Published in final edited form as:
Int J STD AIDS. 2009 April ; 20(4): 278–284. doi:10.1258/ijsa.2008.008324.

Syphilitic Hepatitis among HIV-Infected Patients

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Summary

Syphilis is an important public health issue which continues to occur at high rates among HIV-infected patients. Although abnormal liver function tests are common among HIV-infected persons, the incidence of syphilitic hepatitis in this population is currently unknown. We present two cases of syphilitic hepatitis and performed a retrospective study to determine the incidence of hepatitis during early syphilis infections among HIV-infected persons. Our study showed that syphilitic hepatitis is common occurring in 38% (12/32) of HIV-positive patients with early stages of syphilis infection. Most cases occurred during secondary syphilis with the most common finding being a maculopapular rash. Syphilis should be included in the differential diagnosis of HIV patients presenting with liver test abnormalities, rash and/or sexual risk factors.

Keywords

HIV; syphilis; hepatitis; liver involvement

Introduction

Syphilis continues to occur at high rates among HIV patients, with numerous outbreaks reported particularly among men who have sex with men (MSM).[1,2] In fact, one fourth of syphilis cases in the U.S. were reported within HIV-infected persons.[3,4] The clinical manifestations of early *Treponema pallidum* infections are protean in nature, as the organism may affect any organ system. Although the reported incidence of syphilitic hepatitis in the general population is quite variable[5–8], it represents a unique manifestation of the early syphilis syndrome.

Elevated liver enzymes are common among HIV-infected persons and before the advent of HAART were often attributed to opportunistic infections (e.g., *Mycobacterium avium* complex, *Cryptosporidium*, and cytomegalovirus) and neoplasms (e.g., lymphoma). More recently, elevated liver tests have been frequently ascribed to viral hepatitis, antiretroviral and other medications, and alcohol use, as well as to fatty liver disease.[9] Only 10 cases of syphilitic hepatitis among HIV-infected patients have been reported in the literature.[10–13] The incidence of acute hepatitis during early syphilis infections and the factors associated with syphilitic hepatitis among HIV-infected patients are currently unknown. We recently diagnosed two cases of syphilitic hepatitis in our HIV clinic and subsequently performed a retrospective study

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to examine the incidence of hepatitis complicating early syphilis infections among HIV-infected persons.

Case Reports

Case 1

A 39-year-old Caucasian male presented with a rash, arthralgias, flu-like symptoms, and headache in January of 2008. He was diagnosed with HIV infection in 2001 and treated with zidovudine, lamuvidine and nevirapine, which were later switched to tenofovir, emtricitabine and nevirapine. His most recent CD4 cell count was 398 cells/mm^3 with an undetectable viral load (<50 copies/ml). The rash began on his palms and soles, and then spread centrally. The patient denied any recent sexual activities, new medications or exposures, or alcohol use. His examination showed a blood pressure 140/78, pulse 107, and temperature of 97.6 °F. Findings included cervical adenopathy of 2 cm in greatest diameter and a diffuse nonpalpable macular rash. He had no neurological findings. His laboratory values showed an alkaline phosphatase of 1838 IU/L (normal 38–126 IU/L), alanine aminotransferase (ALT) of 264 IU/L (normal 17–63 IU/L), aspartate aminotransferase (AST) of 145 IU/L (normal 15–41 IU/L), total bilirubin of 1.8 mg/dl (normal 0.4–2.0 mg/dl) and lactate dehydrogenase of 167 IU/L (normal 99–192 IU/L). Testing for viral hepatitis had previously shown positive hepatitis B surface antibody and hepatitis A IgG tests secondary to vaccination. Hepatitis B core antibody and surface antigen, as well as hepatitis C antibody, were negative. Secondary syphilis was suspected, and a rapid plasma reagin was positive at 1:128 with a positive confirmatory *T. pallidum* antibody test. Due to complaints of headaches, he underwent a lumbar puncture, which was negative. He was treated with a single dose of 2.4 mU of benzathine penicillin for secondary syphilis. Repeat liver tests eight days later showed an alkaline phosphatase of 937 IU/L and an ALT of 97 IU/L. One month later, liver tests had normalized (ALT 24 and AST 27 IU/L) except for a mildly elevated alkaline phosphatase (136 IU/L) which returned to normal (85 IU/L) after three months. All symptoms resolved and the RPR titer had fallen to 1:32 at the last follow-up visit.

