HIV, Malaria, and Infant Anemia as Risk Factors for Postneonatal Infant Mortality among HIV-Seropositive Women in Kisumu, Kenya

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Background. HIV and malaria in sub-Saharan Africa are associated with poor pregnancy outcome and infant survival. We studied the association of placental malaria, infant malaria and anemia, and infant HIV status with postneonatal infant mortality (PNIM) among infants of HIV-seropositive women.

Methods. During 1996–2001, infants born to 570 HIV-seropositive mothers in Kisumu, Kenya were monitored monthly for malaria (parasitemia or clinical malaria) and anemia (hemoglobin level <8 g/dL) and vital status.

Results. Thirty-nine deaths occurred among 112 HIV-positive infants (420/1000 live births [LBs] [95% confidence interval {CI}, 318–522 LBs]), and 36 occurred among 458 HIV-negative infants (99/1000 LBs [95% CI, 68–130 LBs]) (P < .001). In multivariate Cox regression analysis among HIV-negative infants, PNIM was associated with infant anemia (adjusted hazard ratio [AHR], 5.03 [95% CI, 1.97–12.81]) but not with placental malaria (AHR, 0.34 [95% CI, 0.10–1.10]) or infant malaria (AHR, 0.31 [95% CI, 0.07–1.33]) or anemia (AHR, 1.07 [95% CI, 0.32–3.61]) was significantly associated with PNIM.

Conclusion. In this study population, placental malaria and infant parasitemia were not risk factors for PNIM among infants of HIV-seropositive women. The prevention of infant anemia may decrease PNIM among HIV-negative infants of HIV-seropositive women.

In sub-Saharan Africa, most HIV infections are heterosexually transmitted, and women are more likely to become infected than men [1]. Most HIV infections in children are acquired through mother-to-child transmission (MTCT) [2, 3]. Rates of perinatal transmission range from 13% to 40% among women not treated for their HIV infection [4]. Early child mortality among HIV-positive and HIV-negative children born to HIV-infected mothers have been reported to be ∼4 and 1.3–2 times higher, respectively, than that among children born to HIV-negative women [5] (A.M.v.E., personal observation).

There is geographic overlap between HIV and malaria in sub-Saharan Africa. In areas where malaria is endemic, pregnant women have a higher risk of malaria than nonpregnant women, and this risk is further increased among HIV-infected women [6]. Although these malaria infections are usually asymptomatic, parasites sequester in the placenta, and placental malaria is associated with low birth weight (LBW), intrauterine growth retardation, prematurity, and maternal and infant anemia [7–9].
Malaria is a major contributor to infant mortality in sub-Saharan Africa, directly through infant illness and indirectly through placental malaria and its adverse effects. The effect of the combination of maternal HIV infection and malaria during pregnancy on infant survival is not clear [6]. An early study in Malawi suggested that placental malaria was a risk factor for postneonatal infant mortality (PNIM) in children born to HIV-infected women [10]. Malaria, like other coexisting infections, can cause temporary increases in HIV load [11]. It was hypothesized that PNIM could have been increased either because placental malaria increased MTCT of HIV-1 or because placental malaria enhanced the progression of HIV disease in infected infants directly or indirectly (if placental malaria would be a marker for another disease leading to infant death, such as infant malaria). The HIV vertical transmission study in Kisumu was designed to examine these questions. We previously reported that placental malaria was not associated with increased MTCT of HIV but, by contrast, was found to be protective [12]. In the present article, we study the effect of placental malaria, infant malaria, and anemia on PNIM among the infants.

SUBJECTS AND METHODS

Study site and screening procedures. The study was conducted at the Nyanza Provincial General Hospital in Kisumu, western Kenya; enrollment lasted from June 1996 to August 2000, and infant follow-up ended in August 2001. Screening procedures have been described elsewhere [12]. Briefly, healthy pregnant women with an uncomplicated singleton pregnancy of ≥32 weeks’ gestation were invited to participate. After informed consent was obtained and HIV counseling performed, a questionnaire on medical and obstetric history was completed, and blood was obtained for HIV testing. All screened women received routine antenatal care [13] and were encouraged to deliver at the hospital; ~50% did, which reflects the low rate of deliveries at health care facilities in this area (37.4%) [14]. For women who gave birth in the hospital, placental smears and blood for maternal hemoglobin and viral load determinations were collected. Within 24 h of birth, infants were weighed, and their gestational age was assessed [15].

