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SYPHILIS IN THE HIV ATLANTA VA COHORT: RISK FACTORS AND EPIDEMIOLOGY

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SYPHILIS IN THE HIV ATLANTA VA COHORT: RISK FACTORS AND EPIDEMIOLOGY

By

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Abstract

SYPHILIS IN THE HIV ATLANTA VA COHORT:
RISK FACTORS AND EPIDEMIOLOGY

By Katherine Dunne

Background: Despite the availability of effective treatment, syphilis continues to be a significant public health problem in the United States, particularly among HIV-positive individuals. This analysis seeks to determine whether there are specific risk factors for syphilis infection among HIV-positive individuals and to describe the distribution of syphilis stages within that population.

Methods: We performed a retrospective matched case-control study of members of the HIV Atlanta VA cohort study (HAVACS) from 2006-2010, comparing demographic, clinical and laboratory data of HIV-positive individuals with at least one episode of syphilis during the study period to those with no documented syphilis during that period. We performed a similar comparison of individuals with repeat syphilis infection to those with a single episode of syphilis during the study period. Additionally, a descriptive analysis of syphilis stages within the cohort was performed.

Results: The only significant differences in cases and controls were age and HIV risk factor. On average, cases were younger than controls ($p<0.0001$) and were more likely to be men who have sex with men (MSM) ($p<0.0001$). There were no significant differences between repeat and single episode syphilis cases in any of the study variables. 40.8% of syphilis episodes among HIV-positive individuals at the Atlanta VA between 2006 and 2010 were in the early latent stage.

Conclusions: HIV-positive veterans who are younger and MSM are more likely to become infected with syphilis. A high proportion of syphilis cases among HIV positive individuals at the Atlanta VA Medical Center (VAMC) between 2006 and 2010 were in the early latent stage. These findings emphasize the need for increased surveillance of latent disease and intensified counseling of high risk, HIV-positive individuals.

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CHAPTER I: BACKGROUND/LITERATURE REVIEW

Introduction

Syphilis is a sexually transmitted disease (STD) caused by the bacterium *Treponema pallidum* which continues to represent a significant public health burden in the United States despite the availability of effective treatment. Although rates of syphilis in the US declined for many years, reaching their lowest point in 2000 since reporting began, primary and secondary (P&S) syphilis increased annually from 2001–2009 (1). In 2010, P&S syphilis rates decreased for the first time in a decade, but there was an increase in the rates of both early latent and late latent syphilis (1).

Elimination of syphilis has become a national priority. The National Plan to Eliminate Syphilis from the United States was launched in October 1999 and defined an operational goal of less than 1000 cases of P&S syphilis reported per year. Syphilis elimination was considered plausible in the US at that time due to historically low rates of infection, geographically limited disease incidence, and the availability of diagnostic tests and effective therapy. From 1999 to 2004, the Centers for Disease Control and Prevention (CDC) invested over $107 million to areas of the country with sustained syphilis transmission. CDC also provided a considerable amount of technical assistance to the elimination effort through outbreak investigation, research and evaluation support. Despite enhanced surveillance and a national agenda to eliminate the disease, P&S syphilis rose steadily from 2001-2009 (2).

The rising rates of syphilis in recent years have been largely attributed to outbreaks among certain subsets of the population, especially HIV-positive individuals (1). The link between HIV and syphilis is well established, but it is unknown whether, among HIV-positive individuals, there are specific characteristics that increase the risk of acquiring syphilis. The benefit of identifying such risk factors would be the ability to target clinical and educational resources toward individuals at highest risk of co-infection. Also unknown is the distribution of syphilis stages within the HIV-positive

population. Most surveillance reports focus on P&S syphilis because it is the best indicator of incident disease, but there may be a significant amount of asymptomatic, or latent, syphilis that is not being explored.

This analysis seeks to identify risk factors for syphilis infection among HIV-positive individuals at the Atlanta Veterans Administration Medical Center (VAMC) and to describe the epidemiology of syphilis within that population.

Epidemiology of Syphilis in the US

Certain subsets of the population have experienced particularly high syphilis rates in the last decade. Recent increases in syphilis among MSM have been characterized by high rates of HIV co-infection and high-risk sexual behaviors (2). In 2010, two-thirds of reported P&S syphilis cases were among MSM, representing an increase from only 7% in 2000 (3). In response to the surge in syphilis among MSM, the CDC requested in 2005 that all state health departments report the sex of sex partners of individuals diagnosed with syphilis. As of 2010, 82% of reported P&S syphilis among males included information about the sex of sex partners (1).