Case 2

A 25-year-old African American male presented with abdominal pain, loose stools and tenesmus in May of 2007. At this time, laboratory evaluation, including complete blood count and liver tests, were normal. He was diagnosed at the emergency department visit with proctitis and empirically treated with ciprofloxacin and metronidazole. His medical history included HIV infection diagnosed four years previously; the most recent CD4 cell count was 446 cells/mm^3 with a HIV viral load of 11,782 copies/ml; he was not receiving antiretroviral therapy. Three weeks after initial presentation, he presented to his HIV provider with complaints of left eye pain and decreased acuity. Eye examination revealed an erythematous conjunctiva, photophobia and 20/80 acuity. An ophthalmologic examination revealed +2 anterior chamber cells consistent with uveitis. The remainder of the examination was remarkable for cervical adenopathy, a genital chancre and a faint, diffuse macular rash. Laboratory values showed an alkaline phosphatase of 204 IU/L, ALT of 99 IU/L, AST of 84 IU/L and a total bilirubin of 0.3 mg/dl. Hepatitis panel showed immunity to hepatitis A and B without evidence of acute or chronic viral hepatitis; the patient denied alcohol use and was taking no hepatotoxic medications. A liver ultrasound showed diffuse common bile duct wall thickening without stones or signs of acute cholecystitis. Urinalysis showed proteinuria (30 mg/dl) with no pyuria or hematuria. A RPR was positive at 1:32 with a reactive *T. pallidum* antibody test. A lumbar puncture was within normal limits. The patient was treated with 14 days of intravenous penicillin (24 mU daily), as well as prednisolone ophthalmic suspension. Within one week of therapy, liver tests completed normalized (alkaline phosphatase of 120 IU/L, ALT of 25 IU/L, AST of 28 IU/L). At last follow-up (one month after diagnosis), the RPR had decreased to

1:16, with normalization of the urinalysis and the ophthalmologic examination normalized to a visual acuity of 20/40.

Methods

We conducted a retrospective study among all HIV-infected patients attending our HIV clinic at the Naval Medical Center San Diego in February of 2008. All patients in our clinic are military beneficiaries (active duty members, retirees or dependents). We searched computerized and paper medical records for the diagnosis of early syphilis, defined as primary or secondary syphilis, which was confirmed by positive serologic testing and occurred after HIV seropositivity. Syphilis testing, using a rapid plasmin reagin (RPR) test, is routinely performed on an annual or semi-annual basis among our HIV-infected patients. In addition, patients presenting with a clinical syndrome suggestive of syphilis undergo RPR testing. Patients with a positive RPR have confirmatory testing performed using a specific syphilis test (i.e., *T. pallidum* antibody). All cases in this study occurred between January 1, 2000 and December 31, 2007. The study was approved by the local institutional review board.

Syphilitic hepatitis in this study was defined as: 1) a case of confirmed primary or secondary syphilis with a positive RPR and *T. pallidum* antibody which occurred after HIV infection; 2) the presence of a clinical illness consistent with syphilis; 3) elevated liver tests including an alkaline phosphatase level (as it is most commonly elevated in syphilis), which were normal before the diagnosis of syphilis and returned to normal after therapy; and 4) exclusion of other causes of hepatitis (including review of available viral hepatitis serologies, medications, and alcohol use). Patients with pre-existing elevated liver tests, either transient or persistent, within one year before syphilis diagnosis were excluded.

Data collected included demographics (age, sex and race), date of syphilis infection, clinical signs and symptoms of syphilis, RPR titer, treatment administered for syphilis, most recent CD4 cell count and HIV viral load prior to syphilis diagnosis, viral hepatitis serologies, receipt of HAART or other potentially hepatotoxic medications at the time of syphilis infection, and duration of HIV infection. A HIV viral load of <50 copies/ml was considered undetectable (Roche, Amplicor). HAART was defined as two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or one nonnucleoside reverse transcriptase inhibitor (NNRTI). Liver tests were recorded, including the alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin and lactate dehydrogenase (LDH) at the following time points: before syphilis diagnosis, at the time of syphilis diagnosis and after syphilis treatment. Normal values for liver tests were based on local laboratory cut-offs of alkaline phosphatase of 38–126 IU/L, ALT of 17–63 IU/L, AST of 15–41 IU/L, total bilirubin 0.4–2.0 mg/dl and LDH of 99–192 IU/L. In addition, imaging or biopsy specimens performed in the work-up of the diagnosis of syphilis were recorded.

