



Published in final edited form as:

Sex Transm Dis. 2012 June ; 39(6): . doi:10.1097/OLQ.0b013e318249d90f.

Results of a 25 Year Longitudinal Analysis of the Serologic Incidence of Syphilis in a Cohort of HIV Infected Patients with Unrestricted Access to Care

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Abstract

Background—The well described biological and epidemiologic associations of syphilis and HIV are particularly relevant to the military, as service members are young and at risk for sexually transmitted infections. We therefore used the results of serial serologic testing to determine the prevalence, incidence, and risk factors for incident syphilis in a cohort of HIV-infected Department of Defense beneficiaries.

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This work was presented in part at the 16th Conference on Retrovirus and Opportunistic Infections, Montreal, February 16-19, 2009; Abstract number 1057.

Author Contributions: All authors have reviewed and approved this manuscript.

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Methods—Participants with a positive non-treponemal test at HIV diagnosis that was confirmed on treponemal testing were categorized as prevalent cases, whereas participants with an initial negative non-treponemal test who subsequently developed a confirmed positive non-treponemal test as incident cases.

Results—At HIV diagnosis the prevalence of syphilis was 5.8% (n=202). 4239 participants contributed 27,192 person years (PY) to the incidence analysis and 347 (8%) developed syphilis (rate 1.3/100 PY; [1.1, 1.4]). Syphilis incidence was highest during the calendar years 2006 - 2009 (2.5/100 PY; [2.0, 2.9]). In multivariate analyses, younger age (per 10 year increase HR 0.8; [0.8-0.9]); male gender (HR 5.6; [2.3-13.7]); non European-American ethnicity (African-American (HR 3.2; [2.5-4.2]; Hispanic HR 1.9; [1.2-3.0]); history of hepatitis B (HR 1.5; [1.2-1.9]) or gonorrhea (HR 1.4; [1.1 -1.8]) were associated with syphilis.

Conclusions—The significant burden of disease both at and after HIV diagnosis, observed in this cohort, suggests that the cost-effectiveness of extending syphilis screening to at risk military members should be assessed. In addition, HIV infected persons continue to acquire syphilis, emphasizing the continued importance of prevention for positive programs.

Keywords

Seroincidence; Seroprevalence; Risk Factors; Syphilis; HIV infected persons

Background

Syphilis is a sexually transmitted infection (STI) with protean clinical manifestations. In HIV-infected persons syphilis often occurs without overt symptoms¹⁻². Historically syphilis has posed a significant threat to military service members³. With the introduction of penicillin syphilis rates declined in the military. The mid-1980s saw a resurgence of syphilis cases⁴, however, rates declined throughout the nineties and in 1999 rates in the US Navy were similar to that observed in civilian settings⁵. In the last decade syphilis has reemerged as a significant public health problem, largely fueled by an increase in the number of cases among HIV-infected men who have sex with men (MSM)⁶⁻⁷. Syphilis increases the risk of both acquiring and transmitting HIV infection⁸⁻⁹. The biological plausible associations that link syphilis to HIV transmission are of particular relevance to the US military as service members between the ages of 17-24 comprise nearly 40% of the US military, and represent an age group that is at a high risk for STI¹⁰⁻¹¹. Given the resurgence of syphilis among HIV-infected civilians it is important to define the epidemiology and risk factors associated with the disease in the HIV-infected military population. We utilized serial serologic testing results, to examine the seroprevalence, seroincidence and risk factors associated with incident syphilis in a cohort of HIV-infected US military members.

Material and Methods

To achieve our objectives we examined data from the US Military HIV Natural History Study (NHS) a cohort comprised of HIV-infected Department of Defense (DoD) beneficiaries (active duty service members, retirees, and their dependents)¹²⁻¹³. HIV infection is documented at NHS entry using a licensed ELISA based assay and confirmed with a Western Blot.

While on active duty HIV positive service members undergo clinical evaluations every 6 months. In keeping with this schedule NHS visits are conducted every 6 months at one of seven military treatment facilities. During these visits participants undergo blood draws (for both study specific tests and tests required for clinical care), individualized risk reduction counseling by a trained technician, are evaluated by a HIV specialist and attend peer

education in a group setting. Research personnel collect demographics (including self reported ethnicity), clinical information (including history of STIs), and updated medication history (including treatment for syphilis). Results of all laboratory tests including those performed for clinical care are captured in the NHS database.

Before 2006, screening for syphilis was conducted in accordance with the policies of the treatment facility; since 2006 annual serologic testing has been incorporated as a study-specific test. Syphilis screening is performed using a Nontreponemal (NTr) test primarily the rapid plasma reagin (RPR) test. Positive NTr test results are confirmed using any licensed treponemal (Tr) test. For this sub-study, eligible participants were enrolled in the NHS between 1986 and 2009, and had HIV, NTr and Tr testing results documented in the database. This sub-study was approved by a central institutional review board.

Definitions

To assess the prevalence of syphilis at HIV diagnosis, we examined all participants who had testing performed within a 6-month window of HIV diagnosis. To improve the accuracy of our estimates, we examined a subset of seroconverters (i.e. individuals with documented HIV positive and negative dates within a two-year interval). We next examined the incidence of the first episode of syphilis after HIV diagnosis. All participants with a positive NTr test following an initial negative NTr test that was subsequently confirmed by a positive Tr test result were categorized as an incident case, whereas those with a confirmed positive NTr test at HIV diagnosis were considered a prevalent case. The date of the incident episode was defined as the midpoint between the date of last negative NTr test and date of the first positive NTr test. Non-cases included participants with an initial positive NTr test that was followed by all negative Tr tests (false positives). Syphilis staging have not been captured in the NHS database; hence, we used duration of syphilis infection as an approximation to identify participants early in their course of infection. We defined participants as being “early” in infection if they had a negative NTr test in the 365 days prior to the positive NTr test. Because NTr antibody titer correlates with disease activity, for prevalent cases we considered a titer 1:8 as a likely reflection of recent infection¹⁴. Self-reported ethnicity was categorized for analyses as European-American, African-American, Hispanic, or Other. Anti-retroviral therapy (ART) was categorized as none, mono/dual or highly active antiretroviral therapy (HAART). The NHS definition of HAART, defined as the use of three drugs belonging to two or more classes of antiretrovirals or the use of a triple nucleotide regimen, was utilized for this study¹⁵.

