Misdiagnosed HIV Infection in Pregnant Women: Implications for Clinical Care

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Synopsis

Out of nearly 900 women in a research study of human immunodeficiency virus infection in pregnancy, 8 were subsequently found not to be infected.

Misdiagnoses could have resulted from (a) *laboratory errors or specimen mixups;* (b) *failure to follow the testing algorithm recommended by the Centers for Disease Control and Prevention to confirm results;* (c) *women perceiving they were infected by high-risk behavior in the absence of testing, despite the receipt of negative test results, or based on screening results only; or* (d) *factitious disorder, HIV Munchausen syndrome, or malingering.*

Because of the potentially devastating impact of an HIV diagnosis and the toxicity of HIV therapies, health care providers should obtain independent confirmation of the diagnosis before initiating treatment or followup for HIV based on patient report or provider referral. Quality test interpretation and counseling must be ensured. Therapeutic interventions may be indicated for persons intentionally and falsely presenting themselves as HIV-infected.

The Women and Infants Transmission Study (WITS) has been enrolling pregnant women infected with the human immunodeficiency virus (HIV) since December 1989 in a study evaluating factors related to mother to infant transmission of HIV. As of February 1994, nearly 900 women living in Boston, Chicago, New York, and San Juan, PR, have been referred to WITS clinical centers in these cities; 860 were enrolled in the study. Referrals were made by freestanding anonymous testing sites, prenatal care providers, sexually transmitted disease treatment facilities, and community groups serving populations at high risk for HIV infection. All pregnant, HIV-infected women willing to be followed during and after pregnancy, and willing to have their infants followed after delivery, were eligible to join WITS. The study has been approved by Institutional Review Boards at each center. Eight of the subjects who presented to the study after referral because of positive HIV test results or from self-referral were subsequently found to be seronegative.

Results

Herewith are profiles of the eight:

1. A 26-year-old married Hispanic woman, who denied HIV risk factors, was referred to WITS by a health care provider. The patient stated she had been informed by her physician that she was infected, and a referral letter from the provider included copies of laboratory slips from repeat enzyme-linked immu-

noassay (EIA) tests and a Western blot, all of which were positive. Subsequent serologic tests (EIA and Western blot) by WITS investigators were all negative. Upon followup after receipt of the negative test results, WITS staff members learned that the original provider had also ordered repeat tests which were negative.

2. A 28-year-old Hispanic woman, who denied HIV risk factors, was referred to WITS after receiving HIV test results confirmed positive by Western blot from a local health provider. A serum sample subsequently obtained for WITS was negative on a duplicate EIA and a Western blot. This finding was reconfirmed by WITS staff members who repeated this testing algorithm on a separate sample taken 3 weeks later.

3. A 20-year-old African American woman, who reported that she was at risk for HIV infection from an intravenous drug-using sexual partner, was referred to WITS by a hospital resident physician. Upon reviewing the chart prior to enrolling her in WITS, staff members noted that the chart contained only a single positive EIA, and that the Western blot results were still pending. According to the chart, the resident referred her for post-test counseling for HIV infection based on EIA results only. The pending Western blot result came back as indeterminate. On followup, WITS staff members learned that the patient was retested a year after the original test and had one positive EIA, one negative EIA, and an indeterminate Western blot.

4. A 28-year-old African American woman, who denied HIV risk factors, was referred to WITS by her obstetrician. The physician had received telephone notification from the hospital laboratory that the patient's serologic tests were positive for HIV. Repeat EIAs and a Western blot ordered by WITS staff members were all negative. On further communication with the referring physician, copies of the laboratory slips were obtained, showing a single initial positive EIA with an indeterminate Western blot. The woman was retested by WITS staff members and had negative EIA and Western blot tests. The referring physician was notified about the discrepant results.

5. A 26-year-old Hispanic woman, who admitted to cocaine use, was referred to WITS by a provider at a local health center. The provider had followed her for HIV disease for approximately 1 year, based on the patient's self-report of positive serologic test results. CD4 cell counts obtained by the health care provider were between 500 and 600 per cubic millimeter (mm^3). Subsequent serologic testing for the WITS protocol (EIA and Western blot), reconfirmed on two separate samples, revealed negative results. On later inquiry, the woman told WITS staff members she had been tested at a mobile van that provided results on the spot and failed to follow up on a referral for additional testing at a local hospital. Instead, she reported directly to an HIV treatment center and told their staff she was HIV infected. Upon confirming that she was uninfected, WITS staff gave her referrals to social work services and primary care providers.

