Misdiagnosis of HIV Infection by HIV-1 Plasma Viral Load Testing: A Case Series

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Background: The availability of sensitive assays for plasma HIV viral load and the trend toward earlier and more aggressive treatment of HIV infection has led to the inappropriate use of these assays as primary tools for the diagnosis of acute HIV infection.

Objective: To describe limitations in the use of plasma viral load testing for the diagnosis of HIV infection.

Design: Case series.

Setting: Academic medical centers in Providence, Rhode Island, and Worcester, Massachusetts.

Patients: Three persons in whom HIV infection was falsely diagnosed by plasma viral load testing.

Measurements: Laboratory measures and clinical outcomes.

Results: Two cases of false-positive results obtained by using branched-chain DNA plasma viral load assays and one case of a false-positive result obtained by using reverse transcriptase–polymerase chain reaction plasma viral load assay are reported. All three plasma viral load tests yielded positive results with low values (1254 copies/mL, 1574 copies/mL, and 1300 copies/mL). Infection with HIV was initially diagnosed in all three patients, but each patient subsequently tested negative by HIV-1 enzyme-linked immunosorbent assay and repeated plasma viral load testing.

Conclusion: Physicians should exercise caution when using plasma viral load assays to detect primary HIV infection, particularly when the pretest probability of infection is low.

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The current standard of care for patients infected with HIV includes plasma viral load tests to monitor the effectiveness of antiretroviral regimens (1, 2). The assays approved for this use detect cell-free plasma viral RNA by using various amplification techniques (2). Access to these sensitive techniques and the trend toward earlier and more aggressive treatment approaches have led to the use of these assays as primary tools for the diagnosis of acute HIV infection (3, 4). Plasma viral load tests for HIV-1 were neither developed nor evaluated for the diagnosis of HIV infection; therefore, their diagnostic specificity is not well delineated when applied to persons who are negative for HIV antibody (5). We report two cases of false-positive results obtained by using branched-chain DNA assay (Chiron Quantiplex, Emeryville, California) and one case of a false-positive result obtained by using HIV reverse transcriptase polymerase chain reaction (RT-PCR) (Roche Amplicor Monitor, Basel, Switzerland) plasma viral load assay. These three cases demonstrate the potential problems of using HIV-1 plasma viral load tests for diagnosis of HIV infection.

Case One

A previously healthy 12-year-old boy, whose HIV-infected mother is cared for at one of our institutions, presented for evaluation of a positive plasma viral load of 1254 copies/mL determined by using the branched-chain DNA assay (Chiron Quantiplex) for HIV-1 RNA. The patient's mother had received a diagnosis of HIV infection around the time of his birth, and the patient had tested negative for HIV-1 by enzyme-linked immunosorbent assay (ELISA) several times in the years after his birth. Although the patient reported no risk factors for HIV infection, he underwent plasma viral load testing after his primary care physician noted a skin lesion that was interpreted as herpes zoster. At our institution, the patient subsequently had a negative result on HIV-1 ELISA, a normal CD4 cell count and CD4:CD8 ratio, and a negative plasma viral load (also determined by using the branched-chain DNA assay). His skin lesion was diagnosed as impetigo, and he remains in excellent health 3 months after his initial presentation.

Case Two

A previously healthy, pregnant 40-year-old woman presented for an HIV test. Her male sexual partner, with whom she had recently had repeated unprotected vaginal intercourse, had been given a diagnosis of HIV infection 1 week before her office visit.

The patient tested negative for HIV-1 antibody on the oral mucosal transudate (OraSure, Epitope, Inc., Beaverton, Oregon) HIV-1 oral specimen collection device but continued to be concerned about her HIV status. One week after her initial presentation, she underwent a plasma viral load test (Chiron Quantiplex) for HIV-1 RNA that yielded a positive value of 1574 copies/mL. The patient was told that she was probably infected with HIV. During the next 3 months, she had a negative result on an HIV-1 ELISA, a normal CD4 cell count and CD4:CD8 ratio, and three HIV-1 plasma viral load tests (all done by using branched-chain DNA assay) that showed an undetectable viral load. When the patient delivered a healthy baby 7 months after her initial presentation, another HIV-1 ELISA yielded negative results.

