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Cofactors for HIV-1 Incidence during Pregnancy and Postpartum Period

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Abstract

Objectives—To estimate HIV-1 incidence and cofactors for HIV-1 incidence during pregnancy and postpartum.

Design—Retrospective study among women who were HIV seronegative during pregnancy.

Methods—Mothers accompanying their infants for routine 6-week immunizations at 6 maternal child health clinics in Nairobi and Western Kenya were tested for HIV-1 after completing a questionnaire that included assessment of sociodemographics, obstetric history and HIV-1 risk perception.

Results—Of 2,135 mothers who had tested HIV-1 seronegative antenatally, 2,035 (95.3%) accepted HIV-1 re-testing at 6 weeks postpartum. Of these, 53 (2.6%) were HIV-1 seropositive yielding an estimated HIV-1 incidence of 6.8 (95% CI: 5.1-8.8) per 100 woman-years). Mothers who seroconverted were more likely to be employed (45.3% *vs* 29.0%, p=0.01), married (96.2 *vs* 86.6%, p=0.04) and from a higher HIV-1 prevalence region (60.4% in Western Kenya *vs* 28.8% in Nairobi, p<0.001). Among married women, those in polygamous relationship were significantly more likely to seroconvert (19.6% *vs* 6.7%, p<0.001). In multivariate analysis, region and employment independently predicted seroconversion.

Conclusions—Repeat HIV-1 testing in early postpartum was highly acceptable and resulted in detection of substantial HIV-1 incidence during pregnancy and postpartum period. Within prevention of mother-to-child HIV-1 transmission programs strategic approaches to prevent maternal HIV-1 acquisition during pregnancy are urgently needed.

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Keywords

Seroconversion; pregnancy; incidence; sub Saharan Africa; risk factors; heterosexual transmission

INTRODUCTION

In sub-Saharan Africa, the region of the world most heavily affected by HIV-1, women account for nearly 60% of HIV-1 infections [1]. The primary risk factor for HIV-1 infection among these women is unprotected heterosexual intercourse. The high prevalence of HIV-1 infection in women has in turn resulted in the region having 90% of the world's HIV-1 infected children [1]. Over the last few years, increased implementation of prevention of mother-to-child transmission of HIV-1 (PMTCT) programs in Sub-Saharan Africa has provided an opportunity for more women to know their HIV-1 status during prenatal care or at delivery, facilitating utilization of interventions to minimize HIV-1 transmission to their infants [2].

Although most pregnant women in sub-Saharan Africa are HIV-1-uninfected, they remain at risk of HIV-1 infection. Keeping these HIV-1 seronegative women uninfected is an important component of efforts to eradicate pediatric HIV-1 infections [3]. There is increasing evidence to suggest relatively high HIV-1 incidence (1.3-10.7 per 100 women-years) during pregnancy and the immediate postpartum period [4-6]. The increased risk of HIV-1 during pregnancy may be due to the woman's or her partner's sexual behavior, genital mucosal changes, or hormonal changes [3]. During late pregnancy, there is marked increase in progesterone levels which has been associated with increased CCR5 co-receptor expression on genital mucosal T-cells and macrophages (target cells for HIV-1) which may increase susceptibility to HIV infection [7]. After deliv ery, resumption of sexual activity before complete healing may also be a risk factor for HIV-1 acquisition.

Cofactors for HIV-1 acquisition during pregnancy and postpartum period are not well-defined; defining these cofactors is therefore a useful first step for development of strategies to decrease HIV-1 acquisition during this period. To estimate HIV-1 seroincidence during the pregnancy and postpartum period and to determine risk factors for incident HIV-1 infections, we offered HIV-1 testing to women previously determined to be HIV-1 uninfected during pregnancy, who had brought their infants for 6-week immunizations.

METHODS

Study Setting and Population

This was a retrospective study involving mothers coming to 6 public sector Maternal and Child Health (MCH) clinics in Kenya for routine infant 6-week immunizations; 4 in Nairobi (Dandora, Mathare North, Babadogo and Kangemi City Council Clinics) and 2 in Nyanza province of Western Kenya (Kisumu and Bondo District hospitals). HIV-1 prevalence in these settings differs appreciably with an estimated 10% prevalence in Nairobi and 15% in Nyanza [8].

