Serological Evidence of HIV-Associated Infection among HIV-1–Infected Adults in Botswana

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In industrialized countries, it is recommended that adults with human immunodeficiency virus type 1 (HIV-1) infection undergo baseline screening for pathogens that might cause latent or active infections, such as syphilis, hepatitis B, hepatitis C, infection due to Toxoplasma gondii, and cytomegalovirus infection. A paucity of data exist from sub-Saharan Africa describing the prevalence of these pathogens. We report data for HIV-1–infected adults referred for initiation of highly active antiretroviral therapy in Botswana.

Adult patients with HIV infection and/or AIDS are at risk for coinfection with other sexually transmitted pathogens, such as hepatitis B virus (HBV), hepatitis C virus (HCV), Treponema pallidum, and herpes simplex virus, depending on their risk factors for HIV-1 infection. HBV is the leading cause of liver disease worldwide [1, 2], and HIV-1 infection is associated with an increased risk for the development of chronic hepatitis B after HBV exposure. Numerous studies have documented a high rate of HCV infection (50%–90%) among HIV-1–infected injection drug users and persons with hemophilia [3–5]. Other possible modes of HCV transmission include mother-to-infant, needlestick, or sexual transmission [5–10]. Documentation and close monitoring of persons who are coinfected with HIV-1 and HCV is needed, because long-term studies now predict that 2%–20% of patients with chronic HCV infection develop cirrhosis within 20 years [11], and this rate of progression increases with older age, alcoholism, and HIV-1 infection [11–13].

HIV-1 infection also appears to alter the diagnosis, natural history, management, and outcome of T. pallidum infection [14–16]. In addition, HIV-1–infected adults with more-advanced disease (i.e., those with CD4+ cell counts of <100 cells/mm3) are at risk for illness caused by reactivation of various viral and protozoan pathogens, including cytomegalovirus (CMV; which causes retinitis, colitis, and encephalitis) and Toxoplasma gondii (which causes encephalitis).

Very limited data are available on the serologic prevalence of syphilis, HBV infection, HCV infection, T. gondii infection, and CMV infection among HIV-1–infected adults in sub-Saharan Africa, especially among HIV-1–infected individuals who are presenting for HAART initiation and, therefore, have evidence of advanced HIV-1 disease. The majority of existing literature is from West or East Africa and reports the serologic prevalence of these important disease pathogens among at-risk adult populations (i.e., women, blood donors, and prisoners) with unknown HIV-1–infection status [17–25].

Methods. A total of 160 adult patients presenting for longitudinal care between May 2001 and January 2002 at the Infectious Disease Care Clinic for outpatient HIV care at Princess Marina Hospital in Gaborone, Botswana, were consecutively evaluated for the presence of syphilis, HBV infection, HCV infection, toxoplasmosis, and CMV infection. Baseline HIV-1 antibody levels, CD4+ cell counts, and plasma HIV-1 RNA levels were also obtained. Not all adults were tested for HCV, T. gondii, and CMV antibodies, because once a consistent test result trend was found (i.e., ≥40 patients with test results negative for a particular pathogen), serologic testing for that pathogen was discontinued.

Nontreponemal tests for syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratory tests) were performed using the RPR test (Randox Laboratories) according to the manufacturer’s instructions. Tests for HBV and HCV were performed using Murex test kits (version 3.0 for hepatitis B surface antigen and anti-HCV version 4.0 for HCV) according to the manufacturer’s instructions.

Descriptive univariate analyses included mean values, median values, and SDs for normally distributed continuous data and percentages for categorical data. To evaluate for potential differences by sex, age, and CD4+ cell count, analyses were performed with the Statistical Product and Service Solutions software, version 14.0 (SPSS), using the Kruskal-Wallis 1-way analysis-of-variance test. Unpaired Student’s t test was used to compare differences between the groups. P values <.05 were considered to be statistically significant. This study was approved by the Health Research and Development Committee of the Botswana Ministry of Health and Wellness.
of the Botswana Ministry of Health and the Harvard School of Public Health Human Subjects Committee.

Results. Our patients were all citizens of Botswana and were referred by senior medical officers practicing in the outpatient medical department at Princess Marina Hospital. Of the 163 patients referred, 3 were found to be HIV-1 negative and were excluded from analysis. The remaining 160 adults were antiretroviral treatment naive. The median age of these patients was 35.8 years, and 63.6% were female. Median CD4+ cell count was 104 cells/mm³ (interquartile range, 37–195 cells/mm³), and median plasma HIV-1 RNA level was 325,000 copies/mL (interquartile range, 116,026 to >750,000 copies/mL). A total of 66 (47.6%) of the screened patients had CD4+ cell counts <100 cells/mm³ (table 1).

Serologic data evaluating evidence of prior syphilis were available for 143 patients in the initial cohort; 19 (13.3%) had positive nontreponemal (RPR) test results. One patient had a maculopapular truncal rash that involved the palms and soles, consistent with secondary syphilis. Analyzing by age, we found that 6 (10.3%) of 58 adults <35 years of age had positive RPR test results, and 9 (14.3%) of 63 adults ≥35 years of age had positive RPR test results (P = .51). Analyzing by baseline CD4+ cell count, we found that 11 (16.7%) of 66 patients with baseline CD4+ cell counts of <100 cells/mm³ had positive RPR test results, and 8 (11.8%) of 68 with baseline CD4+ cell counts of ≥100 cells/mm³ were had positive RPR test results (P = .42).