High syphilis rates have also disproportionately affected certain areas of the country, especially the South (1, 3). The South currently accounts for about half of P&S syphilis cases in the US. Georgia ranks second among states for P&S syphilis with 8.1 cases per 100,000 individuals, which is close to two times the national rate of 4.5 cases per 100,000. Even higher rates of P&S syphilis were reported within the Atlanta metropolitan statistical area in 2010, with 11.9 cases per 100,000 (1).

The Veterans Administration Medical Center (VAMC) in Atlanta serves patients from this region of disproportionately high syphilis rates. Since 1993, 25-75% of incident syphilis cases in Atlanta VAMC patients occurred among HIV-positive individuals who only account for 1.6-1.9% of the total clinical population (D. Rimland, personal communication, December 23, 2011). Nationally,

the VA screened 52% of its HIV-positive patients for syphilis in 2009 and the VA Southeast Network, of which the Atlanta VAMC is a member, screened 70% of its HIV-positive patients (4); the Atlanta VAMC screened 90% for that year (D. Rimland, personal communication, December 23, 2011). Despite high syphilis screening rates in the VA population, epidemiologic trends in syphilis stages are unknown.

Syphilis and HIV

The association between syphilis and HIV is well established. Syphilis has been shown to facilitate HIV transmission (3) and there is evidence to suggest an increased risk of incident and repeat syphilis in HIV-positive individuals (5-7). In 2010, the prevalence of P&S syphilis in HIV-positive MSM was over four times that of HIV-negative MSM and MSM of unknown status (1). The CDC recommends that all individuals diagnosed with syphilis be tested for HIV infection and that syphilis screening be performed at least annually for all sexually active, HIV-positive individuals (8).

The co-occurrence of HIV and syphilis is not surprising given the overlap of risk factors for the two diseases. For example, gender affects syphilis risk as well as HIV risk. The male-to-female ratio for P&S syphilis rose from 1.2 in 1996 to 7.2 in 2010 (1) and males account for three quarters of all HIV diagnoses among adults and adolescents (9). Race is also a significant risk factor for both syphilis and HIV. Syphilis rates remain high among non-Hispanic blacks at 16.8 cases per 100,000 population (1) and, although blacks represent approximately 14% of the US population, they account for an estimated 44% of new HIV infections (9). Age is also an important risk factor, with individuals aged 20-24 showing the highest rates of both P&S syphilis (1) and HIV (9). Finally, behavioral risk factors impact both syphilis and HIV infection rates. In 2010, MSM accounted for 67% of P&S syphilis (1) and, although MSM account for just 2% of the US population, they accounted for 61% of all new HIV infections in 2009 (9). While HIV positive individuals may be at

higher risk of syphilis infection, it is not known if markers of HIV infection such as CD4 count or viral load correlate with syphilis risk.

Syphilis Screening

T. pallidum, the causative agent of syphilis, is a thin, elongated bacterium of the Spirochaetaceae family. It cannot be visualized by light microscopy and instead requires darkfield microscopy of samples from skin lesions or lymph nodes. Darkfield microscopy involves the oblique application of light so that no direct light enters the microscope objective, resulting in an illuminated object against a dark background. A positive result on darkfield examination is an almost certain diagnosis of primary, secondary, or early congenital syphilis. This type of microscopy is particularly useful in patients with early primary syphilis or advanced acquired immunodeficiency syndrome (AIDS), as it can diagnose syphilis in the absence of antibodies to *T. pallidum* (10).

Adding to the difficulty of syphilis diagnosis, *T. pallidum* cannot be cultured. For this reason, laboratory tests for syphilis either detect components of *T. pallidum* (antigen detection tests) or antibodies produced in response to *T. pallidum* infection (antibody detection tests)(10). The diagnosis of primary and secondary syphilis is generally made with a combination of antigen detection tests and serologic tests while early and late latent syphilis is diagnosed with antibody detection tests alone (10).

Serologic tests for syphilis are divided into two categories: nontreponemal and treponemal. Two widely used nontreponemal tests for syphilis are the rapid-plasma-reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests. RPR and VDRL tests detect immunoglobulin G (IgG) and IgM antibodies to *T. pallidum* formed in response to the release of lipoidal material from damaged host cells and lipoprotein-like material and possibly cardiolipin from treponemes (10).

Quantitative titers can be obtained using both RPR and VDRL methods via serial twofold dilutions. This quantification is useful in monitoring response to antibiotic therapy. RPR and VDRL titers decline even without therapy and in about one fourth of untreated patients, VDRL tests eventually become nonreactive (11). While nontreponemal test titers generally rise during active infection and decline after treatment, treponemal tests rise early in syphilis infection and may remain detectable for the life of the individual despite effective treatment.