Mothers were recruited at the time of infant vaccination. The Study nurse assisted the mother to get her infant weighed and vaccinated and then invited her to the study room to explain the study aims and procedures. Mothers who were interested in study participation signed a study consent form and were enrolled. A questionnaire was administered to determine maternal so ciodemographic characteristics, previous HIV testing and results, history of physical assault by the partner and perception of HIV infection risk in the previous 12 months. Following administration of the questionnaire, mothers received

individual pre-test counseling by a trained counselor, and were then offered HIV-1 testing. Those who accepted re-testing signed a HIV-1 test consent form. The result of the HIV-1 test in pregnancy was confirmed from the antenatal care (ANC) cards which was required for the infant to be registered prior to vaccination at the clinics where the study was conducted. Mothers who did not have their antenatal card were offered HIV-1 testing before their infants were vaccinated.

The Abbott Determine test kit (Abbott Japan, company, limited) was used for screening, and those specimens that tested negative were reported as negative. Those that tested positive were confirmed using Bioline test kit (Standard diagnostics, incorporated, Korea). If the second test was positive then the result was reported as positive. When the two tests were discordant, the results were reported as indeterminate and specimens sent for HIV ELISA test. Results of the ELISA test were reported as the true results. Women found to be HIV-1 infected were referred to Comprehensive Care Clinics (CCC) either at the study clinic, Kenyatta National Hospital or their preferred center for further evaluation, follow-up and care.

Stata version 10 (StataCorp, College Station, Texas, USA) was used to analyze the data. To compare variables between those women who seroconverted and those who did not, we used Chi square and Fisher's exact test for categorical variables and t tests for continuous variables. Logistic regression was used for multivariate analysis of factors that were significantly ($p<0.05$) different on univariate analysis and were not collinear. To estimate incidence rates, we assumed that mothers were tested at their first ANC care clinic visit and that they delivered at 40 weeks of gestation. The median duration of pregnancy at initiation of ANC care among Kenyan women is 5.9 months (~26 weeks) [9], giving an interval of 20 weeks between initial and repeat testing at 6 weeks after delivery.

The study was approved by Human Subjects Division at the University of Washington and the Kenyatta National Hospital (KNH) Ethics and Research Committee (ERC). Authorization was also obtained from the Nyanza Provincial Medical Officer of Health and the Nairobi City Council Medical Officer of Health.

RESULTS

During the study period, 2,700 mothers were enrolled of whom 2,135 (79.1%) had tested HIV-1 seronegative antenatally and were offered repeat HIV testing. Of these, 2,035 (95.3%) accepted retesting. Mothers who retested had a mean age of 23.7 years (SD 4.9); most had less than secondary education (74.2%), were unemployed (70.6%) and were married (86.8%). Among those married, 122 (7.1%) were in polygamous relationships (partner had more than one wife). Economic status was assessed by amount paid in rent, ownership of a television set and gas cooker. The mean monthly rent was $23.0 (SD 14.5), 975 (47.5%) women owned a television set, and 211 (10.4%) owned a gas cooker. This was the first pregnancy for 39% of mothers, and 33.6% of mothers perceived themselves to have been at risk of HIV-1 infection in the previous 12 months. Almost a quarter (24.4%) of mothers reported they had previously been physically assaulted by their partners (Table 1).

Of the 2,035 women who re-tested, 53 (2.6%) tested HIV-1 positive. The estimated HIV-1 seroincidence in this cohort was 6.8 (95% CI: 5.1-8.8) per 100 woman-years; 13.8 (95% CI: 9.6-18.9) and 3.9 (95% CI: 2.4-5.8%) per 100 woman-years in Nyanza and Nairobi respectively. Seroconverting women were more likely to be employed (45.3% *vs* 29.0%, p=0.01), married (96.2% *vs* 86.6%, p=0.04) and from Nyanza (60.4% *vs* 28.8%, p<0.001). Among married women, those in polygamous relationship were significantly more likely to seroconvert (19.6% *vs* 6.7%, p<0.001). There was a trend for the mothers who

seroconverted to have more than one child (73.6% *vs* 60.6%, p=0.06). Age, educational level, perception of HIV risk in the previous year, history of assault by partner and economic status did not differ between mothers who seroconverted and those who did not (Table 2). Women in Nyanza province were significantly more likely to be in polygamous relationships (12.1 *vs* 5.1, p=0.001) and to be employed (33.4 *vs* 27.7, p=0.009). In multivariate analysis, factors independently associated with seroconversion were employment (OR=1.9, 95% CI: 1.1-3.3, p=0.03) and region (OR 3.6, 95% CI: 2.1-6.4, p<0.001).