Statistical analyses included descriptive statistics of the study population and HIV-infected patients with syphilitic hepatitis. To examine potential factors associated with the development of syphilitic hepatitis, HIV-infected patients with early syphilis with and without concurrent hepatitis were compared using Fishers exact tests and logistic regression models. Variables included demographics, RPR titer, CD4 cell count, HIV viral load, HAART and duration of HIV infection. Pearson correlation analyses with scatter plots were utilized to examine the relationship between RPR titer and the CD4 cell count, viral load and use of HAART; in addition, regression analyses were conducted to examine potential relationships between HIV factors and the RPR titer. A p-value <0.05 was considered statistically significant. All analyses were conducted using STATA 9.0 (StataCorp, College Station, TX).

Results

Our study population consisted of 600 HIV-infected patients with a median age of 40 years (range 18–75 years); 92% were male, and race was 51% Caucasian, 28% African American, 16% Hispanic and 5% other. The median duration of HIV infection for the participants at the time of the study was 9 years (range: newly diagnosed to 23.5 years). Six percent (33/600) of HIV patients were diagnosed with early syphilis, including 27 with secondary syphilis and six with primary syphilis during the study period.

By our definition, 12 of the 32 (38%) early syphilis cases had hepatitis (Table 1); one case was excluded from this study due to absence of liver tests drawn at the time of syphilis diagnosis. Of note, all 12 cases had no other definable cause for the abnormal liver tests; this included no significant history of alcohol use, no receipt of new medications with potential hepatotoxic effects, and negative viral hepatitis serologies when available (Table 1). Five additional patients had mildly abnormal liver tests, but were excluded in our case series since they did not meet our strict case definition. Of these five, four had mildly elevated AST or ALT levels which had been previously normal and resolved with syphilis treatment, but which had normal alkaline phosphatase values; one of these patients had hepatitis C co-infection with normal liver tests before and after syphilis, but a mild increase in the AST during the syphilis infection. In addition, one participant had an elevated alkaline phosphatase, which resolved after syphilitic therapy, but also had a history of abnormal liver tests; hence this patient was excluded from our cases. The remaining 15 patients had normal liver tests at the time of the diagnosis of syphilis.

The median age of the 12 HIV-infected patients with syphilitic hepatitis was 37 (95% CI, 32–42) years, all were male, and race was Caucasian in seven (58%), Hispanic in three (25%), and African American in two (17%). Their median CD4 cell count was 339 (95% CI, 252–442) cells/mm^3, 42% had an undetectable viral load (<50 copies/ml) and 75% were receiving HAART at the time of the diagnosis of syphilis. All cases had elevated alkaline phosphatase (median 186 IU/L, range 129–1836); 9/12 (75%) had elevated ALT (median 105, range 82–614 IU/L); 9/12 (75%) had elevated AST (median 60, range 44–347 IU/L and 4/12 (33%) had an elevated LDH (median 355, range 220–519 IU/L). No patient had an elevated total bilirubin level.

All liver enzyme abnormalities normalized after penicillin therapy. The duration of antibiotic therapy ranged from one dose of benzathine penicillin G to a 14-day course of intravenous penicillin G therapy (Table 1). The timing of repeat liver tests after syphilis treatment was variable and dependent on the HIV clinicians caring for the patient; all liver tests abnormalities resolved within five days to three months of receipt of syphilis therapy. Two (6%) of our 32 syphilis cases developed the Jarish-Herxheimer reaction following β-lactam therapy; both cases occurred among those without concurrent hepatitis. Several patients were instructed to use anti-inflammatory medications after receipt of penicillin therapy, which may have dampened the number of reported reactions.

