the incidence of syphilis can be confounded with different classes of antibiotic, duration of medication use, and whether the patient should have optimal medication adherence during the time of syphilis infection. More importantly, those who are on antibiotic prophylaxis have more advanced HIV disease, and may not be well enough to engage in sex. This is consistent with the CD4 and VL results.

Socio-demographic characteristics including age, ethnicity, employment and insurance coverage have all been shown to be independently associated with disparities in the incidence of syphilis. We did not find the relationship between HIV risk factors and incident of syphilis was confounded by race. We observed few racial or ethnic differences in syphilis, with the exception that non-Hispanic men were much more likely to be diagnosed with syphilis. Moreover, non-Hispanic black men tend to have higher rates of syphilis diagnosis compared to non-Hispanic white men. Moreover, rates in the cohort were highest at the University of Illinois site, followed by the Dupont site, as might be expected according to cohort database. Dupont has more than twice as many enrolled HOPS patients in the cohort compared to UIC, and their total syphilis numbers are greater, but their rate is lower.

This analysis has certain limitations. Firstly, there may be an under-estimation of the true syphilis incidence due to lack of a standardized screening and testing protocol. Secondly, we may

have inaccurately defined and classified syphilis diagnoses. We attempted to define variables based on the CDC definition adjusting for the available data in the HOPS database. Thirdly, there may have been selection bias due to variable practices in centers that care for HOPS patients and differences in the methods of syphilis diagnosis at each site, which limit generalizability. Moreover, there is a strong bias in the number and percentages because the HOPS is represented by a greater number of MSM than women, blacks and whites than Hispanics. Fourthly, treatment failure cannot be ruled out, as that the majority of re-diagnoses were presumed re-infections, given our case definitions and standards of care for syphilis treatment for HIV patients. Treatment failure may be overestimated and may actually reflect a higher rate of re-infection, or vice versa. Current diagnostic methods can't clearly make the distinction.

Nevertheless, the overall rate of new syphilis diagnoses would not have been affected by false classification of recurrent infection as " new onset" diagnoses since both were counted equally. Cohort participants are generally representative of HIV diagnoses in HOPS in terms of sex, geographic region, age at diagnosis, and HIV exposure category.

Nevertheless, CDC continuously supports complementary data collection systems to describe people living with HIV infection to better inform HIV prevention and treatment efforts. Still there is no gold standard data collection system that can be considered as an indicator for HIV patient care. This analysis was not powered to assess the contribution of individual antiretroviral therapy agents to syphilis events.

In sum, despite these inconsistencies, our data suggest that the clinical and laboratory-based case definitions along with the treatment regimens we used may be adequate for monitoring

trends in syphilis co-infection among HIV-positive MSM and for determining whether controlling the risk factors and applying public health interventions may produce rate decreases especially in this population. Moreover, men with HIV who experience a syphilis diagnosis may require additional support to prevent re-infection.

VI. CONCLUSIONS

In conclusion, the increased risk of syphilis among HIV-infected patients has been associated with traditional factors that are highly prevalent in the HOPS cohort and in other HIV-infected cohorts. We did find a positive link between MSM and the incidence rate of syphilis among HOPS participants. We found that high-risk groups (young men who have sex with men, non-Hispanic ethnicity, being employed and having private insurance cove) had a higher rate of syphilis in HOPS. MSM is an independent risk factor for incident syphilis in the HIV outpatient study cohort. This does not mean other HIV risk factors and HIV transmission groups linked to incidence rate of syphilis should be ignored. Future studies that follow HOPS patients for a longer period of time are needed to determine whether these results can be replicated. The HOPS provides continually updated information on the changing socio-demographic characteristics, conditions, and therapy of ambulatory HIV-infected patients and can show trends in syphilis over time with continued follow up.

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VITA

NAME:	Abdelhamid Ghanem
EDUCATION:	M.B.CH.B University of Sebha, Libya, 2008
TEACHING	Department of Anatomy, University of Sebha, Libya 2008-2009
EXPERIENCE:	Research Assistant at Infectious Disease section at University of Illinois at Chicago (UIC) since 2011
	General Physician Tripoli Medical Center (TMC), University of Tripoli 2008-2009
	Department of Anatomy, University of Sebha, College of Medicine 2008-2009
HONORS:	Postgraduate Scholarship, University of Sebha, College of Medicine
PROFESSIONAL:	Infectious Diseases Research
MEMBERSHIP:	Libyan Medical Doctors Association Member since 2008
	Interns and new doctors graduate association Member since 2008
PUBLICATIONS:	Ashley R. Styczynski, Khandaker N. Anwar, Habiba Sultana, Abdelhamid Ghanem, Nell Lurain, Aishi Chua, Mahmood Ghassemi and Richard M. Novak (In vitro antiretroviral activity and in vivo toxicity of the potential topical microbicide copper phthalocyanine sulfate)…… Styczynski et al. Virology Journal (2015) 12:132 DOI 10.1186/s12985-015-0358-5