DISCUSSION

We found high acceptability of repeat HIV-1 testing with 95% of women who had tested HIV-1 negative at ANC accepting HIV-1 re-testing after an interval of approximately 20 weeks. Of those tested, 53 (2.6%) women acquired HIV-1 infection between late 2nd trimester and 6 weeks postpartum. The estimated HIV-1 incidence was 6.8 per 100 woman-years. Because most women had their first HIV test after the first trimester, our estimates likely excluded HIV incidence during early pregnancy and may have underestimated overall HIV-1 incidence in pregnancy. Our findings are consistent with recent studies that have reported high HIV-1 incidence among women during pregnancy and in the postpartum period [4-6]. High HIV-1 incidence among women who have participated in prenatal HIV prevention programs is of concern and highlights the importance of identifying and addressing needs of HIV-1 negative women who currently receive fleeting attention in PMTCT programs. Notably, HIV-1 incidence in pregnancy appears to be as high or higher than has been reported in sex worker or discordant couple cohorts [10-12], suggesting that HIV uninfected pregnant women are an important but generally unperceived ‘high-risk’ target group for HIV-1 prevention efforts in women. Unfortunately, current HIV-1 prevention trials exclude women who are pregnant despite their particular need for enhanced interventions during this period. It is critical to develop pregnancy-targeted interventions and messages to prevent HIV-1 seroconversion in what appears to be a particularly risky period.

We found that HIV-1 seroconversion was associated with the region the mother resided in, employment and marital status. The association of seroconversion with residing in Nyanza province could be due to higher prevalence (15.3%) of HIV in the province compared to Nairobi (~10%) [8]. As a result mothers from Nyanza may have a higher chance of being involved sexually with a HIV-1 infected partner compared to those from Nairobi thereby increasing their risks of getting infected. There are conflicting data on the role of marital status on HIV-1 incidence during pregnancy [4, 13]. Our study suggests that married women were at increased risk of incident HIV-1 infection during pregnancy and in puerperium. Consistent with findings from another Kenyan study, women in polygamous marriages were more likely to have incident infections during pregnancy[1]. It has been suggested that polygamy reduces sexual exclusivity, increasing the possibility of women to have other partners [14]. Additionally, infection of any of the partners in the network puts everyone else at risk [15]. Women seen in Nyanza were more likely to be in polygamous relationships and to be employed. Although not explored in this study, low rates of male circumcision and high prevalence of HSV-2 in the province could be additional factors contributing to the higher incidence of HIV-1 among mothers seen in Nyanza province by increasing the risk of the male partner’s acquisition and transmission of HIV-1 [8, 16]

[1]Njiri F, Chung M, Kinuthia J, *et al.* HIV-1 incidence after Antenatal Counseling and Testing International AIDS Conference, Toronto, Canada XVI, 13-18 August 2006.

Similar to the population in our study, the majority of women participating in perinatal PMTCT programs are in marital relationsh ips. Sexual intercourse within marital relationships are often not perceived as risky in terms of HIV-1 acquisition, and are associated with low condom use [17]. Only an estimated 1.7% of married women in Kenya reported using condoms in 2003 [9]. Several studies report married women's greatest risk of contracting HIV-1 is through sexual intercourse with their husbands [10, 11, 18]. Partner testing in PMTCT programs is low especially when the woman tests HIV-1 negative [19], with most men assuming that they are also HIV-1 negative. Our study suggests that it is critical for PMTCT programs to highlight potential risks to HIV-seronegative mothers and to promote partner HIV-1 testing and safe sex (ie, monogamy, condom use) during pregnancy and encourage delay in resumption of sexual after delivery until after complete healing.