Enrollment in the follow-up study. All HIV-seropositive mothers and their normally delivered, live-born infants were eligible for enrollment in the follow-up study. One month postpartum, maternal blood was collected for the determination of CD4+ cell counts. Infants were scheduled to be seen every 4 weeks until the age of 1 year or death. During routine visits, we obtained information on the health of the infant during the preceding month. Capillary blood was collected by finger stick for a blood smear, hemoglobin determination, and polymerase chain reaction (PCR) testing for HIV. CD4+ cell counts were not determined in infants. Infants with malaria parasitemia were treated, regardless of clinical symptoms, with an appropriate antimalarial (sulfadoxine-pyrimethamine [SP] or amodiaquine). Clinical staff treated infants with anemia or complaints in accordance with their findings [9]. If a routine visit was missed, we visited the participant’s home to determine whether the caretaker remained interested in participating and to assess the vital status of the infant. For infant deaths, we obtained additional information using verbal autopsy.

Laboratory procedures. Details on standard procedures for blood smears, hemoglobin determination, and maternal HIV testing have been reported elsewhere [12]. Maternal CD4+ cell counts were assessed using commercial, dual-label monoclonal antibodies (Becton-Dickinson Immunocytometry) and standard fluorescence-activated cell sorting analysis after whole-blood lysis [16]. The maternal HIV-1 load was determined in the delivery sample using the Roche Amplicor HIV-1 monitor test (version 1.0; Roche Diagnostics), which has a quantification limit of 400 viral copies/mL. HIV testing of the infants was done by PCR of proviral DNA extracted from peripheral blood mononuclear cells [17].

Definitions. PNIM was a death occurring between 29 and 364 days of delivery. HIV-positive infants were infants of HIV-seropositive mothers who had ≥2 consecutive positive PCR tests with the first positive PCR test at age ≤4 months; HIV-negative infants were infants of HIV-seropositive mothers who had ≥2 consecutive negative PCR tests and for whom the PCR test at the last visit was negative. Infants for whom we had

Figure 1. Kaplan-Meier survival curve of postneonatal infant mortality by infant HIV status and placental malaria, Kisumu, Kenya, 1996–2001. Log rank tests: A vs. B, \( P = .7 \); A vs. C, \( P = .2 \); A vs. D, \( P < .001 \); B vs. C, \( P = .4 \); B vs. D, \( P < .001 \); C vs. D, \( P = .07 \). Neg, negative; pos, positive.
was available for 514 women (90.2%); viral load was available for 505 women.

Moderate to severe anemia among infants was defined as a hemoglobin level <8 g/dL. Maternal anemia (Hb level <11 g/dL) at delivery was explored in a separate table using the geometric mean HIV viral load results were then log_{10} transformed. Crude mortality rates were calculated using survival tables. Kaplan-Meier curves were created, and the log rank test was used to compare survival times. Cox regression analysis was used to calculate hazard ratios (HRs) to assess the effect of placental malaria and infant HIV infection on PNIM, using a model that allowed both time-fixed and time-varying variables. Variables examined were those previously associated with infant death and included low maternal level of education, low/medium socioeconomic status (SES), LBW, and male sex. Because of the potential confounding effect of parity (primiparae vs. multiparae) on other exposures in the model (e.g., placental malaria, LBW, and infant malaria), this variable was kept in all models independent of significance [7, 18]. Placental malaria was retained in all models because it was one of the main exposures of interest. Time-varying variables included infant malaria parasitemia and hemoglobin levels <8 g/dL. Maternal viral load was not available for all participants; because the association between maternal viral load and PNIM was not significant in multivariate analyses (P = .2), this variable was removed from the model. Models were stratified by infant HIV status because of significant interactions between infant HIV status and other variables of interest; variables that were significant in the main model were maintained in the stratified models to allow comparison. The interaction between maternal viral load and placental malaria was explored in a separate table using the geometric mean HIV load.

All tests were 2-sided, and P < .05 was considered to be statistically significant. Analysis was done using SPSS (SPSS for Windows 9.0; SPSS) and SAS (version 8; SAS Institute) software.

**Ethical review.** The study protocol was approved by the ethical review boards of the Kenya Medical Research Institute, Nairobi; the Centers for Disease Control and Prevention, Atlanta, GA; and the Academic Medical Center of the University of Amsterdam, The Netherlands. During the study years, programs for the prevention of MTCT had not yet been introduced in the hospital; this started late 2000, after enrollment of infants had finished [12].