Statistical Methods

Descriptive statistics were used to describe the population. Median values are provided with interquartile ranges (IQRs) and compared using the Kruskal-Wallis test. Proportions were compared using either the chi-square or Fisher’s exact tests.

Incidence rates were calculated per 100 person years of follow up (PY), with exact Poisson 95% confidence intervals (CI). Follow up time was calculated from the initial negative NTr test to the time of censoring, defined as the time of incident infection or last NTr test. Poisson regression was used to test for trends in rates by calendar year. Univariate and multivariate Cox proportional hazards methods, stratified by era of diagnosis of HIV infection (pre-1996 vs. 1996 and beyond) and treatment facility, were used to model associations between factors and incident syphilis. Time-updated covariates used all available measurements during the period of observation.

Significance for the multivariate models was defined at $P < 0.05$; all P values were 2-sided. Age, sex, ethnicity and time from HIV diagnosis were included in the multivariate model, in

addition to the variables with a $P < 0.15$ in univariate analyses. Hazard ratios (HRs) and rates are presented with 95% confidence intervals (CIs). The proportional hazards (PH) assumption was assessed for all fixed effects. Analyses were conducted using SAS software, version 9 (SAS Institute). Figures were generated using the R programming language, version 2.10.1. The “loess” and “predict loess” functions in R were used to generate the local linear robust fit smoothing lines and pointwise 95% CIs depicting both the prevalence and incidence of syphilis infection (span=2/3, degree=1)¹⁶.

Because testing rates varied by enrollment center (supplementary table 1), sensitivity analyses were performed using data from a single center, at which the testing rates have exceeded 90% since the inception of the study.

Results

Of the 5125 eligible participants, 4977 (97%) had at least one evaluable NTr test, and were included in this analysis (Figure 1). Study participants were 92% male, 43% European-American, and 44% African-American. The proportion of NHS participants tested for syphilis varied by calendar year and was lowest (78%) in 1998 and since 2003 has exceeded 90% (Figure 2A). The proportion tested for syphilis at the time of HIV diagnosis also varied by calendar year, exceeding 80% since 1993, (Figure 2B).

Syphilis Prevalence

3486 (70.0%) participants had NTr testing performed at HIV diagnosis, 202 (5.8%) participants, 56 European-American and 123 African-American, had concurrent syphilis. Approximately half the prevalent cases (n=98) were likely recently infected. 1676 HIV seroconverters had NTr testing at HIV diagnosis, 4.1% (n=68) had prevalent disease, 42 (67%) seroconverters met our criteria for recent syphilis infection. Since 2003, the proportion of newly diagnosed HIV infected participants who are also co-infected with syphilis has increased (Figure 3). The majority of the participants diagnosed with syphilis (52%) were likely recently infected as evidenced by a titer 1:8 (Figure 3).

Syphilis Incidence

Participants with an initial positive NTr test (n=319), no follow up testing (n=403), or no confirmatory Tr tests following an initial negative NTr test (n=16) were excluded from the incidence analysis (Figure 1). The remaining 4239 participants contributed 27,192 person years (PY) of follow up. The median number of NTr tests per subject was 8 (IQR 5, 16) and the median duration of follow up was 4.9 years (IQR 2.2, 9.0). African-American and European-American participants had similar median numbers of NTr tests [European-American: 8 (IQR 5, 15) and African-American: 9 (IQR 5, 17), $p=0.23$].

During follow up, 347 participants met the definition of an incident case. Among participants with incident syphilis, 98.6% were male, 68.3% African-American, 21.3% European-American, and 6.7% Hispanic. The median age and CD4 count at syphilis diagnosis were 35.0 years (IQR 28.8, 40.4) and 509 cells/ μ L (IQR 386, 695) respectively. The median time from HIV diagnosis to syphilis infection was 4.0 years (IQR 1.6, 8.0), (Supplementary Figure 1). Of the participants with incident syphilis, 278 (80.1%) met criteria for early disease. Figure 4 summarizes incidence rates by calendar year for all participants (4A), those with early stage disease (4B), and for African-American and European-American participants (4C).

The overall incidence of syphilis was 1.3 /100 PY (95% CI 1.1, 1.4) of follow up. Incidence rates varied across calendar time and race. Rates of incident syphilis were lowest between

1994 and 1999 at 0.5/100 PY (95% CI 0.3, 0.6). A resurgence of syphilis cases was observed during the calendar years 2000-2005 (1.6 /100 PY; 95% CI 1.3, 1.8), and a continued increase has been observed during the calendar years 2006-2009 (2.5 /100 PY; 95% CI 2.0, 2.9), (Figure 4A). The overall incidence of early disease was 1.0/100 PY (95% CI 0.9, 1.1) and exhibited similar trends (Figure 4B). The overall incidence of syphilis was higher among African-Americans (2.1 /100 PY; 95% CI 1.8, 2.4, $p<0.0001$) and Hispanics (1.1/100 PY; 95% CI 0.7, 1.6, $p=0.005$) in comparison to European-Americans (0.6 /100 PY; 95% CI 0.4, 0.7). Differences in the incidence of syphilis between European-Americans and African-Americans have been consistently observed over calendar time except more recently, (2008-2009), during which infection rates were not significantly different (European-Americans: 2.0 /100 PY; 95% CI 1.1, 3.0) versus (African-Americans: 3.3 cases/100 PY; 95% CI 1.9, 4.6, $p=0.13$). Since 2000, syphilis cases have increased in all three ethnic groups, for example, between 2001 and 2009 incident syphilis increased 7 fold among European-Americans (from a rate of 0.53/100 PY to 3.8/100 PY), African-Americans exhibited an approximately 4 fold increase (1.4/100 PY to 5.0/100 PY) and Hispanics had nearly a doubling of the rate (1.1/100 PY to 2.1/100 PY). In a sensitivity analysis, similar trends were observed at the single center where testing rates have exceeded 90% (data not shown).

