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Original Article

High False-positive Rate of Human Immunodeficiency Virus Rapid Serum Screening in a Predominantly Hispanic Prenatal Population

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OBJECTIVE:

To identify the characteristics of the gravidas delivering at our birthing center that place them at risk for false-positive human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELISA).

STUDY DESIGN:

The medical records of all rapid HIV-ELISA-positive gravidas that delivered at our hospital between January 2000 and October 2001 were retrieved, and information was gathered regarding maternal demographics. The results of the Western blot tests were also retrieved and correlated to the ELISA results, across varying maternal characteristics. χ^2, Student's t-test and multivariate analysis were performed, as appropriate, using the SAS software; statistical significance was denoted by $p<0.05$.

RESULTS:

A total of 69 patients had a positive rapid HIV-ELISA out of 9,781 deliveries. Of those, 26 were confirmed as HIV infected by Western blot (overall HIV prevalence: 0.27%, ELISA-positive predictive value: 37.7%). The subgroup prevalence of HIV and positive predictive value of ELISA were 1.53 and 75% among Caucasians; 2.43 and 82.6% among African-Americans; and 0.05 and 9.8% among Hispanics, respectively ($p<0.05$ for the comparisons between Hispanics and non-Hispanics only). A history of multiple (≥ 5 lifetime) sexual partners was elicited in the majority of HIV-infected patients.

CONCLUSIONS:

The positive predictive value of rapid HIV-ELISA during pregnancy varies widely, depending on maternal race/ethnicity and sexual behavior. The routine disclosure of rapid intrapartum HIV serum screening results prior to Western blot confirmation should be avoided in very low-risk populations.

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INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC[1]) and Institute of Medicine (IOM[2]) guidelines, human immunodeficiency virus (HIV) screening for pregnant women should be universally offered and performed with maternal consent. The administration of peripartum AZT (azidothymidine-zidovudine) prophylaxis to HIV-infected parturients, based on the 1994 PACTG 076 protocol, and highly active antiretroviral treatment protocols have contributed to a dramatic decline in perinatal HIV transmission.[3] CDC data confirm that the pediatric incidence of AIDS declined by 75% between 1992 and 1998 as a result of these practices.[1]

Unfortunately, 200 to 400 infants are stillborn with HIV each year in the US, which underscores the importance of continued vigilance and routine screening during pregnancy. It is estimated that 120,000 to 160,000 women are HIV positive in the US, of which 80% are of childbearing age.[1] Among young women the main mode of HIV transmission is heterosexual contact. African-American and Hispanic women have been disproportionately affected by the HIV epidemic, accounting for 80% of AIDS cases reported in US women in 1999. Notably, AIDS is the leading cause of death among African-American women between the ages of 25 to 44 years in the US.[1]

The CDC recommendations[4] have resulted in a very high HIV screening rate in obstetrical practices, in the United States. However, in many public hospitals a significant proportion of patients receive late or no prenatal care and thus the first and only chance for screening is at the time of labor. It is estimated that as many as 40% of cases of perinatal HIV transmission occur in mothers with unknown HIV status at the onset of labor.[5] Along with the opportunity of detecting previously undiagnosed HIV cases,

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however, routine intrapartum serology screening carries the obvious risk of alarming the parents in the case of false-positive ELISA results (i.e. negative Western blot (WB) test).

Several risk factors have been found[6–9] to predispose to false-positive HIV ELISAs: autoimmune disease, renal failure, cystic fibrosis, multigravidity, blood transfusions, hepatic disorders, lymphomas, intravenous drug abuse, hemodialysis, or recent vaccinations for hepatitis B, rabies, or influenza. It is presumed that these conditions lead to a generalized immune stimulation that induces the production of anti-HLA-DR or other antibodies that crossreact with the HIV antigens of the ELISA assay. Autoimmune phenomena (e.g. thyroiditis, lupus, rheumatoid arthritis) are most common during the female reproductive years and multiparas frequently have a history of peripartum hemorrhage requiring transfusion. It is, therefore, no surprise that the otherwise extremely specific and sensitive (>99% each) HIV ELISA test is frequently false-positive during pregnancy.[6,7]