**RESULTS**

**Description of the study population.** Infants from 835 HIV-seropositive mothers were enrolled. Of these, 265 infant/mother pairs were excluded: 165 infants never made a follow-up visit, 77 infants visited once only, 6 infants had an indeterminate HIV status despite ≥2 visits, and 17 infants seroconverted after
the age of 4 months. The 265 excluded infants had a significantly lower mean birth weight (table 1). Although 27 of the excluded infants were known to have died, none of the 17 infants who seroconverted after the age of 4 months died. The prevalence of placental malaria among excluded infants who died or survived was 29.6% and 23.5%, respectively (P = .5).

The majority of the mothers of included infants had a maternal CD4+ cell count ≥500 cells/µL (table 1). Of the 570 included infants, 67.7% completed the study. Primiparous mothers with premature or HIV-negative infants were less likely to complete the study (P = .04, P = .01, and P = .04, respectively); women who did not complete the study had a higher median CD4+ cell count and a lower median log_{10} viral load (P = .05 and P = .01, respectively).

Placental malaria was detected in 141 women (24.7%). All infections were with *Plasmodium falciparum*, and there were 3 mixed infections with *P. malariae*. A blood smear and hemoglobin data were not available for 5 and 85 visits, respectively, of the 5083 visits that were made by the infants. Thirteen percent of blood smears were positive; 7 mixed infections with *P. malariae* and *P. falciparum* were detected, and all other infections were with *P. falciparum*. Moderate to severe anemia was diagnosed at 5.2% of the routine visits.

**PNIM.** Of the 570 infants, 75 (13.2%) died during the postneonatal period. One-third of the deaths occurred at the age of 4–5 months (table 2). As expected, PNIM was significantly more common among HIV-positive infants than among HIV-negative infants (figure 1 and table 2). Factors associated with PNIM in univariate and multivariate Cox regression models are shown in table 3. The adjusted HR (AHR) for placental malaria overall was 0.77 (95% confidence interval [CI], 0.43–1.39). However, effect modifications were observed between placental malaria and infant HIV status (P = .06 for the interaction term) and between infant anemia and infant HIV status (P = .03 for the interaction term).

**Placental malaria.** HIV-positive infants born to mothers with placental malaria tended to be more likely to survive than those born to mothers without placental malaria (AHR, 0.34 [95% CI, 0.10–1.10]; P = .07, log-rank test) (table 3 and figure 1). Placental malaria was not associated with PNIM in HIV-negative infants (AHR, 1.29 [95% CI, 0.62–2.66]) (table 3).

**Infant anemia and infant parasitemia.** Moderate to severe infant anemia was a risk factor for PNIM among HIV-negative infants but not among HIV-positive infants (table 3). There was no interaction between the infant’s HIV status and the effect of infant malaria: malaria parasitemia at a routine visit was a protective factor against PNIM among both HIV-infected and HIV-uninfected infants (table 3). Among HIV-positive infants who died, median survival among 10 infants with at least 1 episode of malaria was 274 days, compared with 134 days among 29 infants without any episodes of malaria (P<.01, Mann-Whitney U test). Among HIV-negative infants, median survival was 263 days (10 infants) and 160 days (26 infants), respectively (P = .08, Mann-Whitney U test).

Parasite prevalence among infants generally increases during the first year of life, and it increased in this study population, from 7% at 4 weeks to 22.0% at 44 weeks of age. To assess whether the association between infant malaria parasitemia and PNIM was not merely a proxy for age, we restricted the analysis to infants who completed the first 6 visits; the overall AHR with respect to malaria parasitemia and PNIM remained indicative of protection (0.53 [95% CI, 0.18–1.56]).