6. A 33-year-old African American woman, who reported a history of crack cocaine and heroin use, and treatment with zidovudine and trimethoprim-sulfamethoxazole for HIV and *Pneumocystic carinii* pneumonia (PCP) infections, was referred for enrollment in WITS by staff members at a homeless shelter whom she had told of her HIV infection. CD4 cell counts obtained as part of the WITS protocol ranged from 466 to 881 per mm^3. Multiple specimens tested in an AIDS Clinical Trials Group-certified laboratory were negative, prompting additional serology tests. WITS staff made two home visits to obtain specimens to reconfirm the negative test results. Repeat EIA and Western blot serology on these samples tested at different laboratories were negative. The woman refused additional followup care or referrals.

7. A 31-year-old African American woman who reported injecting heroin, smoking crack, and having unprotected sex with drug-using partners, was referred to WITS by homeless shelter staff members whom the woman had told of her HIV infection. Subsequent serology tests (repeat EIA and Western blot) and an HIV culture performed for WITS were negative. Inquiries by WITS staff members revealed that, prior to informing shelter staff that she was infected, she had sought care at an HIV clinic, claiming to be HIV infected and had been informed by clinic health providers that she was uninfected. WITS staff members referred her for primary care and social work services. She subsequently sought care from an HIV treatment clinic despite having been told she was uninfected.

8. A 34-year-old African American woman, who reported intravenous drug use, crack use, and multiple drug-using sexual partners, was referred to WITS by a drug treatment center. She had told staff members

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at the center that she had received a positive HIV test result from an HIV counseling and testing center. Subsequent serology testing through WITS was negative. WITS staff members referred her for additional drug treatment.

Discussion

Of the approximately 900 women referred to the Women and Infants Transmission Study since late 1989 (including about 40 who were referred but decided not to enroll), 8 were subsequently found to be uninfected, based on duplicate EIA and Western blot confirmation tests. In most cases, negative test results were obtained on two or more separate samples to rule out infection definitively; in Case 8, documentation was available only from a single EIA, which was negative, but we believe additional testing was performed. It was not always possible to ascertain what tests had been performed prior to subjects being referred to WITS.

There appear to be four main causes for misdiagnoses of HIV infection among these women.

- Laboratory errors or mixup of specimens may have occurred.
- The diagnostic algorithm recommended by the Centers for Disease Control and Prevention (CDC) (two positive EIAs followed by an independent confirmatory test) (*1,2*), was not followed by laboratory staff or by care providers who reported positive results to patients either based on screening tests alone or based on an indeterminate confirmation test.
- Patients may have perceived that they were infected because of high risk behavior either without getting test results or with receipt of negative results, possibly due to misunderstanding of information from providers.
- There may have been factitious disorder, HIV Munchausen syndrome, or malingering.

Misdiagnoses in the first two women described are most likely from specimen mixups or laboratory reporting errors. Both women denied being at risk for HIV, but WITS staff members were provided with referral information, including documentation of positive repeat EIAs and positive Western blot confirmations. The predictive value of HIV screening by antibody testing varies substantially according to the prevalence of HIV infection in the population screened (*3*). Low prevalence of HIV, however, seems an unlikely explanation for false positive test results in these cases. While the seroprevalence among specimens tested in the laboratories used by the women in this report is not known, the cities with WITS centers, New York, San Juan, Boston, and Chicago, rank 2, 7, 34, and 42 in rates of AIDS cases reported to the CDC in the calendar year ending September 1993. New York State, the Island of Puerto Rico, Massachusetts, and Illinois rank 1, 3, 7, and 14 in rates of cases in women reported during that time period (*4*). It thus seems improbable that any single specimen had two false positive EIAs followed by a false positive Western blot result and more likely reflects specimen mixups or laboratory reporting errors.

In Case 3, the woman was informed she was infected based on a single reactive EIA only, a departure from the CDC's diagnostic algorithm (*1,2*). For the woman in Case 3, whose initial Western blot ultimately came back as indeterminate, and the woman in Case 4, the CDC recommendation concerning indeterminate Western blot results (*5*) should have led to serial retesting over the ensuing 6 months. The patients should have been counseled that their HIV status could not be determined at that time. A recent case control study showed that, among women, parity and autoantibody responses were associated with indeterminate Western blot test results (*6*). In the absence of any known risk factors, clinical symptoms, or other findings (Case 4, for example) patients with continued consistent indeterminate Western blot results for more than 6 months may be considered negative for antibody to HIV-1 (*5*). Additional recommendations by Celum and coworkers regarding counseling and followup testing seem reasonable (*7*).