Trying to explain the rapid HIV screening ELISA results to the baffled parents just hours after the delivery of their infant can be extremely difficult and interpretation of those results is a focus of ongoing debate between obstetric and pediatric services. At our hospital, the pediatric service advocated immediate counseling of the family with a positive peripartum ELISA to begin timely (within 48 hours of life) AZT chemoprophylaxis for the neonate while awaiting the WB results. Obviously, the mere mention of a positive ELISA test to the unsuspecting parents has the potential to cause emotional upheaval. With these concerns in mind we decided to review the records of all HIV-ELISA-positive mothers in our center, in order to identify any information or trends that could help us counsel couples appropriately.

MATERIALS AND METHODS

Starting January 2000, all the serum specimens for Harris County Hospital District to be screened for HIV were analyzed at the diagnostic immunology laboratory of Ben Taub General Hospital, using an FDA-approved rapid HIV ELISA test (Abbott Murex Single Use Diagnostic System HIV-1 test, Abbott Laboratories, Inc., Abbott Park, IL). After approval by the Institutional Review Board, all the HIV ELISA-positive serum specimens were tracked through the hospital laboratory log and the results were cross-referenced to the delivery records from the Ben Taub Hospital birthing center for the period from January 2000 to October 2001. We identified a total of 69 patients that were tested by WB for repeatedly reactive HIV ELISAs during pregnancy in this period.

Subsequently, the electronic and conventional medical records of these subjects were reviewed and data gathered regarding patient demographics and historical risk factors: multiple (i.e. ≥ 5 lifetime) sexual partners, intravenous drug abuse, sexually transmitted diseases (STDs), transfusions, hematologic malignancies, autoimmune diseases, hepatic or renal diseases, cystic fibrosis, or certain vaccinations (rabies, hepatitis B, influenza). The sexual histories were obtained in most cases by the interviewing physician, or with subsequent questioning by the social worker with the aid of interpreters, as needed. The history of drug use was either volunteered by the patient and/or determined by urine toxicology screens on admission. The data were collected by the authors (NZ, IA), recorded in study data sheets (with care taken to exclude potential patient identifiers), tabulated and analyzed with χ^2 or Student's t-test, as appropriate. Multivariate analysis was performed to identify the strongest predictor(s) for false-positive ELISA. All analyses were performed with SAS statistical software (SAS, Cary, NC); $p \leq 0.05$ was considered significant.

RESULTS

Based on the number of deliveries at our center (9781), the overall HIV seroprevalence in our prenatal population was 0.27% during the study period. Based on the racial/ethnic make-up of our population (87% Hispanics, 8% African-Americans, 3% Asians and 2% Caucasians), subgroup rates were highest among African-Americans (2.43%), followed by Caucasians (1.53%) and Hispanics (0.05%).

The demographic characteristics of the cases are summarized in Table 1. Of the 69 women with positive ELISA test, 26 were confirmed as HIV infected by WB, giving the rapid HIV ELISA screening test an overall positive predictive value (PPV) of 37.7%. Two mothers had repeatedly indeterminate WB (persistent p24 bands) and were being followed with repeat titers. The PPV of the test varied significantly by maternal race/ethnicity, as summarized in Table 2.

The correlation of maternal characteristics and WB results is depicted in Table 3. Women with a false-positive ELISA were more likely to be Hispanic, married, of lower parity and have no history of multiple sexual partners or STDs, reflecting the majority of our prenatal population. Of the mothers with false-positive/indeterminate ELISAs, five (12%) had clinical or laboratory evidence of autoimmune phenomena (e.g. thyroiditis, antinuclear antibodies) and three (7%) had hepatic or renal disease. We did not identify any patients with a documented history of multiple transfusions, cystic fibrosis, specified vaccinations, or hematologic malignancy in this population.

On multivariate analysis, maternal race was the strongest predictor of a false-positive result; a Hispanic gravida was at least 35 times more likely to have a false-positive ELISA screen than an African-American gravida, even when gravidity, marital status, h/o STDs and h/o multiple sexual partners were taken into account (Table 4).