Infants born to mothers with placental malaria have been reported to have a higher risk of infant malaria [18] and anemia

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**Table 2. Postneonatal infant deaths among infants of HIV-seropositive women by infant HIV-status, Kisumu, Kenya, 1996–2001.**

<table>
<thead>
<tr>
<th>Deaths</th>
<th>All</th>
<th>HIV-positive infants</th>
<th>HIV-negative infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, % (no./total)</td>
<td>13.2 (75/570)</td>
<td>34.8 (39/112)*</td>
<td>7.9 (36/458)</td>
</tr>
<tr>
<td>Crude postneonatal infant mortality rate/1000 LBs (95% CI)</td>
<td>164 (130–199)</td>
<td>420 (318–522)</td>
<td>99 (68–130)</td>
</tr>
<tr>
<td>Placental malaria status, no./total, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present among deaths</td>
<td>14/75 (18.7)</td>
<td>3/39 (7.7)</td>
<td>11/36 (30.6)</td>
</tr>
<tr>
<td>Present among survivors</td>
<td>127/495 (25.7)</td>
<td>16/73 (21.9)</td>
<td>111/422 (26.3)</td>
</tr>
<tr>
<td>Timing of deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 2–3</td>
<td>5 (6.7)</td>
<td>2 (5.1)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Month 4–5</td>
<td>28 (37.3)</td>
<td>17 (43.6)</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>Month 6–7</td>
<td>14 (18.7)</td>
<td>8 (20.5)</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Month 8–9</td>
<td>14 (18.7)</td>
<td>6 (15.4)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Month 10–12</td>
<td>14 (18.7)</td>
<td>6 (15.4)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Age at death, median (IQR), days</td>
<td>161 (111–243)</td>
<td>158 (111–229)</td>
<td>190 (109–261)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of deaths, unless otherwise indicated. CI, confidence interval; IQR, interquartile range; LBs, live births.

* P<.01, HIV-positive vs. HIV-negative infants, χ² test.
HIV-positive infants

HIV-negative infants

... included ethnicity, construction material of the house, periurban residence, employment status, marital status, and season at the time of delivery. CI, 

34

Time-varying factors

Infant factors

Maternal factors

Factor

HIV-positive infants

HIV-negative infants

All infants

Adjusted

HIV-positive infants

Adjusted

HIV-negative infants

Adjusted

HR (95% CI)

HR (95% CI)

HR (95% CI)

Maternal factors

Age <20 years

0.82 (0.40–1.68)

0.57 (0.24–1.36)

Primiparae

1.17 (0.62–2.21)

1.25 (0.66–2.37)

1.66 (0.51–5.40)

2.71 (0.83–8.87)

2.36 (1.02–5.43)

0.35 (0.10–1.21)

2.36 (1.03–4.22)

4.05 (1.21–13.53)

4.05 (1.21–13.53)

2.36 (1.03–4.22)

2.36 (1.03–4.22)

4.05 (1.21–13.53)

4.05 (1.21–13.53)

Maternal geometric mean viral load and PNIM. Infant HIV infection and death were associated with a significantly higher maternal viral load (table 4). Placental malaria was not associated with a significantly higher viral load. However, among women who transmitted HIV, maternal viral load was significantly higher when placental malaria was present. Among HIV-positive infants, the geometric mean viral load among the 14 survivors of mothers with placental malaria (16,846 copies/mL) was not significantly different from the viral load among the 31 infants who died and whose mothers did


<table>
<thead>
<tr>
<th>Factor</th>
<th>All infants</th>
<th>HIV-positive infants</th>
<th>HIV-negative infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Maternal factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;20 years</td>
<td>0.74 (0.43–1.30)</td>
<td>0.82 (0.40–1.68)</td>
<td>0.57 (0.24–1.36)</td>
</tr>
<tr>
<td>Primiparae</td>
<td>0.97 (0.61–1.57)</td>
<td>0.92 (0.57–1.49)</td>
<td>1.17 (0.62–2.21)</td>
</tr>
<tr>
<td>Grande multiparae</td>
<td>2.36 (1.02–5.43)</td>
<td>NS</td>
<td>1.68 (0.51–5.40)</td>
</tr>
<tr>
<td>Low education level</td>
<td>1.42 (0.89–2.25)</td>
<td>1.41 (0.73–2.70)</td>
<td>1.65 (0.85–3.18)</td>
</tr>
<tr>
<td>Low/medium SES</td>
<td>1.88 (0.94–3.78)</td>
<td>2.09 (1.03–4.22)</td>
<td>3.26 (1.01–10.6)</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>0.66 (0.37–1.18)</td>
<td>0.77 (0.43–1.39)</td>
<td>0.34 (0.11–1.11)</td>
</tr>
<tr>
<td>CD4+ cell count &lt;500 cells/μL</td>
<td>2.15 (1.36–3.42)</td>
<td>1.93 (1.21–3.08)</td>
<td>2.44 (1.21–4.89)</td>
</tr>
<tr>
<td>High maternal viral load</td>
<td>2.28 (1.36–3.82)</td>
<td>NS</td>
<td>1.59 (0.80–3.14)</td>
</tr>
<tr>
<td>Infant factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>5.29 (3.36–8.32)</td>
<td>4.61 (2.90–7.32)</td>
<td>NA</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.34 (0.84–2.12)</td>
<td>1.13 (0.59–2.16)</td>
<td>1.12 (0.59–2.16)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>2.38 (1.18–4.77)</td>
<td>2.17 (1.07–4.39)</td>
<td>1.98 (0.83–4.75)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>0.86 (0.35–2.14)</td>
<td>0.81 (0.25–2.62)</td>
<td>0.75 (0.18–3.13)</td>
</tr>
<tr>
<td>Time-varying factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant malaria</td>
<td>0.44 (0.18–1.09)</td>
<td>0.35 (0.14–0.90)</td>
<td>0.29 (0.07–1.22)</td>
</tr>
<tr>
<td>Infant Hb level &lt;8 g/dL</td>
<td>2.29 (1.13–4.63)</td>
<td>2.18 (1.05–4.51)</td>
<td>0.86 (0.26–2.82)</td>
</tr>
</tbody>
</table>

