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High Maternal HIV-1 Viral Load During Pregnancy Is Associated With Reduced Placental Transfer of Measles IgG Antibody

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Abstract

Background—Studies among HIV-1–infected women have demonstrated reduced placental transfer of IgG antibodies against measles and other pathogens. As a result, infants born to women with HIV-1 infection may not acquire adequate passive immunity *in utero* and this could contribute to high infant morbidity and mortality in this vulnerable population.

Methods—To determine factors associated with decreased placental transfer of measles IgG, 55 HIV-1–infected pregnant women who were enrolled in a Nairobi perinatal HIV-1 transmission study were followed. Maternal CD4 count, HIV-1 viral load, and HIV-1–specific gp41 antibody concentrations were measured antenatally and at delivery. Measles IgG concentrations were assayed in maternal blood and infant cord blood obtained during delivery to calculate placental antibody transfer.

Results—Among 40 women (73%) with positive measles titers, 30 (75%) were found to have abnormally low levels of maternofetal IgG transfer (<95%). High maternal HIV-1 viral load at 32 weeks' gestation and at delivery was associated with reductions in placental transfer ($P < 0.0001$ and $P = 0.0056$, respectively) and infant measles IgG concentrations in cord blood ($P < 0.0001$ and $P = 0.0073$, respectively). High maternal HIV-1–specific gp41 antibody titer was also highly correlated with both decreased placental transfer ($P = 0.0080$) and decreased infant IgG ($P < 0.0001$).

Conclusions—This is the first study to evaluate the relationship between maternal HIV-1 viremia, maternal HIV-1 antibody concentrations, and passive immunity among HIV-1–exposed infants. These data support the hypothesis that high HIV-1 viral load during the last trimester may impair maternofetal transfer of IgG and increases risk of measles and other serious infections among HIV-1–exposed infants.

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Written informed consent was obtained from all study participants and the study received ethical approval from the institutional review boards of the University of Washington and the University of Nairobi.

The authors have no commercial or noncommercial associations that might pose a conflict of interest.

Keywords

placental antibody transfer; maternal HIV-1 viral load; measles IgG; HIV-1–specific gp41 antibody; mother-to-child HIV-1 transmission

During the past decade the HIV epidemic has resulted in increased infant mortality in sub-Saharan Africa and has reversed gains made in part through childhood immunization programs. Infants born to HIV-1–infected mothers have a ~2- to 3-fold increased risk of death, and HIV-1–exposed, uninfected infants tend to have higher rates of hospitalization, severe pneumonia, and measles.[1–4] A Malawian study reported a ~4-fold increased risk of measles among HIV-1–infected infants and a ~2-fold increased risk among HIV-1–exposed uninfected infants compared with infants born to HIV-1–uninfected women.[1] Measles also occurs at a younger age among HIV-1–infected infants, with up to one-third of cases reported before 9 months of age, and infection is more likely to result in death with maternal HIV-1 infection regardless of infant HIV-1 status.[5–7]

Maternal immunosuppression and HIV-1 viremia may influence infectious morbidity among infants by reducing passively acquired humoral immunity against important pathogens, including measles. It has previously been reported that placental transfer of IgG against measles virus is lower among HIV-1–infected than HIV-1–uninfected women[8] and that concentrations of measles IgG prior to immunization are reduced among HIV-1–exposed infants compared with infants born to HIV-1–seronegative mothers.[9,10] However, determinants of reduced placental transfer among HIV-1–infected women are not well characterized.

In this study, we hypothesized that women with advanced HIV-1 infection would have the greatest reductions in transplacental transfer of measles IgG. In a cohort of HIV-1–infected mothers and their infants, we evaluated the relationship between placental IgG transfer, infant measles antibody concentrations, and several modifiable and nonmodifiable factors, including maternal $CD4^+$ T-cell count, HIV-1 viral load, and IgG directed against HIV-1 gp41.

MATERIALS AND METHODS

HIV-1–infected pregnant women were enrolled in a prospective study in Nairobi from 1999–2004 and mother–infant pairs with maternal CD4 counts <200 or >500 cells/μL were selected on baseline immune status and specimen availability.[11] At 32 weeks' gestation, HIV-1 RNA levels and CD4 T-cell counts were obtained and at 34 weeks' gestation, short-course oral zidovudine was initiated according to the Thai Centers for Disease Control protocol.[12] Women provided blood at delivery for HIV-1 RNA, measles IgG, and HIV-1–specific gp41 IgG. Infant cord blood was obtained at delivery for measles IgG and HIV-1–specific IgG, and a peripheral blood sample was taken from the neonate at birth and 1 month of age to determine HIV-1 infection status.