Treponemal tests such as the fluorescent treponemal-antibody absorption (FTA-ABS) test, the microhemagglutination assay for T. pallidum (MHATP), and the hemagglutination treponemal tests are required for confirmation of positive nontreponemal tests. Treponemal tests target *T. pallidum* proteins and are highly sensitive but, compared to nontreponemal tests, are more expensive and difficult to perform and therefore are not used for screening (11). Reverse sequence testing, which involves treponemal enzyme and chemiluminescence immunoassays with cloned *T. pallidum* antigens followed by reflexive nontreponemal testing, is now being used by many laboratories. However, due to a high percentage of discordant results from reverse sequence screening (12), CDC continues to recommend the traditional algorithm (13).

Importantly, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are co-infected with *T. pallidum* and HIV (4). Although CDC recommends annual syphilis screening for HIV-positive individuals (8), annual syphilis screening among veterans with HIV is lower than the national average (14). In general, most epidemiologic information reported on syphilis focuses on primary and secondary syphilis, therefore there may be a large burden of asymptomatic latent disease, particularly among high risk HIV-positive veterans.

Treatment of Syphilis

Syphilis is easily treated in its early stages (15). Parenteral penicillin G is the preferred treatment and is the only available therapy proven to be effective in pregnancy. Response to treatment of early syphilis should be monitored at 3, 6, 9, 12 and 24 months following therapy. Similar monitoring should be performed for late latent syphilis with nontreponemal tests at 6, 12, 18 and 24 months. Despite effective treatment of syphilis, 15-20% of individuals may remain serofast, or have reactive serum nontreponemal tests, usually at titers <1:8, for prolonged periods of time (16). In this situation, screening for reinfection should be based on an at least a fourfold increase in titer above the established serofast baseline (16).

An occasional consequence of antibiotic therapy for syphilis is the Jarisch-Herxheimer reaction. This acute febrile illness often involves headache, myalgias and fever and usually occurs within the first 24 hours of syphilis therapy. The Jarisch-Herxheimer reaction most commonly occurs in early stages and is managed with antipyretics (15).

Treatment of late latent syphilis, latent syphilis of unknown duration and tertiary syphilis require a longer duration of therapy, perhaps because *T. pallidum* divides more slowly in those individuals (8). In the event of penicillin allergy, alternative antibiotic therapies exist for nonpregnant patients. However, for pregnant patients with penicillin allergy, penicillin therapy should be administered following desensitization (8). Treatment of syphilis at any stage is the same regardless of HIV status (8).

Syphilis Staging and Clinical Presentation

Syphilis is a reportable disease in the United States and, for the purposes of contact investigation, individuals with primary, secondary, and early latent syphilis are considered infectious (17). Transmission of *T. pallidum* may occur during vaginal, anal or oral sex (8) and transmission is estimated to occur in about one third of patients exposed to early syphilis (11). Additionally, syphilis

can be transmitted from mother to child in pregnancy. Perinatal death can occur in up to 40% of untreated early syphilis in pregnant women and, if it is acquired within 4 years prior to pregnancy, can lead to infection of the fetus in 80% of cases (1).

Syphilis is categorized into different stages based on clinical signs and symptoms. Primary infection generally results in a painless chancre at the site of inoculation. The incubation period can range from 10-90 days with an average of 31 days. The chancre can resolve spontaneously in 3 to 6 weeks, but can progress to secondary syphilis if left untreated.

The secondary stage results from hematogenous dissemination of the organism and is characterized by skin rash which may appear as the primary chancre is healing or several weeks later. In some cases, the rash may appear to mimic that of other diseases, contributing to syphilis' reputation as "the great imitator." Other symptoms associated with secondary stage are varied and nonspecific, including fever, fatigue, generalized lymphadenopathy, alopecia and condylomata lata, or gray papular lesions occurring in the anus, vulva or scrotum. Like primary syphilis, signs and symptoms of secondary syphilis will resolve spontaneously but will progress to latent stages without treatment (15).

Latent or asymptomatic syphilis can last for many years and is only detectable with serologic testing. Latent syphilis is divided into early and late stages depending on the length of infection. According to CDC definitions, latent syphilis infection of less than one year is early latent syphilis and latent infection of more than one year is considered late latent syphilis.

Latent syphilis, if left untreated, can lead to severe health consequences. Approximately one third of untreated individuals with late latent disease will develop late, or tertiary, syphilis which generally appears 10-20 years after initial infection (18). Late syphilis can affect multiple organ systems, causing significant disability or death. Tertiary syphilis includes gummatous disease, cardiovascular syphilis and neurosyphilis. Gummatous disease manifests as ulcerating nodular lesions

involving the skin as well as bones and upper respiratory tract (18). Cardiovascular syphilis consists primarily of aortitis of the ascending aorta, which may affect the aortic valve and coronary ostia. Neurosyphilis consists of a range of overlapping manifestations including asymptomatic, meningeal, meningovascular, parenchymatous and gummatous disease (10).