Risk factors associated with incident syphilis

Because the PH assumption was violated for age, a time-dependent age term was included in the final multivariate model. Risk factors for incident syphilis were younger age (HR 0.82; 95% CI 0.75-0.91), male gender (HR 5.63; 95% CI 2.31-13.73), ethnicity (African-Americans: HR 3.24; 95% CI 2.48-4.24; Hispanic: HR 1.85; 95% CI 1.15-2.96; Other: HR 2.37; 95% CI 1.30-4.29; referent European-Americans), history of hepatitis B (HR 1.52; 95% CI 1.22-1.91), and gonorrhea (HR 1.42; 95% CI 1.12-1.80) (Table 1). HAART use was not associated with disease (HR 0.92; 95% CI 0.69-1.23). HIV specific risk factors including CD4 count, viral RNA levels, and the presence of an AIDS defining illness were not associated with syphilis.

Discussion

Using results of serial serologic testing to identify syphilis cases, this longitudinal twenty five year study among HIV-infected DoD beneficiaries estimated an overall prevalence of syphilis at HIV diagnosis of ~ 6% and subsequent incidence of 1.3 cases/100 PY of follow up.

To our knowledge this is the first study that examines the seroincidence of syphilis over a 25 year period. Compared to other studies in HIV-infected persons, seroincident syphilis rates in the NHS are lower^{1, 17-18}, and are comparable to case-based estimates from a managed care setting in the US¹⁹. NHS participants have unrestricted access to healthcare and medications, undergo close clinical monitoring, report low rates of illicit drug use, and possess either a minimum of a high school educational equivalent (enlisted) or an undergraduate college degree (officers)¹²⁻¹³. Further, active duty members of this cohort have stable employment. As low rates of drug use and improved access to health care have been associated with a lower risk of acquiring STIs²⁰⁻²⁵; we postulate that the close clinical monitoring and unrestricted access to healthcare and medications that NHS participants enjoy may in part explain the lower incidence of syphilis observed in this study. Reliance on serologic testing to derive estimates reduces the likelihood that the lower incidence is caused by participants seeking care outside the military health care system, as declines in titers following treatment would be captured at subsequent testing, but does not eliminate the possibility. HIV-infected MSM are disproportionately affected by syphilis and have been the

primary focus of studies examining the seroincidence of syphilis^{1, 17-18}. Hence, we compared our rates to published reports among HIV-infected MSM. Although ascertainment of sexual behaviors can be difficult in the military, when last examined, in the early nineties, a third of the surveyed NHS participants reported having sex with women exclusively¹². If the cohort composition has remained the same (namely 2/3rd MSM) it may represent an alternative explanation for our lower syphilis incidence.

In the NHS ethnic minorities shared a greater burden of syphilis, however, these differences are not as pronounced as that observed nationwide²⁶. For example, African-American men nationwide were 8 times more likely than European-American men to have a diagnosis of primary or secondary syphilis in 2009, whereas in the NHS we found that African-American men were 1.2 times more likely to be diagnosed with syphilis in that year²⁶. The narrowing of ethnic disparities in the NHS in recent years has not been driven by declines in syphilis cases among African-Americans but rather by increases in syphilis cases among European-Americans. In concordance with the nationwide data we observed increases in incident syphilis rates among Hispanics, however, our sample size for this subset was small²⁷. Our results suggest to stem the tide of new syphilis infections in the DoD effective prevention must be targeted to at risk groups and appropriate within varying racial/ethnic contexts.

Factors associated with incident syphilis in this study are similar to those reported previously²⁸⁻²⁹. Younger age, non European-American ethnicity, male sex, and a prior history of STI were associated with an increased risk of syphilis acquisition. Some studies suggest that in the HAART era HIV-infected men are less concerned about virus transmission thereby increasing sexual risk taking³⁰⁻³². Our results did not find a significant association between syphilis acquisition and HAART use and are in agreement with two large studies which also failed to demonstrate an association with HAART use^{2, 19}.

Historically results of syphilis screening were used to determine military eligibility³. The changes mandated with the introduction of the Clinical Laboratory Improvement Act led military investigators to examine the cost-effectiveness of universal syphilis screening³³. The study concluded that universal syphilis screening was not cost-effective, and screening was discontinued³³. However, this study was conducted in the nineties when syphilis rates were declining both nationwide and in the US military⁵. Since 2000 there has been a resurgence of syphilis cases in HIV-infected persons, our results demonstrate similar trends in the military HIV population²⁶. A recent analysis of the US military also showed an increase in syphilis rates in 2008-2009³⁴. Taken together these observations suggest that the current screening policies should be reviewed and the cost-effectiveness of periodic syphilis screening of at risk military members both at and after enlistment needs examination.

One of the strengths of this analysis is the greater precision of our estimates due to the reliance on serologic testing to derive estimates, however, this strategy too has limitations³⁵. Serologic testing has reduced sensitivity in very early disease and may fail to capture subjects with early treated disease³⁶. Further, incident syphilis is best characterized by measuring rates of early stage disease (i.e. primary and secondary) as latent infection may have been acquired years earlier. As syphilis staging was not captured in the NHS, we tried to overcome this limitation by defining early and late stage disease by measuring duration of infection but misclassification of cases may have occurred, which might affect our estimates. Other limitations of this study include the fact that the prior policy of “Don’t ask Don’t tell” limited our ability to capture patterns of sexual activity in this cohort as well as the need to estimate the date of syphilis seroconversion due to the periodic nature of syphilis screening. We acknowledge that the failure to adjust for risk behavior might have influenced our point estimates. To address the latter, a parallel analysis of time to incident

syphilis with syphilis infection defined as the date of the first positive test found qualitatively similar results. Lastly, the proportion of participants tested in this cohort varied by calendar year and center and this missing data has the potential for introducing bias. Overall 2.5% of the participants never had a syphilis test performed and 30% of the participants did not have a test for syphilis performed within 6 months of HIV diagnosis, although in recent years the proportions of participants tested for syphilis have exceeded 90%. To address this concern, the incidence of syphilis was examined using only data from a center at which the proportion tested exceeded 90% throughout the study period and we found the pattern of incidence over the years to be similar.