In Cases 5 and 6, the women reported active drug use at the time of enrollment in WITS. The woman in Case 5 reported obtaining test results shortly after providing a blood specimen and a referral for further testing at a local hospital. If true, she probably received only a screening test without confirmation. WITS staff members were unable to locate the facility described by the woman. Upon learning that she was in fact not infected, she did not react as one might expect to the news, according to WITS staff members. Therefore, it is not clear whether she

misunderstood the meaning of a positive screening test or was presenting with factitious AIDS (*8*).

The woman in Case 6, on enrollment in WITS, was 24 weeks pregnant and had been on zidovudine and trimethoprim-sulfamethoxazole throughout her pregnancy, according to medical records obtained from the hospital that treated her. The medical record did not contain laboratory confirmation for the PCP diagnosis or documentation of a CD4 count. Although false-positive serology (repeated false-positive EIA followed by false-positive Western blot) has been reported (*9*), the likelihood of such an occurrence in this testing sequence is sufficiently remote (estimates of 1 in 20,000 and less than 1 in 100,000 have been reported) (*10,11*) as to suggest either laboratory mixups, or patient misunderstanding or misreporting of negative results. Since the woman refused followup, it was not possible to ascertain which explanation was more probable.

The women in Cases 7 and 8 reported long-term drug abuse and possible exposure to HIV through unprotected sex and presented themselves to social service agencies as infected. Several explanations are plausible. The woman in Case 7 may have claimed she was HIV-infected to gain access to the social supports and clinical care available through a research project such as WITS and not widely available elsewhere. In Case 8, the woman may have believed she was infected as punishment for high risk behavior. Such explanations would be consistent with diagnoses of factitious disorder, HIV Munchausen syndrome, or malingering, all of which have been reported in the AIDS literature (*12–18*). Cases 5 and 6 may have fit this profile as well.

Chronic factitious disorder with physical symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised, (DSM-III 301.51) (*19*) is distinguished from malingering, because factitious disorder involves feigning or inducing physical symptoms to obtain treatment whereas malingering involves a motivation to seek material benefit. HIV Munchausen's Syndrome is a subset of factitious disorder where the patient presents with physical symptoms, repeated lies, and a history of treatment at several facilities (*12*). Since these women were not followed by WITS staff after discovery of discrepant serology results, it was not possible to make a definitive diagnosis. It is important for clinicians, particularly those attached to a research infrastructure providing ancillary services, however, to be alert to the possibility of these conditions.

In evaluating potential volunteers for HIV research studies, the possibility of incorrect referral must be considered, and stringent criteria for entry must be used. A positive HIV test result can be a devastating piece of information, potentially leading to irrevocable life choices (*20*). For example, the woman in Case 4 contemplated termination of her pregnancy when told erroneously that she was HIV positive, but she had progressed too far in gestation to do so. The recent finding about the ability of zidovudine taken during pregnancy, delivery, and by neonates to reduce mother-to-infant transmission (*21*) may result in a sense of urgency to refer pregnant women for HIV counseling and testing.

Laboratory and clerical errors in HIV testing have been widely reported. Sullivan and coworkers reported that 2 of the first 15 people referred to a therapeutic HIV vaccine trial as infected were subsequently determined to be uninfected (*22*). Similarly, a report of 4,911 persons in the U.S. military with HIV seropositive tests on two or more samples revealed that 6 had seronegative tests following positive tests. Five of the 6 cases were due to specimen mixups while the sixth was a testing error. Overall, 32 errors were detected in more than 5 million tests, for a rate of 12.4 errors per 1 million specimens tested (*23*). In a report on 660 seropositive persons followed in cohort studies or methadone maintenance clinics, 16 were found to be uninfected. Followup showed that 11 clerical and 8 laboratory errors had been made (*24*). It thus seems likely that HIV followup and treatment of people misdiagnosed with, or feigning HIV infection will continue to occur.