CHAPTER II: MANUSCRIPT

SYPHILIS IN THE HIV ATLANTA VA COHORT: RISK FACTORS AND EPIDEMIOLOGY

Katherine Dunne

ABSTRACT

Background: Despite the availability of effective treatment, syphilis continues to be a significant public health problem in the United States, particularly among HIV-positive individuals. This analysis seeks to determine whether there are specific risk factors for syphilis infection among HIV-positive individuals and to describe the distribution of syphilis stages within that population.

Methods: We performed a retrospective matched case-control study of members of the HIV Atlanta VA cohort study (HAVACS) from 2006-2010, comparing demographic, clinical and laboratory data of HIV-positive individuals with at least one episode of syphilis during the study period to those with no documented syphilis during that period. We performed a similar comparison of individuals with repeat syphilis infection to those with a single episode of syphilis during the study period. Additionally, a descriptive analysis of syphilis stages within the cohort was performed.

Results: The only significant differences in cases and controls were age and HIV risk factor. On average, cases were younger than controls ($p<0.0001$) and were more likely to be men who have sex with men (MSM) ($p<0.0001$). There were no significant differences between repeat and single episode syphilis cases in any of the study variables. 40.8% of syphilis episodes among HIV-positive individuals at the Atlanta VA between 2006 and 2010 were in the early latent stage.

Conclusions: HIV-positive veterans who are younger and MSM are more likely to become infected with syphilis. A high proportion of syphilis cases among HIV positive individuals at the Atlanta VA Medical Center (VAMC) between 2006 and 2010 were in the early latent stage. These findings emphasize the need for increased surveillance of latent disease and intensified counseling of high risk, HIV-positive individuals.

INTRODUCTION

Despite a small decrease in primary and secondary syphilis rates for the first time in ten years (1), syphilis continues to represent a significant public health burden in the United States. There is evidence suggesting increased risk of incident and repeat syphilis in HIV-positive individuals (5-7) but it is unknown if immunologic or virologic markers of HIV infection correlate with syphilis risk. The southern United States experiences disproportionately high rates of syphilis and between one- and three-quarters of syphilis cases at the Atlanta Veterans Administration Medical Center (VAMC) since 1993 have occurred among HIV-positive individuals. However, the epidemiology of syphilis in this high risk population of veterans is unknown.

Currently, most syphilis surveillance as well as national elimination goals refer explicitly to primary and secondary (P&S) syphilis, not latent disease (2). However, latent syphilis may be responsible for considerable public health costs in the US. The burden of asymptomatic syphilis may become evident as routine screening is adopted in HIV-infected populations. This analysis seeks to describe risk factors for syphilis infection among HIV-positive patients at the Atlanta VAMC from 2006-2010 via a retrospective matched case-control study. We also aim to describe the epidemiology of syphilis in this population over the same 5 year period, focusing on the trends and distribution of syphilis stages.

METHODS

Study Population

The study population included members of the HIV Atlanta VA cohort study (HAVACS). This cohort consists of over 3,700 patients and includes a database of prospectively collected information from all HIV positive veterans who have sought medical care at the Atlanta VAMC since 1982. The database includes the full HIV history of patients as collected on standardized forms. The

information collected consists of demographic characteristics, clinical symptoms, HIV-related diagnoses, antiretroviral regimens, vaccinations, inpatient visits and diagnoses, pharmaceutical data and laboratory measurements. These data are updated for every inpatient and outpatient contact with the Atlanta VAMC.

Study Design

We conducted a retrospective matched case-control study of HAVACS patients. Cases were defined as individuals with at least one episode of incident syphilis, defined by positive RPR (RPR≥1:8), documented between January 1, 2006 and December 31, 2010. Controls were chosen from 1,784 HIV-positive individuals with non-reactive RPR titers seen at the Atlanta VAMC during the 5-year study period. For those controls with multiple documented RPR titers, only the first titer was eligible for matching.

We performed 1:1 random matching within 10 days of the date of the first documented positive RPR using a SAS macro from the Mayo Clinic (19). Matching was based on RPR date to control for seasonal variation in syphilis rates (20). Although the study sample initially included 428 subjects, 3 case-control pairs were excluded after 3 controls were matched to an RPR date which occurred before their HIV diagnosis date. A total of 82 subjects had repeat episodes of syphilis that were not utilized in the case-control study, but were analyzed in an investigation of syphilis stage distribution.

Variables

Data was collected from the HIV Atlanta database and the VA electronic medical record software, Computerized Patient Record System (CPRS). Demographic information collected included gender, race, and age in years at the time of the RPR test. CDC classification and HIV exposure category were also collected (Tables A1-A2). RPR titer and dates of RPR test as well as the dates of HIV and/or AIDS diagnosis were recorded along with duration of HIV and/or AIDS at the time of RPR. Whether the individual was on highly active anti-retroviral therapy (HAART)

within one month of their RPR test was noted. Syphilis stage as documented in CPRS was collected. If documentation of syphilis stage was not available, stage was assigned using the available clinical information in the medical chart in accordance with CDC case definitions for syphilis. Additionally, laboratory data was collected for all subjects including CD4 count and viral load on the date of the RPR test and/or within 6 months of the RPR test, depending on which was documented.