Measles IgG antibody concentrations were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Enzygnost, Germany) and HIV-1–specific antibody titers were performed with ELISA and recombinant gp41 (Chemicon International, Temecula, CA), as described elsewhere.[13] Maternal CD4 counts were measured with flow cytometry (Becton Dickinson, Franklin Lakes, NJ) and HIV-1 RNA viral load quantified in maternal plasma using the Gen-Probe (San Francisco, CA) viral load assay, a transcription-mediated amplification method sensitive for detection of HIV-1 subtypes A, C, and D.[14] Infant plasma specimens were tested with the same Gen-Probe assay, and infant whole

blood filter paper specimens were assayed for HIV-1 DNA using polymerase chain reaction to amplify HIV-1 *gag* sequences as previously described.[15]

HIV-1 viral load data were log transformed and placental transfer was defined as the ratio of infant-to-maternal measles IgG concentrations in blood at delivery for mother–infant pairs with positive maternal antibody titers. Nonparametric statistical tests were used to compare characteristics between women with CD4 counts <200 cells/μL and those with CD4 counts >500 cells/μL. Univariate and multivariate linear regressions were performed to evaluate associations in the cohort, with CD4 T-cell count (<200 vs. >500) included in the model as an indicator variable.

RESULTS

Maternal and infant characteristics for 55 mother–infant pairs are presented in Table 1. Neonates weighed 3 kg on average and were full term; one infant (2%) born to a woman with CD4 <200 cells/μL was HIV-1 infected at birth, with HIV-1 RNA detected in plasma at <48 hours' postpartum. Overall, measles IgG antibody was detected in 40 maternal (73%) and 38 infant (69%) cord blood specimens. Among the 40 mother–infant pairs with positive maternal titers, 30 women (75%) had infant-to-maternal antibody ratios that were below normal (<95%) and median placental transfer for the entire cohort was ~50% of that expected for HIV-1–uninfected women.[16] When comparing women with CD4 counts <200 and those with CD4 counts >500, we found significant differences in maternal HIV-1 viral load at the antenatal and delivery timepoints ($P < 0.0001$ for both) (Table 1). There were no differences between groups when comparing median maternal or infant measles IgG concentrations, placental transfer, or HIV-1 gp41 IgG midpoint titers (Table 1).

In Table 2, we present associations between maternal and infant measles IgG concentrations, placental antibody transfer, and clinical and laboratory parameters of interest. Maternal measles antibody concentrations did not correlate with HIV-1 viral load at 32 weeks' gestation or at delivery ($P = 0.98$ and $P = 0.83$, respectively) (Table 2). There was also no association between maternal measles IgG and HIV-1 gp41 antibody titers ($P = 0.13$) (Table 2). However, we did observe strong inverse associations between maternal viral load at 32 weeks' gestation and placental transfer and between maternal viral load at 32 weeks' gestation and infant cord blood measles IgG concentrations ($P < 0.0001$ for both) (Table 2). For every 1-log increase in maternal HIV-1 RNA load, the ratio between infant and maternal IgG was reduced by 44% and infant measles IgG levels were reduced by 8.5 mg/mL. A similar association was found between maternal HIV-1 viral load measured at the time of delivery and both placental transfer ($P = 0.0056$) and measles antibody concentrations in infant cord blood ($P = 0.0073$) (Table 2). Women with higher HIV-1–specific gp41 antibody titer at delivery also had reduced maternofetal antibody transfer and lower infant measles IgG concentrations ($P = 0.0080$ and $P < 0.0001$, respectively). Delivery HIV-1–specific gp41 titers were positively correlated with maternal viral load at both 32 weeks of pregnancy and at delivery ($P = 0.0010$ and $P = 0.0002$, respectively).