In conclusion, rates of incident syphilis, in this cohort, continue to increase despite equal access to care and low rates of drug use. Acquisition of syphilis in HIV-infected persons is indicative of unsafe behavior and points to the continued need for prevention in positive programs in the military. Overall African-Americans shared a disproportionate burden of this disease, however, in recent years there has been a marked increase in new infections within our European-American and Hispanic participants. Additional research to understand what risk reduction interventions will work for this and other HIV-positive populations is warranted. The significant burden of syphilis identified at the time of HIV diagnosis in this cohort suggests that the cost-effectiveness of targeted screening of at-risk military members periodically after enlistment needs study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Infectious Disease Clinical Research Program HIV Working Group is comprised of: Susan Banks RN, Irma Barahona RN, CAPT Mary Bavaro MD, Helen Chun MD, Cathy Decker MD, Lynn Eberly PhD, Conner Eggleston, LTC Tomas Ferguson, COL Susan Fraser MD, MAJ Joshua Hartzell MD, MAJ Joshua Hawley, LTC Gunther Hsue, Arthur Johnson MD, COL Mark Kortepeter MD MPH, Michelle Linfesty, Scott Merritt, LTC Robert O'Connell MD, Cpt Jason Okulicz MD, Sheila Peel PhD, Michael Polis MD, John Powers MD, MAJ Roseanne Ressler MD, , ret Col Edmund Tramont, LT Tyler Warkentien, MAJ Paige Waterman MD, Amy Weintrob MD, Timothy Whitman MD, and LTC Michael Zapor MD. We would also like to specifically acknowledge William Bradley for his assistance with data acquisition.

Support for this work (IDCRP-000-26) was provided by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed through the Uniformed Services University of the Health Sciences. This project has been funded in whole, or in part, with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter-Agency Agreement Y1-AI-5072.

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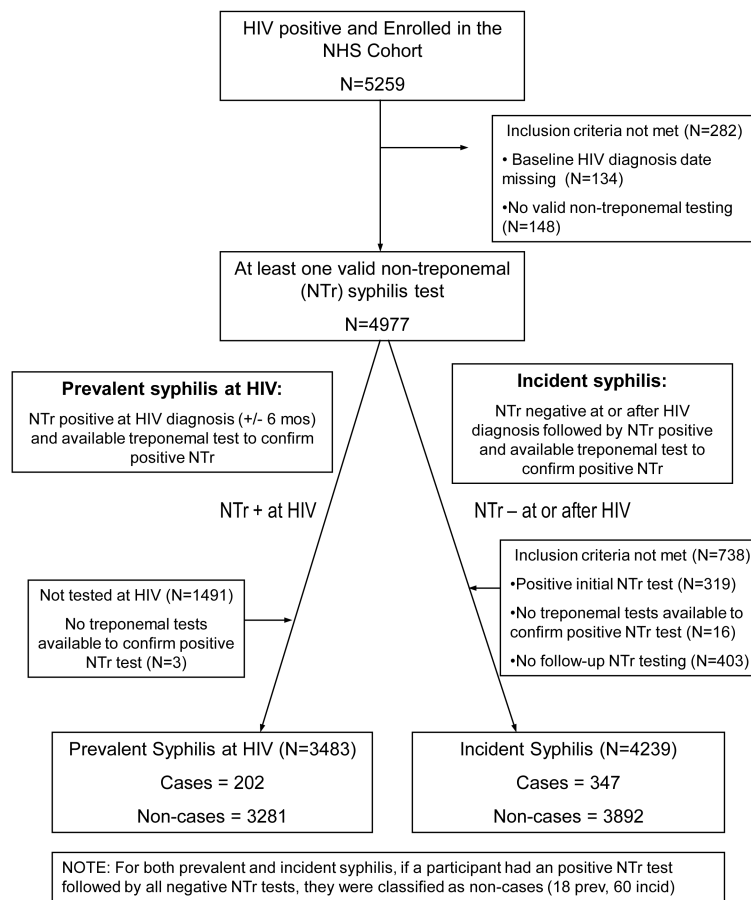
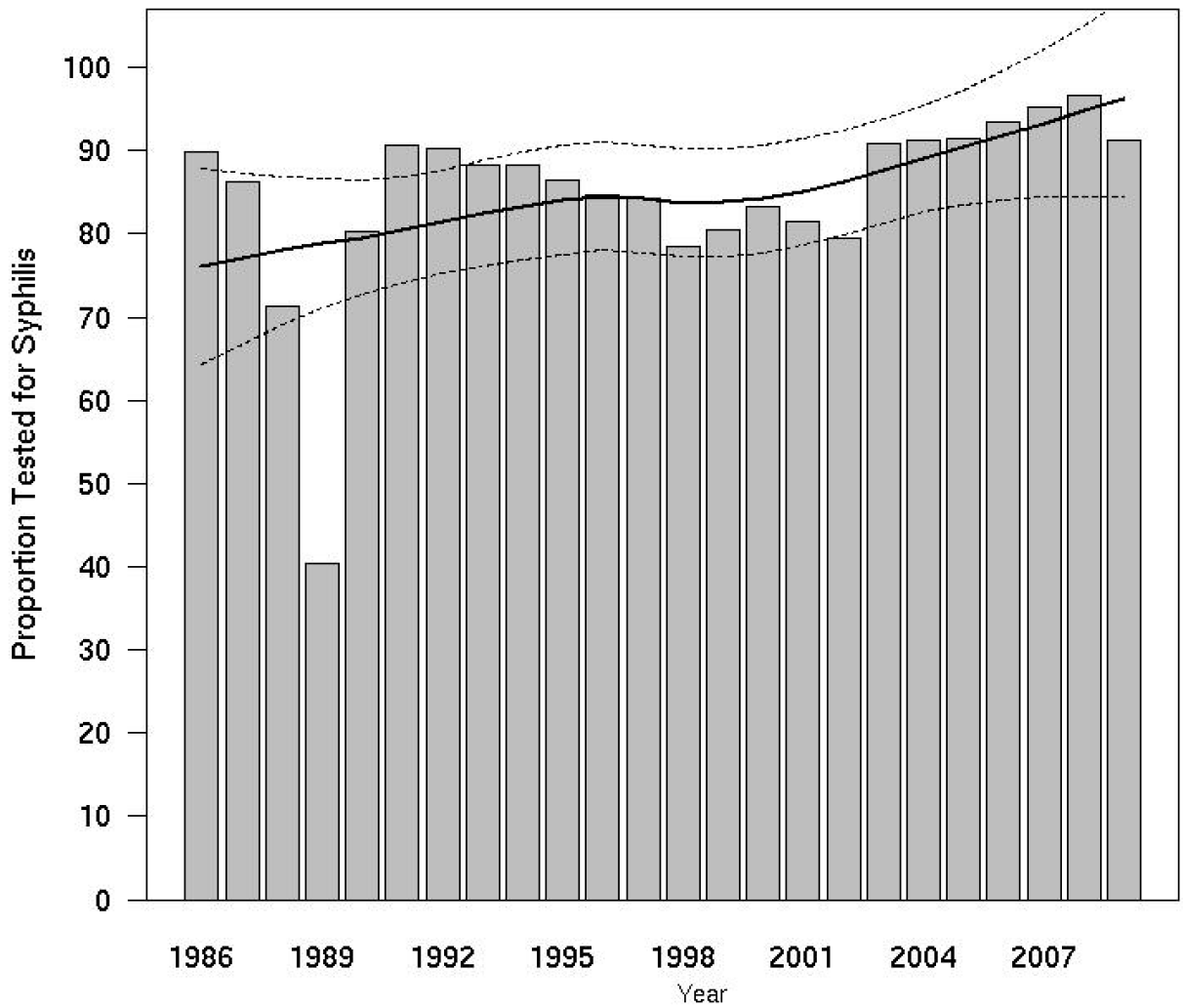