Analysis

Cases and controls were compared using chi-square and t-tests as appropriate. Similar comparisons were made between individuals with multiple episodes of syphilis during the study period and those with a single episode. A significance level of 0.05 was used and all analyses were performed using SAS version 9.3 Carey, SC and OpenEpi (21).

RESULTS

The characteristics of participants in the case-control study are listed in Table 1. Cases and controls were very similar in terms of demographic and clinical factors as well as laboratory values. The majority of subjects were black and male but there was a significant difference in age between cases and controls ($p=0.001$), with cases being younger on average. The majority of subjects had documentation of HAART within one month of RPR and cases and controls demonstrated a similar distribution of CD4 and CDC clinical categories. The majority of subjects had a documented diagnosis of AIDS (60.6% of cases and 69.4% controls) and had similar AIDS and HIV duration at the time RPR testing was performed. Cases and controls varied significantly in terms of HIV risk factors, with cases showing a greater percentage of MSM than controls. Cases and controls were similar in terms of CD4 count and viral load.*

Characteristics of HAVACS members who had single or multiple episodes of syphilis within the 5-year study period are listed in Table 2. More than half (56.4%) of individuals with syphilis had multiple episodes during the study period. Repeat and single episode subjects were similar in terms

of demographic, clinical, behavioral and laboratory data. In terms of demographics, the average age of individuals with syphilis, including single and repeat episodes, was 41.4 years and the majority was black. All individuals with syphilis were male. The majority was documented to have been receiving HAART within one month of their syphilis diagnosis and the two groups showed similar distributions of CD4 categories and CDC clinical categories. Over half of individuals with repeat or single episode syphilis had a documented AIDS diagnosis and both groups showed similar HIV duration, AIDS duration, HIV risk factors, CD4 counts and viral loads.*

Total RPR testing performed at the Atlanta VAMC during the study period is summarized in Table 3. The number of RPR tests performed more than doubled over the 5 year period, rising steadily from 3,616 in 2006 to 7,548 in 2010. Although the number of positive RPR tests also increased during that period, the proportion of positive tests remained constant ($p=0.3698$).

Table 4 summarizes incident syphilis (RPR>4) among HIV-positive and HIV-negative patients by year. Between 2006 and 2010, the number of syphilis cases among HIV-positive individuals increased, but the proportion of HIVpositive syphilis cases remained stable ($p=0.3561$) over that period at approximately 75%.

Table 5 shows the number of HIV patients at the Atlanta VAMC and the RPR testing among them by year. The HIV-positive population at the Atlanta VAMC increased nearly 18% between 2006-2010 but the number of RPR tests conducted in that population increased by over 400%, with some veterans receiving more than one RPR per year.

The distribution of syphilis stages among members of the HIV Atlanta cohort from 2006-2010 is shown in Table 6. The total number of syphilis episodes increased between 2006 and 2010. Overall, early latent syphilis accounted for the greatest proportion of episodes (40.4%) and "other" syphilis the smallest (5.1%). Over the 5 year study period, the proportion of latent disease- both late

*The logarithm of viral load was used in the analysis given the markedly non-normal distribution of viral load values.

and early latent syphilis – increased significantly (p=0.0001). This increase in latent disease is illustrated in Figure 1 in terms of incidence per 1000 HIV patients tested and in Figure 2 in terms of the proportion of syphilis episodes by stage.

DISCUSSION

Approximately three-quarters of incident syphilis cases at the Atlanta VAMC from 2006-2010 occurred among HIV-positive patients. Comparing HIV-positive veterans with syphilis to those without syphilis, syphilis cases were younger and more likely to be MSM, findings which are consistent with previous studies (1). No significant differences were detected between cases and controls in terms of other demographic factors, clinical characteristics or markers of HIV infection. Comparing single episode syphilis cases to repeat episode cases, there were no statistically significant differences in any of the variables studied. Over half of cases had more than one episode of syphilis during the study period. The large number of subjects with multiple syphilis episodes is not surprising in this population given the known association between HIV and risk of repeat syphilis infection (5, 22). Targeting individuals with repeat infection should be a public health priority if syphilis elimination efforts are to be effective (5).