When both maternal HIV-1 RNA levels and HIV-1–specific antibody titer were included in a multivariate model, HIV-1 viral load was found to be a strong independent predictor of placental transfer and infant measles antibody levels ($P = 0.0002$ and $P = 0.0008$, respectively) (Table 2; see footnote). In multivariate analysis, maternal HIV-1 antibody also remained correlated with infant measles IgG ($P = 0.0026$) and there was a trend for an association between maternal HIV-1 gp41 antibody titers and placental antibody transfer ($P = 0.090$) (Table 2; see footnote). Although in univariate analysis there was a trend for women with CD4 <200 to have reduced placental transfer compared with women with CD4 >500 ($P = 0.06$), no association was found between CD4 group, placental transfer, and infant

IgG in the multivariate model. We were not able to evaluate CD4 count as a continuous variable (a more powerful analysis) because the cohort did not include women with CD4 between 200–500.

DISCUSSION

Maternal antibodies transferred via the placenta play a major role in protecting newborns against measles and other infections. In this study, highmaternal HIV-1 viral load and high HIV-1–specific antibody concentrations were associated with significant reductions in maternofetal transfer of measles IgG. It is not known whether HIV-1 impairs active transport of maternal IgG across placental syncytiotrophoblasts and into fetal circulation. Infections such as malaria can cause pathologic damage to placental tissue and may decrease IgG transport by destroying IgG-specific Fc receptors (hFcRn) that mediate transplacental transfer.[17] There is less evidence that HIV-1 infection results in histologic changes in the placenta, and other explanations have been considered, including competition by HIV-1–specific antibodies for a finite number of hFcRn receptors, such as has been observed with herpes simplex virus, tetanus toxoid, and *Streptococcus pneumoniae*.[8] Correlation between high maternal HIV-1–specific gp41 antibody and reduced placental IgG transfer in our cohort would be consistent with this mechanism; high concentrations of HIV-1–specific antibodies in maternal blood during the last trimester could block hFcRn receptors, inhibiting active transport of measles antibodies from mother to infant.

Our finding that HIV-1 viral load and HIV-1–specific antibody levels were inversely associated with placental measles antibody transfer suggests that advanced maternal disease may place HIV-1–exposed infants at increased risk for measles infection and poor outcome, irrespective of infant HIV-1 status. It is possible that controlling maternal HIV-1 viremia with effective antiretroviral therapy prior to the last 4 weeks of gestation, the period when the majority of IgG is transferred from mother to child, could influence placental transfer among infants born to HIV-1–infected mothers. Other interventions may also improve HIV-1–exposed infant antibody levels early in life and merit further investigation. These include passive immunization for select, high-risk infants, as well as active immunization at 6 months for all asymptomatic HIV-1–exposed infants.

In conclusion, immunization guidelines from the World Health Organization address reduced maternofetal IgG transfer in the setting of maternal HIV-1 infection and recommend measles immunization at age 6 months, in addition to 9 months, for HIV-1–infected infants.[18] However, this policy has not been widely implemented and does not reduce risk among HIV-1–exposed infants whose status is negative or unknown. We hope data from the current study will raise awareness and promote new approaches to preventing morbidity and mortality in HIV-1–exposed infants.

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TABLE 1

Cohort Characteristics

Maternal	Maternal CD4 <200 (n = 25) N	Maternal CD4 <200 (n = 25) Median (IQR) or n (%) of Women	Maternal CD4 >500 (n = 30) N	Maternal CD4 >500 (n = 30) Median (IQR) or n (%) of Women	*P* Value*
Age (y)	25	26 (22–29)	30	23 (21–26)	0.26
$CD4^+$ T-cell count (cells/μL)					
32 weeks of pregnancy	25	151 (108–173)	30	624 (577–869)	<0.0001
HIV-1 RNA viral load (log_{10} copies/mL)					
32 weeks of pregnancy	24	5.3 (5.1–5.8)	30	4.4 (3.9–5.1)	<0.0001
Delivery	25	5.1 (4.7–5.7)	28	4.0 (3.2–4.6)	<0.0001
Antimeasles IgG antibody status					
Positive titer at delivery†	25	21 (84%)	30	19 (63%)	0.0866
Concentration (mg/mL)	21	16.6 (11–28)	19	11.9 (8.9–22)	0.0930
HIV-1 gp41 IgG (midpoint titers)	25	1900 (1050–3000)	30	800 (308–1950)	0.14
Infant					
Gender (female)	25	15 (60%)	30	15 (50%)	0.36
Birth weight (kg)	25	3.0 (2.7–3.6)	30	3.0 (2.7–3.2)	0.53
Infant gestational age (wk)	25	40 (39–40)	30	39 (38–40)	0.17
Antimeasles IgG antibody status					
Positive infant cord blood titer‡	25	17 (68%)	30	21 (70%)	0.87
Cord blood concentration (mg/mL)	17	8.9 (6.1–16.4)	21	7.3 (5.3–14.3)	0.45
HIV-1 gp41 IgG (midpoint titers)	25	800 (505–1150)	30	615 (312–1275)	0.47
Placental transfer of antimeasles IgG§	21	0.47 (0.18–0.80)	19	0.48 (0.37–1.0)	0.16

*Mann–Whitney *U* test was performed for continuous variables and Pearson χ^2 test for dichotomous variables.