Table 1 Demographic Characteristics of Mothers with Positive HIV ELISAs

Age (mean): 26.6 years	
Gravidity: Mean = 2.8, Median = 2	
1	15 (22%)
2	20 (29%)
3	15 (22%)
4	7 (10%)
5	7 (10%)
≥6	5 (7%)
Marital status	
Single	32 (46%)
Married	35 (51%)
Divorced/widowed	2 (3%)
Race/Ethnicity	
Hispanic	41 (60%)
Black	23 (33%)
White/Asian	5 (7%)
Western Blot	
Negative	41 (59%)
Positive	26 (38%)
Indeterminate	2 (3%)
Multiple partners	
No	43 (62%)
Yes	26 (38%)
STDs	
No	46 (67%)
Yes	23 (33%)

Table 2 Accuracy and Positive Predictive values for HIV ELISA During Pregnancy, According to Maternal Race/Ethnicity

	African-American (n=23)	Hispanic (n=41)	Caucasian (n=4)	Asian (n=1)	Total (n=69)
False +	3	36	1	1	41
True +	19	4	3	0	26
Indeterminate	1	1	0	0	2
PPV	82.6%	9.8%	75%	N/A	37.7%

Table 3 Correlation of Maternal Characteristics and WB Results

Characteristic	WB− (n = 41)	WB+ (n = 26)	Statistical significance (p)
Race			
Hispanic	36 (88%)	4 (15%)	
Black	3 (7%)	19 (73%)	<0.001
White/Asian	2 (5%)	3 (12%)	NS
Marital status			
Single	14 (34%)	19 (73%)	
Married	27 (66%)	7 (27%)	0.01
Multiple partners			
No	40 (98%)	2 (8%)	
Yes	1 (2%)	24 (92%)	<0.001
STDs			
No	37 (90%)	8 (31%)	
Yes	4 (10%)	18 (69%)	<0.001
Age (mean) (years)	26.5	26.6	NS
Gravidity (mean)	2.5	3.7	0.05

Table 4 Maternal Race/Ethnicity as a Risk Marker for False-positive HIV ELISAs

Race	WB− n = 41	WB+ n = 26	Crude OR	Adjusted OR*	95% CI	p
Hispanic	36 (88%)	4 (15%)	57.0	35.4	2.14- >999.9	0.02
Black	3 (7%)	19 (73%)	1.0	1.0	—	—
White/ Asian	2 (5%)	3 (12%)	4.2	2.99	0.4- 32.82	NS

*Adjusted for marital status, gravidity, h/o STDs, and h/o multiple partners.

DISCUSSION

We found that the PPV of rapid HIV ELISAs is very low in our Hispanic prenatal population. The wide variation of HIV prevalence over different ethnic/racial groups was noteworthy. Our public hospital serves two distinctly different population subgroups: Hispanics (mostly immigrant Mexican-Americans and Central Americans) and non-Hispanics. The former group is characterized by a very low HIV prevalence (0.05%) and paucity of HIV risk factors and the latter by a very high HIV prevalence (1.53 to 2.43%) and much higher-risk behavior. This is in contrast to national statistics;[1] apparently, the non-Hispanic patients that deliver in our hospital are more likely to have historical factors that place them at high risk for HIV infection. Furthermore, in all the cases of HIV-infected Hispanic patients at least one historical risk factor was identified.

Universal HIV ELISA screening during pregnancy would be expected to lead to a number of false-positive results,[10] but we have shown a particularly low PPV for the largely migrant Hispanic population of our center (9.8%). This finding is consistent with prior published reports.[11] The overall HIV prevalence (0.27%) in

our population also correlates with CDC estimates for our area, from a 1993 survey of reproductive health clinics.[1] Additionally, our two indeterminate results on WB analysis (persistent p24 bands) are consistent with the national norm (<1/4000 specimens tested by ELISA[12]).