The HIV-positive population at the Atlanta VAMC increased nearly 18% from 2006-2010 but the number of RPR tests conducted in that population increased by over 400%, with some veterans receiving more than one RPR test per year. While more syphilis testing is being conducted among veterans at the Atlanta VA each year, the proportion of positive tests remains constant. However, the incidence of latent syphilis, particularly early latent syphilis, is rising noticeably among HIV-positive patients and P&S incidence is declining. Since these findings appear to mirror the most recently reported national syphilis trends (1), closer surveillance of latent syphilis, particularly in high risk populations, could be expected to reveal significant asymptomatic disease.

Syphilis screening among HIV-positive veterans at the Atlanta VAMC from 2006-2010 detected a growing proportion of latent disease. While a marked increase in RPR testing in this population may account for the observed increase, the detection of asymptomatic syphilis is significant in terms of morbidity, mortality and economic cost (18, 23). Limitations of this study include its retrospective design and potential for temporal bias. Since early syphilis infection can affect CD4 count and viral load (24), measuring these markers of HIV infection close to the time of a positive RPR could potentially mask a difference between cases and controls.

Our data suggest that CDC recommendations for annual syphilis screening of HIV-positive patients are aggressively followed in our cohort. For those patients who test positive for syphilis, there is an opportunity for intensified counseling by healthcare providers. In fact, CDC considers the occurrence of syphilis in an HIV-infected person to be an indication of high-risk behavior which should prompt intensified counseling messages and possible referral for behavioral intervention (16). Despite the fact that more patients in this cohort are being tested for syphilis each year, there is a growing proportion of latent disease. Increases in early latent disease suggest that syphilis in earlier stages is not being detected. Therefore, high risk populations should be made aware of the signs of early syphilis and the importance of condom use and regular syphilis screening. To aid in this effort, increased surveillance and reporting of latent syphilis is needed.

TABLES

Table 1. Characteristics of participants in a retrospective matched case-control study of risk factors for syphilis infection among members of the HIV Atlanta VA Cohort 2006-2010

	Mean (SD) or n (%)		
Variable	**Cases** (n=170)	**Controls** (n=170)	**P-value**
Age, years	41.2 (8.6)	49.0 (9.7)	<.0001
Race			
Black	148 (87.6)	135 (79.9)	0.0554
White	21 (12.4)	34 (20.1)	
Gender			0.0614
Female	0	4 (2.4)	
Male	170 (100)	166 (97.7)	
ARV			0.5141
Yes	88 (51.8)	94 (55.3)	
No	82 (48.2)	76 (44.7)	
CD4 Category[1]			0.2851
1	14 (8.2)	12 (7.1)	
2	56 (32.9)	44 (25.9)	
3	100 (58.8)	114 (67.1)	
CDC Clinical Category[2]			0.0925
A	101 (59.4)	81 (47.7)	
B	32 (18.8)	40 (23.5)	
C	37 (21.8)	49 (28.8)	
AIDS			0.0881
Yes	103 (60.6)	118 (69.4)	
No	67 (39.4)	52 (30.6)	
HIV Duration, months	116.2 (85.4)	112.1 (87.6)	0.6655
AIDS Duration, months	81.2 (61.3)	72.8 (64.2)	0.3569
Risk Factor			<.0001
Male-to-male sexual contact	140 (82.4)	75 (44.1)	
IV drug use	3 (1.8)	26 (15.3)	

Male-to-male sexual contact and IV drug use	3 (1.8)	2 (1.2)	
Heterosexual contact	3 (1.8)	13 (7.7)	
Other[3]	21 (12.4)	54 (31.8)	
CD4 Lymphocyte count	444.5 (258.6)	407.1 (271.6)	0.2088
Log Viral load[4]	3.8 (1.1)	4.0 (1.2)	0.4275
% with Viral Load ≤50 copies/mL	35.2	41.3	0.2761

1. 1: ≥500 cells/mL; 2:200-499 cells/uL; 3: <200 cells/uL(25)
2. Based on clinical conditions and presence of specific opportunistic infections(25)
3. Includes blood transfusion and risk factors not reported or not identified
4. Logarithm of viral load taken due to non-normal distribution of viral load values

Table 2. Characteristics of participants with single episodes of syphilis versus repeat syphilis among members of the HIV Atlanta VA Cohort 2006-2010