All cases of syphilitic hepatitis occurred in the setting of secondary syphilis, except in one patient who had primary syphilis. One case had secondary syphilis with rash and also had a positive lumbar puncture, suggestive of neurologic involvement and one had uveitis (case report #2). The most common symptom among syphilitic hepatitis cases was rash (67%) as part of secondary syphilis. Other symptoms included pharyngitis (33%), lymphadenopathy (25%), fever (16%), fatigue (16%), eye symptoms (16%) and arthralgias (8%) (Table 1 and Table 2).

The median RPR was 1:32, with a range from 1:4 to 1:128. A liver ultrasound was performed only among three (25%) of the cases of syphilitic hepatitis; one revealed circumferential

thickening of the common bile duct without parenchymal abnormalities and another showed mild hepatomegaly. One patient had a liver biopsy performed due to elevated liver tests of unclear etiology; the biopsy revealed spotty parenchymal and periportal inflammation with infiltration of the interlobular ducts by neutrophils consistent with acute syphilitic cholangitis, however no spirochetes were seen on the Warthin-Starry stain. This patient subsequently had syphilis serologies drawn (RPR and *T. pallidum* antibody), which were positive with a titer of 1:32.

HIV patients with syphilitic hepatitis (n=12) were compared to those without hepatitis (n=15) (Table 2). Those with syphilitic hepatitis had a longer duration of HIV (10 vs. 4 years, p=0.04). Using logistic regression models, there were no associations between the CD4 cell count, HIV viral load or HAART use with the occurrence of hepatitis among HIV-infected patients with early syphilis. We repeated the analyses, including those with mild liver abnormalities that did not meet our definition of syphilitic hepatitis (n=5), and found similar results. We evaluated if the RPR titer was correlated with various HIV factors and found no significant relationships. The correlation between RPR titer and CD4 cell count was $r=-0.15$ (p=0.4) with the scatter plot showing no visible relationship; a regression line was also not significant (p=0.729, R^2 of 0.004). Similarly, no relationships were noted between the RPR titer and the HIV viral load ($r=0.14$, p=0.5; regression line of p=0.833) or receipt of HAART ($r=-0.1$, p=0.5; logistic regression of p=0.32).

Discussion

This study found that 38% of HIV-infected persons with early syphilis infection had liver enzyme abnormalities consistent with syphilitic hepatitis. Given the rising number of *T. pallidum* infections among HIV-infected patients, syphilitic hepatitis should be considered early in the differential diagnosis especially in the setting of disproportional elevation in the alkaline phosphatase level and rash. Our study also showed that the development of syphilitic hepatitis was more common among patients who were infected with HIV for a longer duration of time.

The incidence of syphilis among HIV-infected persons, especially MSM, has been rising in the United States, and several outbreaks have been reported.[1,2,14] In 2002, one fourth of syphilis cases in the U.S. occurred among HIV-infected persons with a prevalence rate of syphilis in the HIV population of 186 per 100,000 compared to 2.4 per 100,000 in the general population.[3] A more recent report from three U.S. cities showed that 45% of primary and secondary syphilis cases are occurring among HIV-infected persons.[15] Owing to the markedly elevated syphilis rates and the frequent occurrence of liver test abnormalities among HIV-infected persons, a study of the incidence of hepatitis complicating syphilis infections is of clinical importance. As such, our study found that nearly 40% of early syphilis cases in HIV-infected patients developed elevated liver enzymes, implying that syphilis may be a common cause of liver abnormalities in this group.

Syphilis may present with protean manifestations, but most commonly manifests as genital ulcerative disease during the primary stage and as rash, fever and adenopathy during the secondary stage. During the secondary stage, dissemination of treponemes throughout the body occurs affecting both mucocutaneous and visceral sites. Although liver involvement due to syphilis has been recognized in the general population for over 400 years,[6] published reports are sparse, with the largest series in the recent literature consisting of only 17 cases.[8] Hepatitis represents an often unrecognized and unique manifestation of the early syphilis syndrome.