Given the proven efficacy of the PACTG 076 protocol[3] in curtailing perinatal HIV transmission and the fact that 60 to 75% of perinatal transmission occurs during labor and delivery, current clinical practice is the administration of AZT within 48 hours of life. Specifically, reanalysis of those data has showed that AZT should be administered within 12 hours of life and that administration at 12 to 24 hours of life does little to curtail vertical transmission.[13] To this end, clinicians violate the basic rule of not communicating HIV screening results to a patient before WB confirmation. The risks of this practice are evident:[14,15] the news can shock the couple, trigger domestic violence and traumatize the whole family, the mother can be pushed into postpartum depression and the neonate denied the benefits of breastfeeding and exposed to potentially dangerous medications, as only 5% of mothers decline chemoprophylaxis in this situation.[4]

However, AZT is not innocuous.[16–19] CDC currently recommends that children perinatally exposed to antiretrovirals should have long-term follow-up, including evaluation for late effects of these therapies, such as tumor onset, neurologic and neurodevelopmental deficits.[20,21]

With an HIV seroprevalence among Hispanic mothers of 0.05% in our population, the number needed to screen would be more than 16,000 Hispanic gravidas to prevent a single case of perinatal transmission of HIV (based on a 25% baseline risk of vertical transmission and an optimal decrease to 8% with peripartum AZT). In other words, at our center the time needed to avert a single case of neonatal HIV infection among our Hispanic population — assuming 100% screening — would be more than 3 years, on average.

From a health economy perspective, recently published models indicate that peripartum HIV screening is cost-effective if the HIV seroprevalence is at least 0.17 to 0.21% in the screened population.[22–24] Our study raises the issue of cost-effectiveness and questions the safety of routine disclosure of preliminary rapid intrapartum HIV screening results in very low-risk populations. Targeted disclosure of these results to our Hispanic gravidas seems more appropriate, taking action (disclosure, offer of AZT) only in cases where historical risk factors for HIV infection are present.

Obviously, if one is to avoid the pitfalls of rapid intrapartum HIV screening, one should offer HIV serum screening during earlier stages of the prenatal care, if at all possible. Unfortunately, the very same risk factors that lead to HIV infection are associated with lack of prenatal care: 15% of HIV-infected pregnant women in the US receive no prenatal care, compared with only 2% of the general population.[1] As a result, 35% of children with perinatally acquired AIDS delivered in 1995 to 1997 were born to mothers that were not tested for HIV antepartum. The CDC has, therefore, focused on making HIV screening available to all pregnant women. In this context, the Food and Drug Administration recently approved another rapid HIV screening method for commercial use;[25] and the CDC-funded MIRIAD (Mother–Infant Rapid Intervention At Delivery[4]) study in communities with high rates of inadequate prenatal care and high HIV seroprevalence in women of childbearing age shows that fast and accurate results can be obtained with this rapid HIV screening method.[26–28] Based on our results, such screening methods can be marred by poor PPV and lack of cost-effectiveness when applied to very low-risk populations (regardless of racial composition). Establishing effective systems for early prenatal testing for HIV should remain a top priority for the public health authorities, in order to avoid the pitfalls of rapid intrapartum screening.

In conclusion, our findings underscore the fact that not all patients are at the same risk for HIV infection. Any screening program must consider the characteristics of the target population;[29] health providers should keep in mind the effect of population prevalence on the predictive value of a given test. In fact, the CDC states that informed refusal of intrapartum HIV screening is a reasonable option for the parturient without historical risk factors for HIV infection.[4] Finally, release of preliminary test results and counseling for the HIV ELISA-positive mother and her family must consider her *a priori* risk status, particularly in low-risk women, such as immigrants from Mexico and Central America.