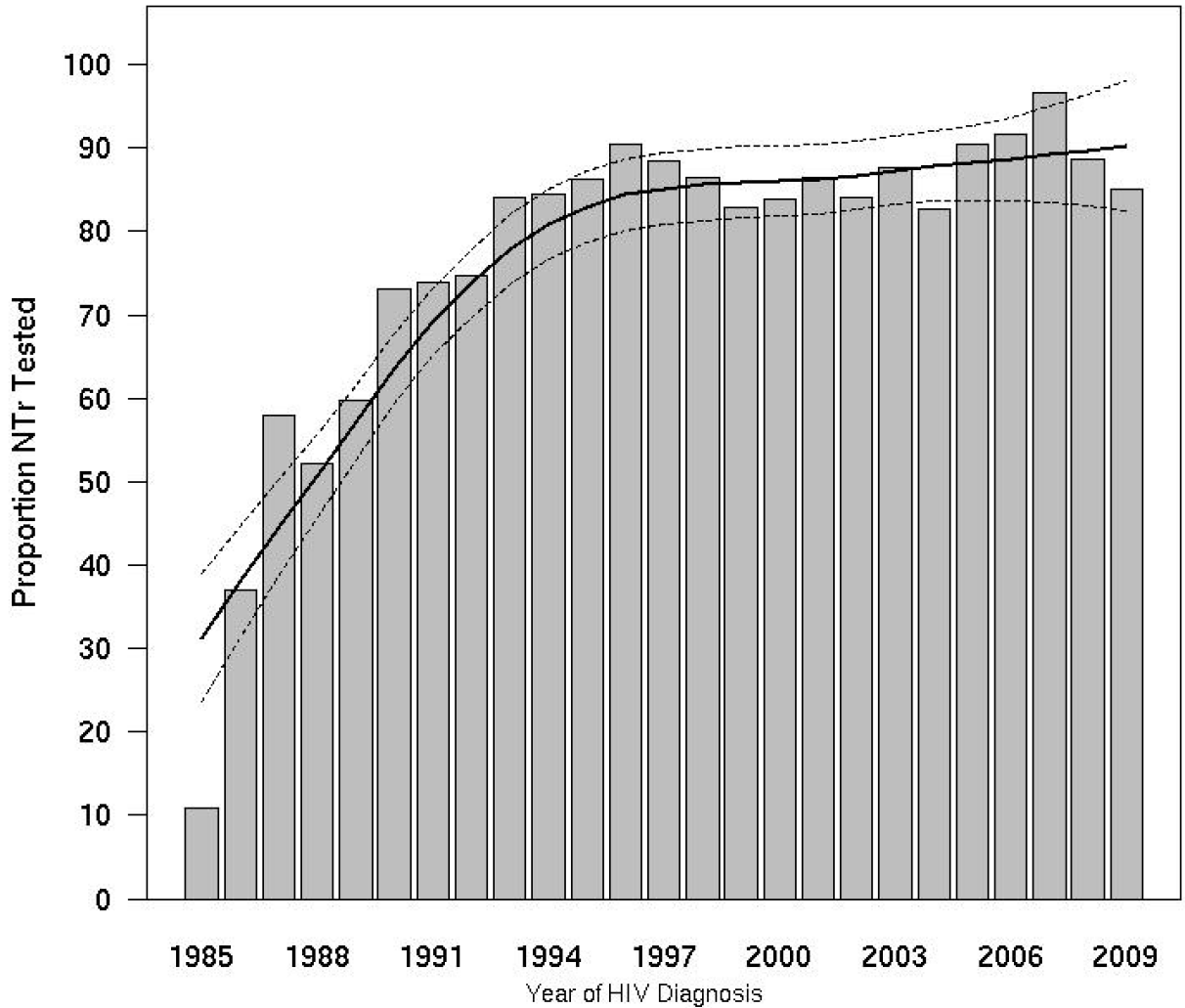
Figure 1. Flow diagram describing participant selection for the Incidence and Prevalence analyses



Pts with a Visit:	89	138	247	620	860	1479	1905	1893	1781	1632	1549	1431	1450	1512	1414	1386	1437	1494	1450	1349	1312	1458	1474	1606
Pts Tested for Syphilis:	80	119	176	250	691	1340	1720	1671	1572	1410	1312	1205	1137	1217	1177	1130	1143	1356	1324	1233	1226	1388	1425	1467
% Tested:	90	86	71	40	80	91	90	88	88	86	85	84	78	80	83	82	80	91	91	91	93	95	97	91

Figure 2A. Syphilis Testing Rates by calendar year

The solid and dotted lines represent the local linear robust fit smoothing line and the pointwise 95% confidence intervals respectively for the prevalence of syphilis at HIV diagnosis. The shaded bars represent testing rates by year.



