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Low neutrophilss in African mothers and newborns and HIV transmission risk

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TO THE EDITOR: Ethnic neutropenia is highly prevalent in individuals of African descent.[1,2] It was also observed in the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study of 2,369 HIV-infected mothers and their newborns in Malawi.[1, 3] Low neutrophil counts in Africans are thought to represent a variation with undefined and largely unexplored consequences. A recent study suggested that low pre-infection neutrophil counts were associated with increased risk of sexually transmitted HIV infection in South African black women.[4] Notably, in genome-wide association analyses, an African-specific polymorphism in the promoter of Duffy antigen receptor for chemokines (the Duffy-null trait that imparts resistance to malaria) was significantly predictive of (and thought to be causal for[5]) low neutrophil counts.[4] We examined the association of neutrophil counts in mothers and newborns with risk of infant perinatal HIV infection in the BAN cohort. Timing of infant perinatal HIV infection was determined by a confirmed positive HIV PCR test result in the first 48 hours of life (*in utero*) or by 2 weeks of age (intrapartum). The BAN protocol was approved by the Malawi National Health Sciences Research Committee and the institutional review boards of the University of North Carolina and the Centers for Disease Control and Prevention.

Maternal and infant neutrophil counts of perinatally HIV-infected infants (N=119) were lower than those of perinatally uninfected infants (N=2250) (Table 1). Almost all (N=114) infants acquired their infection *in utero*, since mothers in BAN started antiretroviral prophylaxis at onset of labor. Infant WBC and neutrophil counts were collected on the day of or the day after birth in 90.1% of cases, with no difference in timing between HIV-infected and uninfected infants. Higher neutrophil counts in the mother (risk ratio [RR], 0.93; p=0.02) and in the newborn (RR, 0.89; p<0.001) were associated with lower risk of perinatal HIV infection (see Web Supplement Figure). The association of infant neutrophil counts with perinatal HIV infection persisted after adjustment (adjusted RR, 0.88; p=0.03) for maternal CD4+ levels, cotrimoxazole use during pregnancy, infant gender, birth weight, and maternal $\log_{10}$ viral load. Each 1,000-cell/μl increment in the infant's neutrophil count

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was associated with 11% reduction in the risk of perinatal HIV infection. Maternal neutrophil count was associated with perinatal HIV infection after adjustment for cotrimoxazole use, CD4+ count, infant gender and birth weight (p=0.045).

Association of low neutrophil counts in the mother and the newborn with increased susceptibility to perinatal HIV infection is a novel observation. Neutropenia in the newborn is not typically a feature of in utero HIV infection, and a concomitant decrease in the lymphocyte/monocyte fraction was not seen (Table 1). Pregnant women with low neutrophil counts may need more targeted and earlier approaches to prevent intrauterine transmission of HIV to the infant. New paths to prevention may result from genetic studies to investigate the relationship of Duffy-null trait or other genetic polymorphisms that underlie low ethnic neutrophil counts in individuals of African ancestry and increased susceptibility to perinatal HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Appendix

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Table 1

Neutrophil Counts and Select Other Characteristics of Perinatally HIV-Infected vs. Uninfected Infants in the Breastfeeding, Antiretrovirals and Nutrition (BAN) Study[§]

	Perinatally HIV-Infected (N=119)	Not Infected Perinatally (N=2250)	P-Value[‡]
Maternal characteristics			
CD4+ count (cells/μL)[†]	396 (304–518)	439 (330–582)	0.02
White Blood Cell (WBC) count (10^3/μL)[†]	9.4 (7.3 –11.5)	10.1 (8.1 –12.8)	0.02
Neutrophil count (10^3/μL)[†]	6.1 (4.5 –8.0)	7.0 (5.2 –9.4)	0.02
(WBC less Neutrophil) count (mostly lymphocytes/monocytes) (10^3/μL)[†]	2.9 (2.4 –3.6)	3.1 (2.5 –3.8)	0.39
Log_{10} viral load[*†]	4.6 (4.0–5.0)	2.9 (2.3–3.7)	<0.001
Infant characteristics			
Gender (male) (%)	45.3	50.4	0.28
Birth weight (kg)[†]	2.9 (2.6–3.2)	3.0 (2.7–3.3)	0.002
WBC count (10^3/μL)[†]	13.6 (11.0–17.4)	15.0 (12.1–17.8)	0.36
Neutrophil count (10^3/μL)[†]	6.4 (4.8–8.7)	8.0 (6.1–10.0)	<0.001
(WBC less Neutrophil) count (mostly lymphocytes/monocytes) (10^3/μL)[†]	6.9 (5.6 –8.7)	6.7 (5.5 –8.2)	0.005

[§]Data were available for all n=2369 mother-infant pairs with the following exceptions: one mother had an infeasible pair of WBC and neutrophil counts which were set to missing; birth weight was missing for two infants; WBC counts were missing for 60 infants (4 HIV-infected); neutrophil counts were missing for 58 infants (5 HIV-infected); and the WBC less neutrophil variable was missing for 61 infants (5 infected). Maternal viral loads were obtained using case-control sampling, with measurements from all infected infants with available specimens (97 of the 119 total cases) and a sample of controls with available specimens (122 of the 2250 total controls).

[‡]P-values from log-binomial regression models, except for log_{10} viral load which is based on a logistic regression model due to case-control sampling of maternal viral load

[†]Median (interquartile range)

[*]Viral load below the limit of detection of 400 copies/mL was set to 200