Case Three

A 20-year-old healthy woman was referred for further evaluation by her primary care physician when she had a positive result on HIV-1 ELISA and an indeterminate result on a Western blot test. The patient's only risk factor was heterosexual intercourse, but she stated that her partner had used condoms consistently during the previous year. During a 4-month period after her indeterminate result on the Western blot test, she had a positive result on ELISA and an indeterminate result on a Western blot test on separate occasions. Five months later, both ELISA and a Western blot test yielded negative results, but the patient had a plasma viral load of 1300 copies/mL (determined by using RT-PCR assay [Roche Amplicor Monitor]). She was subsequently counseled that she was probably infected with HIV. Nearly 6 months after her initial indeterminate HIV test result, she was tested by a third laboratory and was negative for HIV-1 antibodies on both ELISA and Western blot test. She had a normal CD4 cell count and CD4:CD8 ratio and a plasma viral load that was undetectable on RT-PCR assay (Roche Amplicor Monitor). She remains healthy 8 months after her initial presentation.

Discussion

These three cases, which were observed in one region during a 2-month period, are probably examples of false-positive results on HIV-1 plasma viral load tests. Only one other case of a false-positive HIV-1 plasma viral load has been fully documented; that test had been performed by using RT-PCR, and the result was thought to be related to the administration of an HIV-1 vaccine (6). The patients described here had normal CD4 cell counts and CD4:CD8 ratios, low plasma viral loads, and subsequent negative results on HIV-1 ELISA and plasma viral load tests. To our knowledge, the lowest reported plasma viral load during seroconversion is more than 17 times higher than the highest viral load detected in our three patients (7). Although transient HIV infection has been reported in infants, it is unlikely in two of our patients because they had not recently been exposed to HIV (8, 9). Other potential explanations of false-positive HIV-1 plasma viral load include laboratory error, cross-contamination, and mix-up of specimens. From the patient's perspective, false-positive results on an HIV test are potentially devastating, regardless of the cause. Further clinical experience is required to determine whether specific clinical circumstances correlate with an increased incidence of false-positive HIV-1 plasma viral load results.

The current standard diagnostic protocol for HIV infection is based on detection of HIV-1–specific antibodies. The combination of screening ELISA followed by a confirmatory Western blot assay has been more than 99% accurate in detecting HIV infection (10, 11). This protocol has a relatively low rate of false-positive results (approximately 0.0006%) but can have negative or indeterminate results during the 3 to 4 weeks before seroconversion (12–14). Although host antibody responses may be undetectable during this acute infection period, the viral load in plasma is usually very high and initial viremia usually occurs in 4 to 11 days (4, 7, 15, 16). The occurrence of high levels of viremia during primary HIV infection has led some physicians to use plasma viral load assays as diagnostic tests to detect early HIV infection. However, plasma viral load assays are designed for monitoring the effectiveness of antiretroviral therapies and for measuring the quantity of virus in patients with confirmed HIV infection, not for the diagnosis of HIV infection. Their performance in patients who are not infected with HIV is unknown (1, 2).

The first case illustrates the importance of following the most recent testing protocol for the diagnosis of HIV infection. The patient's pediatrician requested a plasma viral load assay because the patient, whose mother has asymptomatic HIV infection, presented with a skin rash thought to be consistent with herpes zoster. In this case, because primary HIV infection was not suspected, an HIV-1 ELISA should have been ordered and, if reactive, followed by a Western blot assay. In the second case, a plasma viral load assay was ordered despite a negative result on an oral mucosal transudate test (OraSure) because the patient was pregnant and was at substantial risk for recent exposure to HIV.

However, on the basis of current knowledge about viral replication during primary HIV infection, the patient's plasma viral load would probably have been much higher if she had been infected with HIV in the previous 2 weeks (15). In the third case and in other cases described in the literature, plasma viral load testing was used to further analyze an indeterminate result on an HIV-1 Western blot assay (3).

To minimize the occurrence of false-positive results, testing protocols for the diagnosis of HIV infection should include tests that complement each other. The HIV-1 ELISA assay, which has excellent diagnostic sensitivity, remains an important, inexpensive screening tool. Because of its high specificity, the HIV-1 Western blot assay is a reliable confirmatory test after reactive ELISA. Only patients who have a high pretest probability of a positive result should be evaluated for primary HIV infection by using plasma viral load testing. Such patients include those who are at high risk for recent exposure to HIV and present with indeterminate or negative results on Western blot tests and especially those with an appropriate accompanying clinical syndrome (4). A patient with a high HIV-1 plasma viral load is most likely in the process of seroconversion; although it is theoretically possible that a patient with an undetectable or low plasma viral load may have recently been infected with HIV, that possibility is much less likely.

It is important to consider the pretest likelihood of acute infection when counseling patients with negative results on serologic testing and a low plasma viral load. Physicians should explain that the patient may not be infected with HIV-1 but should take precautions to avoid infecting others until follow-up testing provides a definite result. If HIV-1 plasma viral load testing is used in the diagnosis of primary HIV infection before the development of serum antibodies, low positive plasma viral load results should be interpreted with caution and the patient's true disease status should be confirmed with repeated plasma viral load testing and follow-up serologic testing.

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