To assess test performance, we performed treponemal hemagglutination (TPHA) syphilis tests for all screened adult patients and found that 5 (3.5%) of 143 patients had positive RPR test results and negative TPHA test results; these patients were defined as having false-positive RPR test results. Of the positive RPR test results, 5 (26.3%) of 19 were not confirmed by the TPHA test. Conversely, 8 (5.6%) of 143 patients had negative RPR test results and positive TPHA test results; these patients were defined as having no active syphilis disease, and they most likely had experienced previous syphilis infection or received past treatment for syphilis and were without evidence of active disease.

Fifteen (10.6%) of 141 patients tested had test results positive for hepatitis B surface antigen; hepatitis B e antigen was detected in 6 (40%) of the 15 hepatitis B surface antigen–positive adults. Of 140 evaluated patients, 82 (58.2%) had results positive for core IgG antibody, and 52 (37.1%) had results positive for surface antibody. HCV antibody was not detected in any of the 50 patients screened.

Anti–toxoplasmal IgG antibody was found in 3 (6.5%) of 46 patients screened. None of the 46 patients screened had IgM antibody against T. gondii. CMV IgG antibody levels were positive in 41 (95.3%) of 43 patients. None of the 41 patients screened had anti-CMV IgM antibody.

Discussion. Evidence of prior syphilis infection was common among the first group of HIV-1–infected patients to initiate HAART in the Botswana National Antiretroviral Treatment program (found in 13.3% of patients). Recent Botswana syphilis prevalence data (from 2002) among adults with unknown HIV-1 status documented positivity rates of 1.7%–5.1% [26] among adults presenting with symptoms of sexually transmitted disease and attending family planning clinics; the rate was 6.6%–9.9% among pregnant women presenting for antenatal care as part of the 2003 National Sentinel Surveillance [27]. Both syphilis and HIV-1 infection share a common epidemiological mode of transmission; therefore, a higher prevalence of coinfection among patients with known advanced HIV-1 disease is not surprising.

By performing both nontreponemal (RPR) and treponemal (TPHA) tests for all patients, we were able to document that ~25% of positive RPR test results were not confirmed by the TPHA test. This suggests that ~25% of patients receiving a diagnosis of syphilis using RPR as a screening test (and not confirmed by TPHA test) were treated unnecessarily. More data will need to be obtained via random TPHA confirmatory testing among patients with positive RPR test results to determine whether all patients with positive RPR test results should have the diagnosis confirmed by TPHA testing before receiving penicillin treatment, which can cause allergic drug reactions in susceptible hosts. The rate of asymptomatic patients with positive RPR test results does, however, provide public health justification for continued syphilis screening by routine RPR testing at entry to care.
HBV infection is also common among HIV-infected adults in Botswana; 58.2% of our initial cohort had antibody evidence of past infection, and 10.6% had circulating hepatitis B surface antigen, indicating chronic hepatitis. The 10% rate of chronic HBV infection, coupled with 40% of these carriers also being hepatitis B e antigen positive, suggests that the long-term complications of HBV infection may become a greater problem as many more persons receive HAART as part of Botswana’s National Antiretroviral treatment program. Emtricitabine, lamuvidine, and tenofovir each have activity against both HIV-1 and HBV, and the discontinuation of these drugs may potentially cause significant hepatocellular damage, which results from a flare of HBV disease [28]. With very large numbers of adults now receiving lamuvidine-containing HAART in Botswana (and in the region as a whole), those persons who experience failure of first-line therapy and, therefore, require full HAART regimen switches will need to be monitored for clinical flares of HBV infection, especially during the first 6–8 weeks following discontinuation of therapy.

Fortunately, no patients were found to be infected with HCV, which is a significant cause of additive hepatotoxicity among HIV-1 subtype B–infected adults receiving HAART in developed nations. However, it will be important for Botswana to perform periodic surveillance to assure that its penetration into the population will not be missed, especially because the chronic hepatic complication rates associated with HCV infection are more significant. The absence of HCV infection most likely reflects the fact that the overwhelming majority of HIV-1 subtype C transmission in Botswana is through heterosexual contact, with little documented injection drug use.

Serological evidence of prior infection with T. gondii was quite uncommon in our population (infection rate, 6.5%), and clinical toxoplasmosis encephalitis is rare. On the other hand, prior CMV infection (indicated by anti-CMV IgG antibody and lack of IgM antibody) was almost universal, and CMV-related retinitis does occur. This high frequency of CMV infection is common for most developing nations, where infection is acquired early in childhood. Both of these organisms, upon reactivation, may cause serious CNS complications, although, at present, in the AIDS population in sub-Saharan Africa, cryptococcal meningitis, Mycobacterium tuberculosis, and AIDS dementia complex [29–31] are the most common causes of CNS disease.

This study potentially overestimates the prevalence of prior and/or active infection with these HIV-associated pathogens, because it was performed among a group of mostly symptomatic patients presenting for outpatient HIV care. Results may have been more reflective of population trends if this sero-prevalence study was conducted among at-risk, asymptomatic patients. In addition, serological tests for CMV and toxoplasmosis may have poor clinical significance and predictive value among persons with very advanced HIV disease. In addition, not all adults had the full panel of serological tests performed as part of our screening approach. These serological tests were not done within the context of a clinical trial, and therefore, once 40 consecutively screened patients had test results negative for a particular serological test, for cost purposes, that particular test was no longer performed.

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