It is not possible to infer a rate of misdiagnoses from these data because statistics are not maintained on total numbers of women referred to WITS. Nevertheless, because of the potential for misdiagnosis of HIV in referred patients, the WITS enrollment procedure was modified to require original documentation of repeat EIA and Western blot laboratory test results or repeat testing by WITS personnel. These case reports underscore the importance of following the CDC-recommended HIV diagnostic algorithm (*1,2*) for both research purposes as well as clinical care.

In response to the HIV-AIDS epidemic, HIV counseling and testing have become available in many settings throughout the country. The amount and quality of counseling and followup may vary from one setting to another (*25*). It is important for providers giving HIV test results to ensure that patients understand the meaning of the results, particularly if the confirmation test is indeterminate or if no HIV risk has been acknowledged. Because of the potential for misunderstanding of test results, it

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may not be appropriate to provide only screening tests if a facility does not also have the capacity to ensure that referrals for confirmation tests are followed up. This recommendation is especially salient where clients' mental state may be altered by substance abuse.

Conclusions

Based on the experience in WITS, we recommend that any health care provider considering initiating prophylactic or therapeutic treatment or followup for HIV follow the CDC-recommended diagnostic algorithm (*1,2*). Furthermore, if a patient denies HIV risk, we would recommend repeating the serology tests on a separate sample to rule out specimen mixup. Low CD4 counts should not be regarded as presumptive evidence of HIV infection in the absence of positive HIV serology. A recent literature review reported that CD4 counts are an unreliable surrogate marker of HIV disease progression in AIDS clinical trials (*26*); their use for HIV diagnostic purposes should also be avoided. If the client expresses disbelief of initial test results either associated with denial of risk or mistrust of the reliability of results, the tests should be repeated. If the results of repeat testing are discordant with the initial results, a third sample should be tested. While retesting could offer short-term false hope and subsequent anguish to truly infected persons, it could help avoid misdiagnoses and unnecessary treatment among uninfected people. With careful discussion about the reasons for retesting, the possible harms could be minimized.

Clients who refuse to believe repeatedly negative test results should be referred for appropriate psychosocial services. These might include social work services, drug treatment, and psychiatric evaluation and therapy. These case reports also indicate the need for additional quality control of laboratory efforts (*27*) and counseling procedures.

Finally, when clients are referred for HIV research studies or treatment and turn out to be uninfected, providers discovering the discrepancies should follow up with referring sources to determine the reasons. If referral sources misunderstand the protocol, additional information should be provided. On the other hand, if community-based providers are seeking opportunities for entry into the health care system for clients lacking other means, research staff members should be prepared to provide referrals to appropriate service providers.

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Comparison of HIV-Risk Behaviors and Demographics of Adolescents Tested or Not Tested for HIV Infection

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Synopsis

In a survey of 2,548 adolescents, 11.5 percent reported ever having had the human immunodeficiency virus (HIV) antibody test. Those who had been tested were significantly more likely to be male, black, and to reside in metropolitan areas than those who had not been tested. Tested adolescents were more than three times as likely to report having injected drugs and were more than twice as likely to have had sexual intercourse, had sexual intercourse at earlier ages, and with multiple partners. More than half of adolescents who had been HIV-tested had no reported risks for HIV infection. More than one-quarter of adolescents not tested reported at least one HIV risk factor. These data suggest the importance of discussing the HIV testing and counseling process within any HIV education program directed to adolescents.

Adolescents' risk for infection with the human immunodeficiency virus (HIV) is a growing concern in connection with the acquired immunodeficiency syndrome (AIDS) epidemic. Adolescents are seen as at increased risk for HIV infection because they engage in sexual intercourse more often and earlier than previous generations, are infected with sexually transmitted diseases at high rates, use alcohol and other drugs that often lead to high-risk behaviors, and use condoms inconsistently as a method of protection (*1–5*).

As a result of growing public awareness of AIDS and recent efforts by schools to implement HIV education programs, increasing numbers of adolescents are expected to seek HIV counseling and testing to determine their HIV status and to try to allay their fears, rational as well as irrational, of being infected. Although there is a growing body of research on the characteristics of adults who seek HIV antibody testing (*6*), and on the effects of HIV testing on adult HIV risk behavior (*7–9*), there are few corresponding data on adolescent populations. Of particular interest is whether adolescents who seek HIV testing and counseling differ from those who do not.

We surveyed 2,548 Colorado students in grades 9 through 12 who were enrolled in an evaluation of a