NOTE. Significant hazard ratios (HRs) are in bold type. Additional factors examined but not associated with postneonatal infant mortality (and thus not presented) included ethnicity, construction material of the house, periurban residence, employment status, marital status, and season at the time of delivery. CI, confidence interval; Hb, hemoglobin; NA, not applicable; NS, not significant; SES, socioeconomic status.

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<table>
<thead>
<tr>
<th>Association</th>
<th>All infants</th>
<th>HIV-positive infants</th>
<th>HIV-negative infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All women</td>
<td>PNIM</td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td>1888 (505)</td>
<td>10,195 (33)</td>
<td>2390 (29)</td>
</tr>
<tr>
<td></td>
<td>5172 (62)</td>
<td>22,202 (16)</td>
<td>1217 (9)</td>
</tr>
<tr>
<td></td>
<td>1640 (443)</td>
<td>16,846 (14)</td>
<td>1596 (101)</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>2187 (126)</td>
<td>5151 (85)</td>
<td>3238 (20)</td>
</tr>
<tr>
<td>PNIM</td>
<td>2932 (11)</td>
<td>153,179 (2)</td>
<td>1237 (294)</td>
</tr>
<tr>
<td>Alive</td>
<td>2126 (115)</td>
<td>1561 (110)</td>
<td></td>
</tr>
<tr>
<td>No placental malaria detected</td>
<td>1799 (379)</td>
<td>5847 (51)</td>
<td>1498 (328)</td>
</tr>
<tr>
<td>PNIM</td>
<td>5847 (51)</td>
<td>8561 (31)</td>
<td>3849 (54)</td>
</tr>
<tr>
<td>Alive</td>
<td>1498 (328)</td>
<td>1327 (294)</td>
<td>1243 (274)</td>
</tr>
</tbody>
</table>

NOTE. Data are maternal viral load, in copies per milliliter (no. of infants). The Mann-Whitney U test was used for comparisons. PNIM, postneonatal infant mortality.

* P < .05 for viral load of mothers of HIV-positive infants vs. mothers of HIV-negative infants.

** P < .05 for viral load of mothers of infants who died vs. that of mothers of infants who survived.

† P < .05 for mothers with placental malaria vs. those without placental malaria.

‡ P = .04 for mothers of HIV-positive infants with placental malaria vs. mothers of surviving HIV-positive infants without placental malaria.

not have placental malaria (8561 copies/mL; P = .4), whereas it was significantly higher than the maternal viral load of the 54 survivors whose mothers did not have placental malaria (3849 copies/mL; P = .02), which indicates that placental malaria may change the association between a high maternal viral load and HIV progression in the infected infant. The mothers with placental malaria of the 2 HIV-infected infants who died had very high maternal viral loads, and this was significant, compared with the HIV-infected survivors of mothers without placental malaria.

Probable causes of death. For 63 deaths, a probable cause of death was assigned using verbal autopsy. There were no significant differences by infant HIV status, but numbers were small (figure 2).