References

1. Centers for Disease Control and Prevention. Guidelines and Statistics for HIV Available at: http://www.cdc.gov/hiv/dhap.htmRetrieved July 21, 2003.
2. Stoto M, Almario D, McCormick M. Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States. Committee on Perinatal Transmission of HIV, Institute of Medicine, and Board on Children, Youth, and Families, National Research Council, 1999.
3. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of HIV. N Engl J Med 1998;339:1409–14.
4. Centers for Disease Control and Prevention (U.S.). Revised recommendations for HIV screening of pregnant women. MMWR Rep Recomm 2001;50(RR-19):59–85.
5. Office of the Inspector General. Reducing obstetrician barriers to offering HIV testing. 2002 Available at: http://oig.hhs.gov/oei/reports/oei-05-01-00260.pdfAccessed July 10, 2003.
6. Doran TI, Parra E. False-positive and indeterminate HIV test results in pregnant women. Arch Fam Med 2000;9:924–9.
7. Magee LA, Murphy KE, von Dadelszen P. False-positive results in antenatal HIV screening. Can Med Assoc J 1999;160:1285–6.
8. Mylonakis E, Paliou M, Greenbough TC, Flanigan TP, Letvin NL, Rich JD. Report of a false-positive HIV result and the potential use of additional tests in establishing HIV serostatus. Arch Intern Med 2000;160:2386–8.

9. Mylonakis E, Paliou M, Lally M, Flanigan TP, Rich JD. Laboratory testing for infection with the HIV: established and novel approaches. Am J Med 2000;109:568–76.
10. Meyer KB, Pauker SG. Screening for HIV: can we afford the false positive rate? N Engl J Med 1987;317:238–41.
11. Alexander TS, Lee J, Yen-Lieberman B. Incidence of HIV antibody in a prenatal population at a community hospital. Clin Diagn Lab Immunol 1999;6:140–1.
12. Gwinn M, Redus MA, Granade TC, Hannon WH, George JR. HIV-1 serologic test results from one million newborn dried-blood specimens: assay performance and implications for screening. J Acquir Immune Defic Syndr 1992;5:505–12.
13. Wade N, Birkhead G, French PT. Authors' response [letter]. N Engl J Med 1999;340:1041–2.
14. Sheon AR, Fox HE, Alexander G, et al. Misdiagnosed HIV infection in pregnant women: implications for clinical care. Pub Health Rep 1994;109:694–9.
15. Ahdieh L. Pregnancy and infection with HIV. Clin Obstet Gynecol 2001;44:154–66.
16. Scalfaro P, Chesaux JJ, Buchwalder PA, Biollaz J, Micheli JL. Severe transient neonatal lactic acidosis during prophylactic zidovudine treatment. Intens Care Med 1998;24:247–250.
17. Minkoff H, Augernbraun M. Antiretroviral therapy for pregnant women. Am J Obstet Gynecol 1997;176:478–89.
18. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. Lancet 1999;354:1084–9.
19. Poirier M, Divi R, Al-Harthi L, Olivero O, Nguyen V, Walker B, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. J Acquir Immune Defic Syndr 2003;33: 175–183.
20. Fowler MG. Follow-up of children exposed to perinatal antiretrovirals. Teratology 2000;61:395–6.
21. Centers for Disease Control and Prevention. USPHS task force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal transmission in the United States. Morb Mortal Wkly Rep 1998;47: 1–28.
22. Stringer JS, Rouse DJ. Rapid testing and zidovudine treatment to prevent vertical transmission of HIV in unregistered parturients: a cost-effectiveness analysis. Obstet Gynecol 1999;94:34–40.
23. Grobman WA, Garcia PM. The cost-effectiveness of voluntary intrapartum rapid HIV testing for women without adequate prenatal care. Am J Obstet Gynecol 1999;181:1062–71.
24. Immergluck LC, Cull WL, Schwartz A, Elstein AS. Cost-effectiveness of universal compared with voluntary screening for human immunodeficiency virus among pregnant women in Chicago. Pediatrics 2000;105:e54.
25. Cowley G. In the News: A Quick HIV test Newsweek, November 18, 2002.
26. Minkoff H, O'Sullivan MJ. The case for rapid HIV testing during labor. JAMA 1998;279:1743–4.
27. Centers for Disease Control and Prevention. USPHS Task force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Morb Mortal Wkly Rep 2002; 51:32.
28. Bulterys M, Preliminary MIRIAD study results, presented at the 2003 National HIV Prevention Conference, Atlanta, GA, July 28, 2003.
29. Wald NJ. The definition of screening. J Med Screen 2001;8:1.