Pts Diagnosed with HIV:	82	800	640	357	303	271	283	260	189	161	153	147	129	148	122	111	134	138	129	75	73	108	116	106	80
Pts NTr Tested:	9	296	371	186	181	198	209	194	159	136	132	133	114	128	101	93	116	116	113	62	66	99	112	94	68
% NTr Tested:	11	37	58	52	60	73	74	75	84	84	86	90	88	86	83	84	87	84	88	83	90	92	97	89	85

Figure 2B. Syphilis Testing Rates at HIV Diagnosis by calendar year

The solid and dotted lines represent the local linear robust fit smoothing line and the pointwise 95% confidence intervals respectively for the prevalence of syphilis at HIV diagnosis. The shaded bars represent testing rates by year.

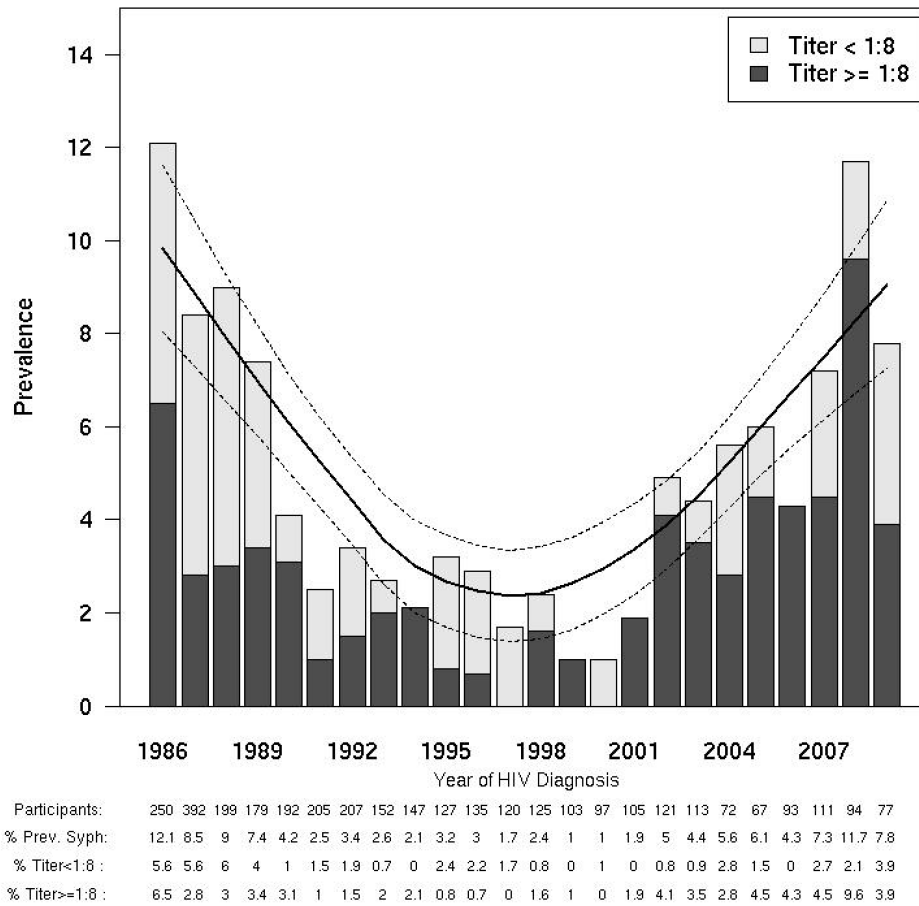


Figure 3. Prevalence of syphilis cases at the time of HIV diagnosis and by calendar year
 The solid and dotted lines represent the local linear robust fit smoothing line and the pointwise 95% confidence intervals respectively for the prevalence of syphilis at HIV diagnosis. The dark shaded bars represent subjects with early disease.

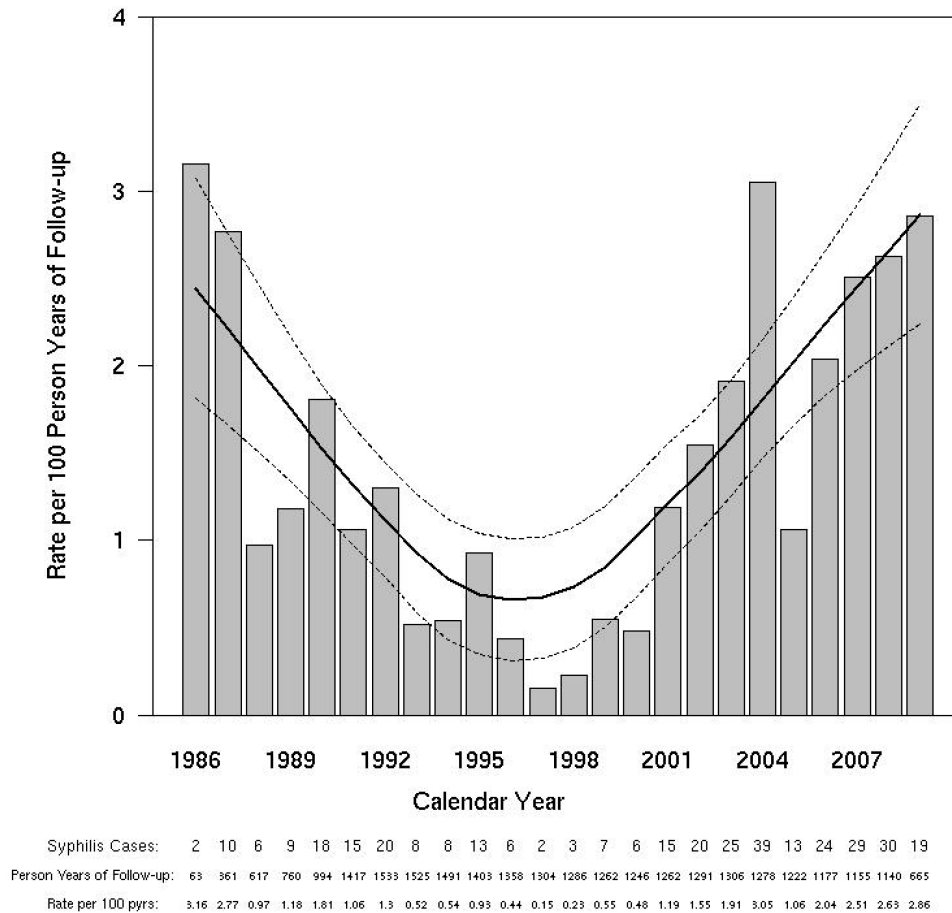


Figure 4A. Incidence of syphilis after HIV diagnosis and by calendar year
 The solid and dotted lines represent the local linear robust fit smoothing line and the pointwise 95% confidence intervals respectively for the incidence of syphilis after HIV diagnosis.