Liver involvement has been classically described as a disproportionally elevated alkaline phosphatase level in the setting of secondary syphilis with rash.[6,16,17] Our case series

exemplifies that HIV-infected patients present similarly to those of the general population. The elevation of the alkaline phosphatase is likely due to pericholangiolar inflammation.[10,18] Cases also may present with elevated AST and ALT levels;[6,19] while no case in our series had an elevated total bilirubin level, jaundice has been previously reported.[20,21] Laboratory studies may also reveal renal involvement, most often seen as isolated proteinuria.[22–24]

The most common clinical finding among HIV-infected patients with syphilitic hepatitis was the rash of secondary syphilis. Other findings included adenopathy, pharyngitis, fevers and eye involvement (including conjunctival erythema and uveitis).[25] The presence of ulcerative proctitis has also been described among cases of syphilitic hepatitis in the general population;[17,23,25–28] two of our cases had proctitis at presentation. The relationship between rectal syphilis and liver involvement may be likely related to the venous drainage pathway from the rectal area into the portal system.[6]

The median CD4 cell count among patients with syphilitic hepatitis in our study cohort was 339 cells/mm^3, but ranged from 18 to 942 cells/mm^3. Although the sole published report of syphilitic hepatitis among HIV-infected persons (n=7) suggested that higher CD4 cell counts may predispose to the development of hepatitis due to a more robust immune response leading to periportal inflammation,[10] we did not find such a relationship. Our study had the advantage of comparing syphilis cases with and without hepatitis, while the prior study[10] lacked a control group. In addition to the CD4 cell count, we examined HIV viral load and HAART use and found no associations between these factors and the development of hepatitis in the logistic regression models.

We did find that the development of syphilitic hepatitis was more common among patients who were infected with HIV for a longer duration of time. Although the exact nature of this association is unknown, it may be the result of the presence of subclinical liver disease, which may become more prevalent with a longer duration of HIV infection. Over time, HIV-infected patients may be at risk for liver disease due to cumulative medication exposure by both direct (e.g., mitochondrial toxicity) or indirect effects (e.g., metabolic abnormalities). Although our study patients in this report had no known underlying liver disease, such as chronic viral hepatitis or alcoholic liver disease, the presence of subclinical liver disease cannot be excluded. The pathogenesis of syphilitic hepatitis has been previously described as treponemal infiltration into periportal areas with an inflammatory response;[8,29] whether this could be intensified by pre-existing liver disease is unknown.[21] Further studies are needed to confirm the potential association between syphilitic hepatitis and HIV duration and to describe the nature of this relationship.

Similar to cases described among HIV-negative persons, β-lactam therapy was associated with rapid resolution of liver enzyme abnormalities among HIV-infected persons. The rapid resolution of liver test abnormalities supports that syphilis was the cause of the hepatitis in our cases rather than another etiology. Because of the rapid resolution of liver tests and the high incidence rate of syphilis among HIV-infected persons, syphilis should be entertained early in the diagnosis of abnormal liver tests to avoid unnecessary evaluations in this population.

Syphilis is known to be an important public health issue as it is associated with an increase in the transmission of HIV infections.[30,31] In addition, syphilis may also impact HIV-infected patients themselves.[4] Recent studies suggest that HIV-infected persons with acute syphilis experience an increase in HIV viral loads and a decline in CD4 cell counts.[4,32–34] Our data provide further support of the adage “prevention for positives” with nearly 40% of patients with early syphilis developing concurrent hepatitis. Although liver enzyme abnormalities rapidly returned to normal following treatment in our cohort, the potential long-term effects of treponemal liver infections is unknown with some reports suggesting a link between

syphilitic hepatitis and the development of chronic liver disease[5,17,35,36]. Whether or not this suggested relationship is confounded by factors such as a high rate of viral hepatitis and alcohol use among patients with syphilis is unclear. Nonetheless, cases of severe and prolonged hepatitis have been reported,[13] including one case of syphilitic hepatitis which required liver transplantation.[37] Liver decompensation after penicillin treatment as part of the Jarish-Herxheimer reaction has also been reported.[11,38] These data suggest that co-infection with syphilis among HIV-infected patients may result in adverse health consequences including liver toxicity. Thus, for both public health reasons and the health of HIV-infected persons, patients should be counseled to avoid syphilis infections by utilizing safe sexual practices.