DISCUSSION

Our results underscore that the complex interaction between HIV and malaria is challenging to study. By contrast to the earlier study by Bloland et al. [10], we did not find that placental malaria was a risk factor for PNIM among infants of HIV-seropositive women. Overall, the risk on PNIM was actually lower, although not significantly so, in infants born to HIV-infected mothers with placental malaria (AHR, 0.77 [95% CI, 0.43–1.39]), and this remained so after adjustment for potential confounders, including maternal CD4+ cell counts and LBW. These results are consistent with those of another study [19] that reported a nonsignificant protective effect of placental malaria against PNIM among infants born to HIV-seropositive women (HR, 0.39 [95% CI, 0.11–1.38]). We previously reported that MTCT was significantly lower in infants born to mothers with placental malaria than in those without placental malaria [12].

Several explanations can be considered for the association between placental malaria in HIV-positive women and increased survival time of HIV-infected infants. First, we speculate that prenatal exposure to malaria may modulate the immune system to generate protective immune pathways (involving innate or classical T cell–mediated pathways), which may slow the progression of HIV-1 and contribute to prolonged survival. There is considerable evidence that maternal exposure to malaria modulates immune responses to malaria in utero [20–23]. Second, it has recently become known that HIV-mediated disease progression is correlated with the down-regulation of a regulatory T cell (Treg) subset (Foxp3+CD4+CD25hi T cells), which may be critical for maintaining CD4+ cell counts [24]. It has been shown recently that placental malaria increases the number of Treg cells in cord blood [25], and this may help protect against any rapid decrease in CD4+ cell counts in infants born to HIV-positive mothers with placental malaria. Third, HIV/malarial coinfection can modulate the cytokine environment in the placenta and/or fetus, which may reduce the initial HIV load or slow HIV replication in the fetus. We have shown previously that HIV/malarial coinfection up-regulates (compared with HIV-positive malaria-negative women) some chemokines, including macrophage inflammatory protein (MIP)–1β, that can compete with the CCR5 receptor for HIV entry [25, 26].

We were also interested in establishing whether malaria in the HIV-positive infant was associated with enhanced HIV disease progression. Infant malaria parasitemia was not a risk factor for PNIM—indeed, median survival was higher among HIV-infected children with at least 1 documented malaria ep-
Among HIV-negative infants of HIV-seropositive women, moderate to severe infant anemia was a significant risk factor for PNIM. Infant anemia may be the culmination of a sequence of events whereby maternal HIV infection, placental malaria, infant malaria, and SES all contribute. Whatever the contributing factor, moderate to severe anemia in infants can be detected and should be responded to, particularly among infants of HIV-positive women.

Our study had several limitations. First, we only enrolled HIV-infected women with no AIDS-defining symptoms; PNIM among women with progressed HIV disease is likely to be higher than our present findings. Our measurement of parasitemia by microscopic examination of smears was inexact compared with other methods, may have misclassified particularly low-density parasitemias, and did not identify intervillos inflammation, but this would have resulted in bias toward the null. The number of HIV-infected infants born to mothers with placental malaria was small; this precludes more-definitive answers and does not rule out a chance finding. An infant needed to make at least 2 follow-up visits for us to be able to make an HIV diagnosis, and loss to follow up was considerable, which may have biased our results. However, the reported PNIM among HIV-infected infants was comparable to results obtained in eastern Africa from a pooled analysis of trials [32], and, consistent with previous reports, a low CD4+ cell count was a significant risk factor for PNIM [32, 33]. Although excluded infants had a lower mean birth weight, the percentage of LBW was similar among both groups, and other characteristics between excluded and included infants were similar as well. Deaths among the excluded infants were not associated with placental malaria. Furthermore, placental malaria was not linked with known factors that have been associated with infant HIV disease progression, such as maternal viral load and maternal CD4+ cell count [12, 33, 34]. Our findings about the effect of placental malaria and infant malaria on PNIM are consistent with reports from other studies [19, 27].

In summary, in this study population of infants of HIV-seropositive women, PNIM was associated with infant HIV infection, moderate to severe infant anemia, LBW, low SES, and low maternal CD4+ cell count. Our results do not confirm the findings of Bloland et al. [10] and do not support our hypothesis that placental malaria may enhance HIV disease progression in the HIV-infected infant. By contrast, we found that infants born to HIV-infected mothers with placental malaria do not have an increased risk of PNIM and that malaria in the HIV-infected infant may further contribute to a protective effect from PNIM, which suggests a complex relationship between maternal and infant immune responses to malaria and HIV. The role of placental malaria in the context of HIV and its effect on PNIM merits further study.
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