Re-testing women during late pregnancy or during labor has been suggested as one way to identify women who seroconvert during pregnancy. A major challenge is the number of women involved. In Kenya, there were over 1.5 million births in 2008 [20]. With almost 90% of these mothers uninfected, this translates to over a million repeat tests. Performing these tests would require additional supplies and place an added burden on an already overstretched workforce. However, the benefits may be substantial. A cost-effectiveness analysis by Sansom *et al.* strongly recommended a repeat HIV-1 test during the third trimester of pregnancy in settings where HIV-1 incidence is 1.2 per 1000 person years or higher [21]. They found at that incidence, the costs of a second test were offset by averted medical costs. However, in settings where women delay initiating antenatal care it may not be realistic to retest during late pregnancy and instead retesting could be performed during labor or at MCH clinics.

The study had several limitations. We did not obtain data on timing of the initial HIV-1 test making it difficult to precisely estimate HIV-1 incidence. We also did not inquire regarding partner's HIV-1 status or sexual behavior of the women during pregnancy or regarding timing of resumption of sexual activity after a delivery making it impossible to determine sexual behavior characteristics associated with seroconversion. A critical strength of the study was verification of the HIV status of the mother using the ANC card.

In summary, the high HIV-1 incidence we observed among women who had participated in Kenyan PMTCT program calls for review of services provided to HIV-1 uninfected women. While PMTCT programs may justifiably need to focus greater attention on HIV-1 infected mothers to prevent transmission of HIV-1 to their infants, the need to ensure that HIV-1 uninfected mothers remain uninfected requires similar attention. This study underscores the importance of primary prevention among women testing HIV-1 negative during pregnancy and highlights the need for targeted advocacy for couple counseling and testing in PMTCT programs. Additionally, there is need for further research on behavioral and biological risk factors for incident HIV-1 infection during pregnancy and postpartum period.

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Table 1

Baseline Characteristics of Women in the Program

Characteristic		**N (%), Mean (SD)**	**N=2034***
Age (years)		23.7	(4.9)
< Secondary education		1509	(74.2%)
Employed (n=2032		597	(29.4%)
Married (n=2022)		1756	(86.8%)
Type of marriage **	Polygamous (N=1714)	122	(7.1%)
Monthly rent ***($) (n=1696)		23.0	(14.5)
Own	Television	967	(47.5%)
	Gas cooker	211	(10.4%)
First Pregnancy		794	(39.0%)
Felt at risk of HIV in previous year		598	(33.6%)
Physically assaulted by partner		495	(24.4%)

SD: standard deviation.

* ELISA result of one indeterminate report missing.

** Excludes mothers who were single, widowed, divorced and in come we stay relationships.

*** Excludes mothers especially from rural areas who owned their homes.

Table 2

Comparison of Selected Characteristics Among Mothers who Seroconverted to those who did not

Characteristic		Seroconversion Mean (SD) or N (%) N=53	No Seroconversion Mean (SD) or N (%) N=1981	P Value
Sociodemographic and Obstetric				
Age		23.8 (4.6)	23.7 (4.9)	0.85
< Secondary education	(n=2022)	43 (81.1%)	1466 (74.0%)	0.24
Married	(n=2022)	51 (96.2%)	1705 (86.6%)	0.04
Type of marriage *	(n=1714)			
	Polygamous	10 (19.6%)	112 (6.7%)	<0.001
	Monogamous	41 (80.4%)	1551 (93.3%)	
Employed	(n=2025)	24 (45.3%)	573 (29.0%)	0.01
Parity	≥ 2	39 (73.6%)	1201 (60.6%)	0.06
Felt at risk of infection in past 1 year **	(n=1779)	15 (33.3%)	583 (33.6%)	0.97
Assaulted (n=2030)		18 (34.0%)	477 (24.1%)	0.10
Economic				
Monthly rent *** $ (n=1696)		23.0 (14.3)	21.7 (21.0)	0.70
Own	TV	23 (43.4%)	944 (47.7%)	0.54
	Gas cooker	4 (7.6%)	207 (10.5%)	0.65
Region				
Nyanza (n=603)		32 (60.4%)	571 (28.8%)	<0.001
Nairobi (n=1431)		21 (39.6%)	1410 (71.2%)	

N=2034 when not indicated.

* Excludes mothers who were single, widowed and divorced.

** Excludes mothers who responded “don’t know”.

*** Excludes mothers especially from rural areas who owned their homes.