In summary, our study demonstrated that hepatitis is common during early syphilis infections among HIV-infected persons. Syphilis should be included in the initial differential diagnosis of HIV-infected patients presenting with liver abnormalities, rash and sexual risk factors. Further studies on the natural history and pathogenesis of treponemal liver involvement may be useful given the high incidence of syphilis among HIV positive persons.

Acknowledgment

Support for this work was provided by the Infectious Disease Clinical Research Program (IDCRP), Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD, of which the TriService AIDS Clinical Consortium (TACC) is a component. The IDCRP is a DoD tri-service program executed through USUHS and the Henry M. Jackson Foundation for the Advancement of Military Medicine in collaboration with HHS/NIH/NIAID/DCR through Interagency Agreement HU0001-05-2-0011.

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Table 1

Summary of HIV-Infected Patients* with Syphilitic Hepatitis

Case Number	Age	Race	Duration of HIV**, years	CD4 Cell Count**, cells/mm^3	HIV Viral Load**, copies/ml	HAART, Yes/No, Regimen (Duration)**	Syphilis Stage**	RPR Titer**	Symptoms**	Liver Work-Up for Other Causes***	ALT, IU/L**	AST, IU/L**	Alkaline phosphatase, IU/L**	Treatment
1	39	W	7	398	<50	Yes Tenofovir, emtricitabine, nevirapine (60 months)	Secondary	1:128	Rash, headache, adenopathy, arthralgias	HAART was stopped, but liver test abnormalities and rash persisted. Immune to hepatitis A (IgG), negative hepatitis B and C.	264†	145†	1,838†	Benzathine penicillin G (2.4 mU) IM × 1
2	25	AA	4	446	11,782	No	Secondary	1:32	Uveitis, proctitis, genital chancre glomerulonephritis	Hepatitis panel showed immunity to hepatitis A and B without evidence of acute or chronic viral hepatitis B or C	99†	84†	204†	Intravenous penicillin G (24 mU daily) for 14 days
3	35	H	13	331	<50	Yes Lamivudine, stavudine, efavirenz (41 months)	Secondary	1:4	Rash, adenopathy, pharyngitis, proctitis	Immune to hepatitis A (IgG) and prior history of B (core antibody positive and surface antigen negative), negative hepatitis C.	148†	59†	167†	Benzathine penicillin G (2.4 mU) IM ×2
4	34	W	14	18	16,358	Yes Zidovudine, lamivudine, abacavir, lopinavir, ritonavir (4 months)	Secondary	1:8	Rash, conjunctivitis, oral ulcer	Stopped HAART, but symptoms persisted. Prior history of resolved hepatitis B (core antibody positive and surface antigen negative). No data on hepatitis A or C.	12	23	144†	Benzathine penicillin G (2.4 mU) IM × 2
5	38	W	14	250	12,802	No	Secondary	1:8	Rash, pharyngitis	Vaccinated against hepatitis A. No other serologies available.	41	53†	186†	Benzathine penicillin G (2.4 mU) IM × 3
6	33	H	6	348	28,586	No	Secondary	1:8	Rash	History of hepatitis A and B vaccination; no other serologies available	82†	60†	343†	Benzathine penicillin G (2.4 mU) IM × 3
7	48	AA	10	863	<50	Yes Tenofovir, stavudine, lamivudine, indinavir (unknown duration)	Secondary	1:8	Unknown	Immune to hepatitis A (IgG) and prior history of B (core antibody positive and surface antigen negative), negative hepatitis C.	94†	75†	164†	Benzathine penicillin G (2.4 mU) IM × 2
8****	55	W	21	200	70	Yes Tenofovir, emtricitabine, fosamprenavir, ritonavir (30 months)	Secondary	1:32	Fever, rash, adenopathy	Immune to hepatitis A (IgG) and prior history of B (core antibody positive and surface antigen negative), negative hepatitis C.	614†	347†	380†	Intravenous penicillin G (24 mU daily) initially then ceftriaxone (2 g daily) for total of 14 days
9	32	H	7	290	<50	Yes Tenofovir, emtricitabine, efavirenz (40 months)	Primary	1:64	Pharyngitis, oral ulcer, eyelid ulcer	Immune to hepatitis A (IgG). Negative hepatitis B and C.	47	40	153†	Benzathine penicillin G (2.4 mU) IM × 1
10	40	W	15	410	3,921	Yes Stavudine, didanosine, nevirapine (16 months)	Secondary	1:64	Fever, rash, weight loss	Prior hepatitis B infection which resolved (cAB positive, surface Ag negative). Negative hepatitis C.	94†	44†	129†	Benzathine penicillin G (2.4 mU) IM × 2
11	29	W	5	942	<50	Yes Tenofovir, emtricitabine, atazanavir, ritonavir (31 months)	Secondary	1:64	Pharyngitis	Immune to hepatitis A (IgG), negative hepatitis B and C.	105†	58†	150†	Benzathine penicillin G (2.4 mU) IM × 3