	Mean (SD) or n (%)		
Variable	**Repeat** (n=144)	**Single** (n=111)	**P-value**
Age, years	41.4 (8.3)	41.4 (8.7)	0.9513
Race			0.1387
Black	129 (91.5)	95 (85.6)	
White	12 (8.5)	16 (14.4)	
Gender			
Female	0	0	NA
Male	144 (56.5)	111 (43.5)	
ARV			0.5997
Yes	80 (55.6)	58 (52.3)	
No	64 (44.4)	53 (47.8)	
CD4 Category[1]			0.0989
1	6 (4.2)	12 (10.8)	
2	46 (31.9)	37 (33.3)	
3	92 (63.9)	62 (55.9)	
CDC Clinical Category[2]			0.1468
A	92 (63.9)	64 (57.7)	
B	19 (13.2)	25 (22.5)	
C	33 (22.9)	22 (19.8)	
AIDS			0.2140
Yes	94 (65.3)	64 (56.7)	
No	50 (34.7)	47 (42.3)	
HIV Duration, months	120.4 (76.9)	118.7 (90)	0.8741
AIDS Duration, months	80.1 (63.0)	84.2 (62)	0.7024
Risk Factor			0.2919
Male-to-male sexual	116 (80.6)	95 (85.6)	

contact			
Other[3]	28 (19.4)	16 (14.4)	
CD4 Lymphocyte count	423.7 (219.3)	461.6 (274.2)	0.2489
Log Viral Load[4]	3.9 (1.2)	3.7 (1.1)	0.2396
% with Viral Load ≤50 copies/mL	37.5	30.9	0.3038

1. 1: ≥500 cells/mL; 2:200-499 cells/uL; 3: <200 cells/uL
2. Based on clinical conditions and presence of specific opportunistic infections
3. Includes IV drug use, heterosexual exposure, blood transfusion and risk factors not reported or not identified
4. Logarithm of viral load taken due to non-normal distribution of viral load values

Table 3: All RPR testing at the Atlanta VA 2006-2010

	2006	2007	2008	2009	2010
Total RPR	3616	4226	5923	6466	7548
Positive >4	49	53	78	102	122
% Positive >4	1.36	1.25	1.32	1.58	1.62

Table 4. Incident syphilis cases at Atlanta VA with RPR titer>4

	2006	2007	2008	2009	2010	Total
HIV	38	33	58	73	69	271
Non-HIV	11	20	20	29	21	101
% HIV	78	62	74	72	77	73

Table 5. RPR testing in HIV positive patients at the Atlanta VA 2006-2010

	2006	2007	2008	2009	2010
HIV patients	1111	1124	1254	1284	1307
HIV patients with RPR	403	582	1000	1096	1132
RPR tests	503	731	2017	2383	2545

Table 6. Syphilis distribution in HIV-positive patients at the Atlanta VA 2006-2010, by stage

	n (%)					
	2006 (n=27)	**2007** (n=30)	**2008** (n=58)	**2009** (n=71)	**2010** (n=69)	**Overall** (n=255)
Primary	1 (3.7)	3 (10)	7 (12.1)	4 (5.6)	7 (10.1)	22 (8.6)
Secondary	13 (48.2)	14 (46.7)	13 (22.4)	11 (15.5)	5 (7.3)	56 (22.0)
Early Latent	4 (14.8)	3 (10)	22 (37.9)	33 (46.5)	42 (60.9)	104 (40.8)
Late Latent	8 (29.6)	6 (20)	14 (24.1)	18 (25.4)	14 (20.3)	60 (23.5)
Other*	1 (3.7)	4 (13.3)	2 (3.5)	5 (7.0)	1 (1.4)	13 (5.1)

*includes syphilis of unknown duration, neurosyphilis and luetic hepatitis

FIGURES

Figure 1. Syphilis Cases per 1000 HIV Patients RPR Tested at the Atlanta VAMC by Year and Stage

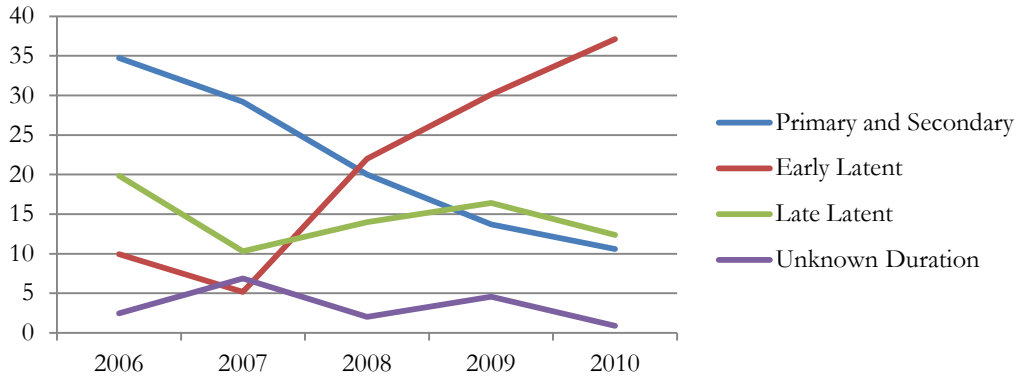
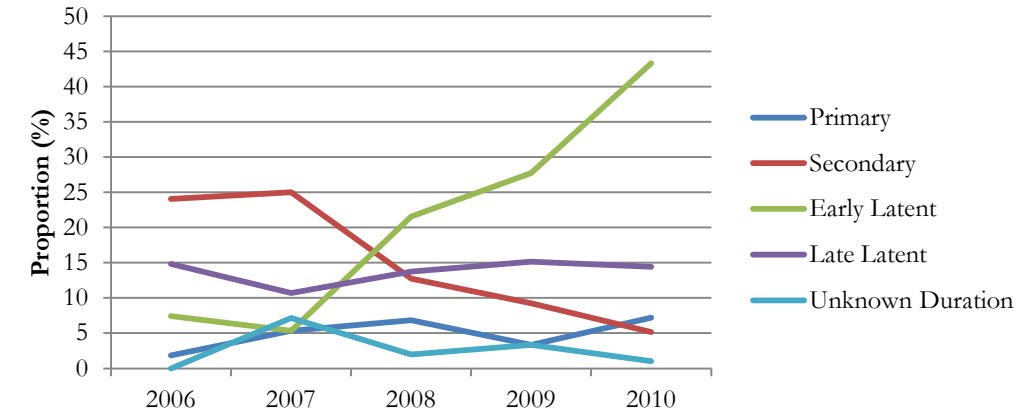