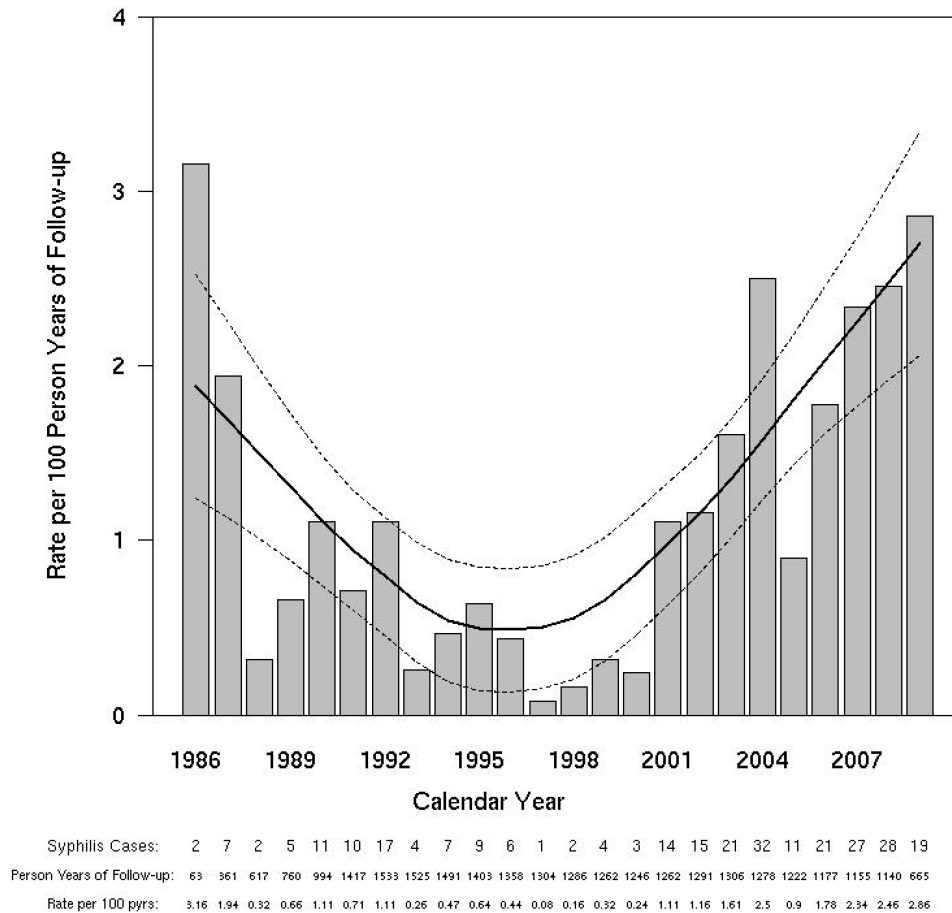
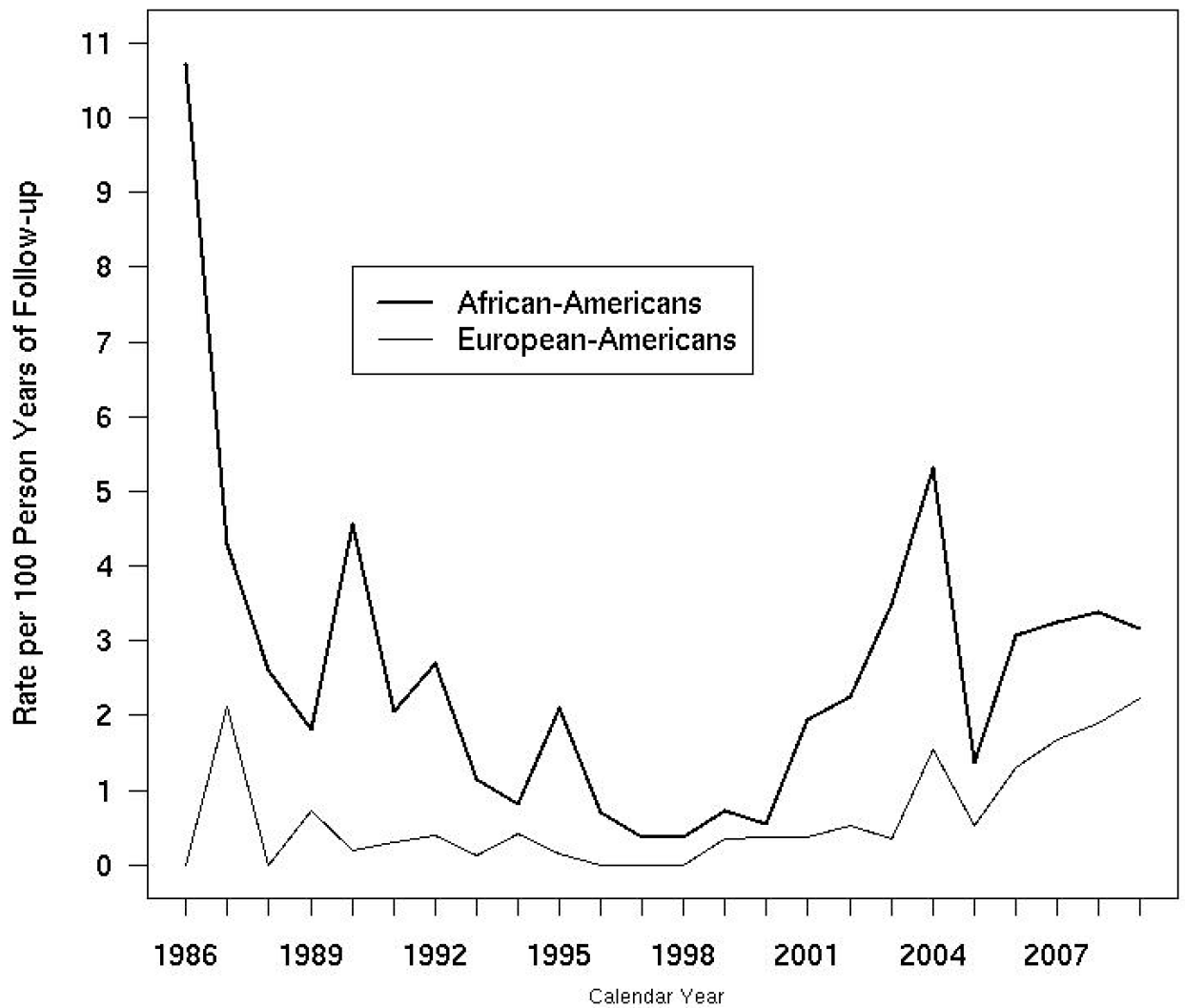


