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Illness during Pregnancy and Bacterial Vaginosis are Associated with *In Utero* HIV-1 Transmission

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Abstract

HIV-1 transmission *in utero* accounts for 20–30% of vertical transmission events in breastfeeding populations. In a prospective study of 463 HIV-1-infected mothers and infants, illness during pregnancy was associated with 2.6-fold increased risk of *in utero* HIV-1 transmission (95% CI 1.2, 5.8) and bacterial vaginosis with a 3-fold increase (95% CI 1.0–7.0) after adjusting for maternal HIV-1 viral load. Interventions targeting these novel risk factors could lead to more effective prevention of transmission during pregnancy.

In developing countries, most effective prevention of mother-to-child HIV-1 transmission interventions target intrapartum and breastmilk transmission. These include single dose nevirapine at delivery, short-course antiretrovirals, highly active antiretroviral therapy during breastfeeding, breastmilk avoidance, early weaning from breastmilk, and infant nevirapine prophylaxis[1–3]. As these interventions become more widely available, *in utero* transmission is likely to contribute to an increased proportion of mother-to-child transmission events. Determining factors associated with HIV-1 transmission *in utero* is an important step towards adapting interventions designed to further prevent infant HIV-1 infection.

A number of maternal, infant and viral factors have been studied in association with *in utero* transmission. Those with the strongest evidence for an association include maternal HIV-1 viral load, antenatal antiretroviral therapy, infant gender, low birthweight, and ascending infections, such as chorioamnionitis[4]. The goal of the current study was to define additional correlates of *in utero* transmission within a prospective cohort of HIV-1-infected Kenyan women and infants.

HIV-1-infected pregnant women were followed biweekly during pregnancy and at 34–36 weeks of pregnancy began oral zidovudine which they continued through delivery. Sexually

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transmitted infections (syphilis, gonorrhrea, chlamydia, trichomoniasis) and candida were treated following Kenya national guidelines. After study completion, slides were evaluated for bacterial vaginosis (BV) using Nugent's criteria and blood collected at 32 weeks gestation was assayed for HIV-1 RNA viral load. Neonatal blood collected at birth was tested for HIV-1 DNA on filter paper specimens and HIV-1 RNA in plasma using PCR[5]. *In utero* transmission was defined as a positive DNA or RNA assay at less than 48 hours after birth. Mother-infant pairs were subsequently followed monthly, with infant HIV-1 PCR assays performed every 3 months until 12 months postpartum.

Between 1999 and 2002, 36,000 pregnant women were screened for HIV-1, of whom 31,731 (88%) accepted testing and 4,512 (14%) were HIV-1-seropositive. One-third of these women accepted referral to the study clinic and 463 (30%) among these consented to study participation and were followed through delivery. Of the 463, 88 (19%) infants were infected with HIV-1, 77 (17%) infants died, and 48 (10%) were lost to follow-up. Twenty-nine (33%) infants among the 88 infected infants were HIV-1 PCR positive within 48 hours of birth and considered infected *in utero*. Thirty-seven (42%) infants were HIV-1-uninfected at birth and infected at month 1, thus infected intrapartum or via early breastmilk exposure, and 10 (11%) infants were infected via breastmilk after 1 month of age. Twelve (14%) infants did not have specimens at birth and precise timing of infection could not be determined; these infants may have been infected *in utero*, intrapartum or early postpartum and were excluded from analyses.

Twenty-nine infants infected *in utero* were compared with 422 infants who were either infected at other time points or remained HIV-1-uninfected during the 12-month study period. Plasma and cervical HIV-1 viral load were found to be approximately one-half $\log_{10}$ higher for women who transmitted *in utero* than those who did not (plasma: 5.0 vs 4.6 log copies/ml; $p<0.001$ and cervical: 3.0 vs 2.4; $p=0.004$). While absolute CD4 count was not different for women in the 2 groups, CD4 percent was lower for transmitting women (19.8% vs 23.6%; $p=0.01$). Women who transmitted were also significantly less likely to have received at least 3 weeks of zidovudine ($p=0.02$) and 57% of transmitting women had not completed a 3-week course of antiretrovirals prior to delivery. There was a trend for more female infants to acquire HIV-1 *in utero* (66% vs 47%; $p=0.06$) and infants infected *in utero* had significantly lower birthweight (2.9 kg vs 3.1 kg; $p<0.001$) and gestational age using modified Dubowitz criteria (38.5 vs 39.3 weeks gestation; $p=0.02$).

Antenatal diagnosis of a sexually transmitted infection (gonorrhea, chlamydia, trichomoniasis) was not associated with increased risk of transmission when examined individually or combined into a single variable. However, BV was significantly more prevalent among women who transmitted *in utero*: 59% of transmitters versus 35% of women who did not transmit had BV in the cohort ($p=0.02$). In addition, transmitting women were more likely to have an AIDS-defining illness during the past 1 year and a greater proportion of women who transmitted *in utero* reported an illness prior to 32 weeks gestation which was characterized by diarrhea, fever, or cough (41% vs 21%; $p=0.01$ and 52% vs 28%; $p=0.01$, respectively).

These factors were assessed in multivariate analyses adjusting for plasma HIV-1 viral load, CD4 percent at 32 weeks, and duration of zidovudine use (Table 1). Using this model, plasma and cervical HIV-1 RNA levels remained significant predictors of *in utero* transmission, conferring a 1.9 and 1.5-fold increase in risk per $\log_{10}$ change in HIV-1 RNA in plasma and cervical secretions, respectively ($p<0.05$ for both). Receipt of zidovudine for at least 3 weeks before delivery also remained protective after adjusting for viral load and disease stage (Odds ratio [OR] 0.4; 95% confidence interval [CI] 0.2, 1.0; $p=0.04$). Other independent predictors of *in utero* transmission in this model were illness during pregnancy and BV. Illness during pregnancy was associated with a 2.6-fold increased risk and BV with a 3-fold increase in the

likelihood of transmission *in utero* (OR 2.6, 95% CI 1.2, 5.8; p=0.02 and OR 3.0, 95% CI 1.0–7.0; p=0.01, respectively)(Table 1).

To our knowledge, neither illness in early pregnancy nor BV has been reported as a risk factor for transmission *in utero*. Illness during pregnancy may be contributing to increased transmission by transiently elevating HIV-1 viral load or by causing immune activation and increased CD4 target cells. Women describing fever and other complaints during pregnancy may also be manifesting symptoms of acute HIV-1, characterized by a sharp and transient increase in viral load that could elevate transmission risk substantially. The association between BV and *in utero* transmission may be due to BV organisms causing upper genital tract infections such as chorioamnionits, endometritis, and placental compromise. Chronic chorioamnionitis has been associated with increased *in utero* transmission and could explain negative results from one large clinical trial designed to treat BV and prevent MTCT[6,7]. Since both illness in early pregnancy and BV are amenable to interventions, these data suggest additional means to target the *in utero* period, a period that is likely to increase in its relative significance.

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