Case Number	Age	Race	Duration of HIV[**], years	CD4 Cell Count[**], cells/mm^3	HIV Viral Load[**], copies/ml	HAART, Yes/No, Regimen (Duration)[**]	Syphilis Stage[**]	RPR Titer[**]	Symptoms[**]	Liver Work-Up for Other Causes[***]	ALT, IU/L[**]	AST, IU/L[**]	Alkaline phosphatase, IU/L[**]	Treatment
12	42	W	9	270	>100,000	Yes Zidovudine, lamivudine, abacavir (55 months)	Secondary[*****]	1:128	Rash	HAART stopped without resolution of rash or elevated liver tests. Immune to hepatitis A (IgG).	105†	39	709†	Intravenous penicillin G (24 mU daily) for 14 days

[*] All patients were male

[**] At time of syphilis diagnosis

[***] Review of patients' medical records revealed no non-HIV hepatotoxic medications or significant alcohol use.

[****] Patient underwent a liver biopsy before the diagnosis of syphilis was considered which showed pathologic changes consistent with syphilitic cholangitis

[*****] Also had positive lumbar puncture with cerebrospinal fluid consistent with syphilis

† Denotes abnormal laboratory value

AA, African American; ALT, alanine aminotransferase; AST, aspartate aminotransferase; H, Hispanic; IM, intramuscular; RPR, rapid plasmin reagin; W, white

Table 2

Characteristics of HIV-Infected Patients with Early Syphilis with and without Hepatitis

Characteristic	Syphilis with Hepatitis N=12	Syphilis without Hepatitis N=15	OR	P-value
Demographics				
Age, years, median (95% CI)	37 (32, 42)	34 (24, 36.0)	1.05	0.14
Race				0.34
Caucasian	7 (58.3%)	6 (40%)	1.0	
African American	2 (16.7%)	2 (13.3%)	0.9	
Hispanic	3 (25.0%)	3 (20%)	0.9	
Other	0	4 (26.7%)	---	
Syphilis Symptoms and Laboratory Values				
Fever	2 (16.7%)	2 (13.3%)	1.3	1.0
Presence of Rash	8 (66.7%)	10 (66.7%)	1.0	1.0
Fatigue	2 (16.7%)	2 (13.3%)	1.3	1.0
Adenopathy	3 (25%)	4 (26.7%)	0.9	1.0
Eye symptoms	2 (16.7%)	1 (6.7%)	2.8	0.57
Pharyngitis	4 (33.3%)	1 (6.7%)	7.0	0.14
Arthralgias	1 (8.3%)	2 (13.3%)	0.6	1.0
RPR titer, median (95% CI)	32 (8, 64)	32 (2, 128)	0.99*	0.94
HIV Factors				
Duration of HIV Infection, years, median (95% CI)	9.5 (6, 14)	4 (1, 7)	1.2	0.04
CD4 Cell Count, cells/mm^3, median (95% CI)	339 (252, 442)	338 (267, 528)	0.96**	0.79
HIV Viral Load, log copies/ml, median (95% CI)	2.7 (1.7, 4.2)	1.9 (1.7, 4.3)	1.1	0.85
HIV Viral Load <50 copies/ml	5 (41.7%)	7 (46.7%)	0.8	1.0
HAART, yes	9 (75%)	11 (73.3%)	1.1	1.0

CI, confidence interval; OR, odds ratio; RPR, rapid plasmin reagin

* OR calculated for two-fold titer change

** OR calculated per 100 cells