Figure 4B. Distribution of incident syphilis cases diagnosed with early disease by calendar year
 The solid and dotted lines represent the local linear robust fit smoothing line and the pointwise 95% confidence intervals respectively for the incidence of early syphilis cases after HIV diagnosis.



Eur Am Cases:	0	4	0	3	1	2	3	1	3	1	0	0	0	2	2	2	3	2	9	3	7	9	10	7
Person Yrs Eur Am:	38	189	336	419	523	678	743	751	729	683	649	608	594	575	555	557	564	588	583	563	544	541	530	312
Rate/100 pyrs Eur Am:	0	2.12	0	0.72	0.19	0.3	0.4	0.13	0.41	0.15	0	0	0	0.35	0.36	0.36	0.53	0.34	1.54	0.53	1.29	1.67	1.89	2.24
Afr Am Cases:	2	6	6	5	17	12	17	7	5	12	4	2	2	4	3	11	13	20	29	7	15	15	15	8
Person Yrs Afr Am:	19	140	230	276	374	583	631	610	611	575	566	559	560	557	559	566	579	571	548	514	491	463	445	254
Rate/100 pyrs Afr Am:	10.7	4.28	2.6	1.81	4.55	2.06	2.69	1.15	0.82	2.09	0.71	0.36	0.36	0.72	0.54	1.94	2.25	3.5	5.3	1.36	3.06	3.24	3.37	3.16

Figure 4C.
Incidence of syphilis cases after HIV diagnosis among African Americans and European Americans in the NHS

TABLE 1

Risk Factors Associated With Incident Syphilis

Characteristic	N	Cases	Person-Years	Univariate HR	P	Multivariate HR*	P
Demographics							
Age (for every 10-yr increase)	4239	347 (8%)	27,192	0.86 (0.74–1.00)	0.05	0.82 (0.75–0.91)	0.0002
Gender							
Male	3903	342 (9%)	24,951	5.97 (2.46–14.44)	[lt]0.0001	5.63 (2.31–13.73)	0.0001
Female	336	5 (1%)	2241	Referent		Referent	
Ethnicity							
European-American	1894	74 (4%)	12,886	Referent		Referent	
African American	1828	237 (13%)	11,310	3.50 (2.69–4.56)	[lt]0.0001	3.24 (2.48–4.24)	[lt]0.0001
Hispanic/Puerto Rican/Mexican	352	23 (7%)	2033	1.85 (1.16–2.97)	0.01	1.85 (1.15–2.96)	0.01
Other	163	13 (8%)	959	2.20 (1.21–3.97)	0.009	2.37 (1.30–4.29)	0.005
HIV-specific characteristics							
Antiretroviral therapy [†]							
None	1185	154 (13%)	3967	Referent		Referent	
Mono-Dual therapy	1136	45 (4%)	5593	0.65 (0.46–0.92)	0.01	0.72 (0.50–1.04)	0.08
HAART	1918	148 (8%)	17,632	0.75 (0.57–1.0)	0.05	0.92 (0.69–1.23)	0.58
CD4 cell count [‡] (cells/uL)							
[lt]200	943	21 (2%)	5293	0.61 (0.38–0.97)	0.04	—	—
200–499	1503	146 (10%)	9583	0.96 (0.77–1.20)	0.72	—	—
[mtequ]500	1756	179 (10%)	12,304	Referent			
Nadir CD4 [‡] (for 100 cell increase)	4202	346 (8%)	27,180	1.06 (1.00–1.11)	0.04	1.02 (0.96–1.08)	0.5
HIV RNA [‡] (log ₁₀ copies/mL) (for each log increase)	3152	247 (8%)	24,102	1.05 (0.94–1.18)	0.36	—	—
AIDS-defining							

Characteristic	N	Cases	Person-Years	Univariate HR	P	Multivariate HR*	P
illness ^{†‡}							
Yes	847	22 (3%)	6177	0.69 (0.44–1.07)	0.10	0.69 (0.43–1.11)	0.12
No	3392	325(10%)	21,016	Referent		—	—
Years from HIV diagnosis	4239	347 (8%)	27,192	0.94 (0.87–1.02)	0.13	0.93 (0.85–1.01)	0.09
Other sexually transmitted infections							
Hepatitis B [†]							
Yes	1890	185 (10%)	14,120	1.71 (1.37–2.13)	[lt]0.0001	1.52 (1.22–1.91)	0.0003
No	2349	162 (7%)	13,072	Referent		Referent	
Gonorrhea [†]							
Yes	1129	130 (12%)	8209	1.89 (1.50–2.38)	[lt]0.0001	1.42 (1.12–1.80)	0.004
No	3085	216 (7%)	18,896	Referent		Referent	

* Model is stratified by the era of HIV-positive test (pre-1996, post-1996) and enrollment center.

[†] Time varying covariate, therefore the columns contain the number in each group at censoring (i.e., incident infection or last NTr).

[‡] AIDS-defining conditions based on the 1993 CDC criteria excluding CD4 count.