Figure 2. Syphilis Trends at the Atlanta VAMC by Stage 2006-2010



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CHAPTER III: SUMMARY, PUBLIC HEALTH IMPLICATIONS AND POSSIBLE FUTURE DIRECTIONS

Summary

Testing for syphilis infection among HIV-positive veterans at the Atlanta VAMC increased between 2006 and 2010 and, although the proportion of positive tests remained stable, the proportion of latent syphilis, particularly early latent disease, increased dramatically. While there were no differences in demographic factors, clinical characteristics or markers of HIV infection between individuals with single syphilis episodes and those with multiple episodes, comparing HIV-positive veterans with syphilis to those without syphilis revealed that syphilis cases were significantly younger and more likely to be MSM.

Public Health Implications

Increased syphilis screening among HIV-positive individuals at Atlanta VA between 2006 and 2010 revealed that the proportion of early latent syphilis is rising. Such an increase in latent disease presents significant public health burden both in terms of illness and cost. Because latent syphilis is asymptomatic, affected individuals are unlikely to receive appropriate antibiotic therapy unless the infection is revealed through serologic screening. Approximately one-third of individuals with untreated syphilis will develop the sequelae of tertiary syphilis which can cause significant disability or death. Because syphilis transmission is possible during the early latent stage, increasing rates of early latent syphilis will hinder syphilis elimination efforts and may be a source of increased HIV transmission within these asymptomatic individuals.

In addition to health concerns, there is significant monetary incentive to minimize the number of individuals with untreated syphilis. The overall average outpatient cost per episode of P&S syphilis was recently estimated to be nearly $200 (26). Furthermore, the prevention of syphilis related HIV transmission could save hundreds of millions of dollars in direct and indirect medical costs (23).

Possible Future Directions

This analysis revealed that the majority of syphilis in the Atlanta VAMC population occurs among HIV-positive veterans, with younger individuals and MSM shown to be particularly vulnerable to syphilis infection. In order to be most effective, syphilis screening, treatment and educational efforts should be targeted toward these high risk subpopulations. Increased awareness among HIV-positive populations of the risk factors for syphilis infections as well as the consequences of asymptomatic disease is necessary. Additionally, healthcare providers should intensify counseling efforts in HIV-positive individuals who test positive for syphilis and other STDs.

The proportion of positive syphilis tests in HIV-positive veterans at the Atlanta VAMC has remained constant in recent years, but the proportion of latent syphilis is on the rise. This finding within a population which is highly representative of groups at high risk for STD transmission underlines the need for increased surveillance and reporting of latent disease. Continuing to monitor latent syphilis in high risk populations will be an important step toward reducing the burden of syphilis in the US.

APPENDIX

Table A1. CDC Classification System for HIV-Infected Adults and Adolescents (27)

CD4 Cell Categories	**Clinical Categories**		
	A Asymptomatic, Acute HIV, or PGL	**B** Symptomatic Conditions, not A or C	**C** AIDS-Indicator Conditions
(1) ≥500 cells/μL	A1	B1	C1
(2) 200-499 cells/μL	A2	B2	C2
(3) <200 cells/μL	A3	B3	C3

Abbreviations: PGL = persistent generalized lymphadenopathy

Table A2. Risk Factors for HIV Transmission (9)

HIV Transmission Category
Male-to-male sexual contact
Injection drug use
Male-to-male sexual contact and injection drug use
Heterosexual contact*
Other**

* Heterosexual contact with a person known to have, or to be at high risk for HIV
**Includes hemophilia, blood transfusion, perinatal exposure, and risk not reported or not identified.