†Borderline results were considered negative and placental transfer was not determined for these mothers. Borderline results occurred in 4 women (8%) with CD4 <200 and in 7 women (23%) with CD4 >500.

‡Borderline results occurred in 1 (4%) and 4 (13%) infants born to mothers with CD4 <200 and CD4 >500, respectively.

§Defined as the ratio of infant-to-maternal antimeasles IgG concentrations at delivery.

IQR, interquartile range.

TABLE 2

Correlates of Maternal Measles IgG Concentrations, Infant Measles IgG, and Placental Transfer of Measles IgG for 40 Mother–Infant Pairs With Positive Maternal Antibody Titers [*]

	Slope [95% CI] (*P* Value)								
	Maternal Antimeasles IgG (mg/mL)			Infant Antimeasles IgG (mg/mL)			Placental Transfer of Antimeasles IgG[†]		
Maternal age (y)	−0.23	[−1.1, 0.59]	(0.57)	−0.80	[−1.7, 0.07]	(0.077)	−0.38	[−0.80, 0.04]	(0.66)
Birth weight (kg)	−0.52	[−13.7, 3.3]	(0.22)	−3.4	[−13.2, 6.4]	(0.49)	0.10	[−0.35, 0.54]	(0.67)
Infant gestational age (wk)	−0.55	[−2.7, 1.6]	(0.61)	0.24	[−2.2, 2.6]	(0.84)	0.07	[−0.04, 0.18]	(0.23)
HIV-1 RNA at 32 weeks of pregnancy (log_{10} copies/mL)	−0.07	[−4.4, 4.2]	(0.98)	−8.5	[−12, −4.8]	(<0.0001)[‡]	−0.44	[−0.62, −0.25]	(<0.0001)[‡]
HIV-1 RNA at delivery (log_{10} copies/mL)	−0.42	[−4.4, 3.5]	(0.83)	−5.6	[−9.3, −1.8]	(0.0056)[§]	−0.26	[−0.44, −0.07]	(0.0073)[§]
Maternal HIV-1 gp41 IgG (log_{10} midpoint titers)	−6.0	[−14.0, 1.9]	(0.13)	−14.4	[−21.1, −7.6]	(<0.0001)	−0.53	[−0.91, −0.15]	(0.0080)[¶]
Infant HIV-1 gp41 IgG (log_{10} midpoint titers)	−6.5	[−14.5, 1.5]	(0.11)	−10.3	[−18.0, −2.6]	(0.0078)[#]	−0.26	[−0.67, 0.16]	(0.22)

[*] CD4 count was included in univariate and multivariate regression models as an indicator variable (CD4 <200 = 0; CD4 >500 = 1).

[†] Defined as the ratio of infant-to-maternal antimeasles IgG concentrations at delivery.

[‡] In multivariate analysis adjusting for maternal HIV-1 gp41 IgG titer, HIV-1 RNA at 32 weeks' gestation was inversely associated with infant antimeasles IgG concentrations and placental transfer (P = 0.0008 and P = 0.0002, respectively).

[§] In multivariate analysis adjusting for maternal HIV-1 gp41 IgG titer, HIV-1 RNA at delivery was inversely associated with infant anti measles IgG concentrations and placental transfer (P = 0.029 and P = 0.026, respectively).

[¶] In multivariate analysis adjusting for HIV-1 RNA at 32 weeks' gestation, maternal HIV-1 gp41 IgG titer was inversely associated with infant antimeasles IgG concentrations (P = 0.0026) and there was a trend for an inverse association with placental transfer (P = 0.090).

[#] In multivariate analysis adjusting for HIV-1 RNA at 32 weeks' gestation, infant HIV-1 gp41 IgG titer was inversely associated with infant antimeasles IgG concentrations (P = 0.042).

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