Polymorphism of Fc Receptor IIa for Immunoglobulin G Is Associated with Placental Malaria in HIV-1–Positive Women in Western Kenya

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Background. Genetic polymorphism of the Fc receptor IIa for immunoglobulin (Ig) G (FcγRIIa) determines IgG subclass binding. Previous studies have shown that individuals with the IgG1/3-binding FcγRIIa-Arg/Arg131 genotype are relatively protected against high-density malaria, whereas individuals with the IgG2-binding FcγRIIa-His/His131 genotype are at increased risk for developing cerebral malaria. The present study was undertaken to examine the relationship between FcγRIIa polymorphism and placental malaria (PM) in pregnant women of known human immunodeficiency virus (HIV)-1 status.

Methods. FcγRIIa genotype was determined in 903 pregnant women who had participated in a study designed to assess the effect that PM has on vertical transmission of HIV-1. FcγRIIa polymorphism was assessed in relation to PM.

Results. Among HIV-negative women, there was no difference in the distribution of the FcγRIIa polymorphism by PM status. However, among HIV-positive women, the frequency of the FcγRIIa-His/His131 genotype was significantly higher in women with PM than in women without PM (31% vs. 22%, respectively [P = .032]). In multivariate analysis, the adjusted odds ratio for PM in HIV-positive women with the FcγRIIa-His/His131 genotype versus women in the FcγRIIa-His/Arg131 reference group was 1.72 (95% confidence interval, 1.11–2.69 [P = .016]).

Conclusions. The present study suggests that the IgG2-binding FcγRIIa-His/His131 genotype is associated with enhanced susceptibility to PM in HIV-positive women but not in HIV-negative women.

In areas where malaria is endemic, pregnant women are at increased risk for Plasmodium falciparum infection, compared with nonpregnant women. The placenta, in particular, is highly susceptible, with infection density in placental blood generally much higher than that in peripheral blood [1]. In areas where malaria is holoendemic, susceptibility to placental malaria (PM) decreases with increasing gravidity (likely due to placental-acquired immunity), whereas, in areas where endemicity is low, gravidity-dependent trends are not evident [1, 2]. Depending on transmission density, the consequences of PM include preterm labor, maternal anemia, and low birth weight of infants, all of which contribute to neonatal mortality [3]. Although malaria during pregnancy is well documented epidemiologically, the underlying biological basis of susceptibility to infection, and of its consequent effects, are not fully understood.

Previous studies of biological factors related to PM and the subsequent pathological manifestations have revealed some possible mechanisms. In areas where malaria is highly endemic, exposure of the placenta to malarial parasites has been found to be associated with infiltration of monocytes into the placental intervillous space [4]. Resultant intervillositis and changes in cytokine profile and/or balance are involved in adverse pregnancy outcomes, such as low birth weight [4–7]. Hormonal changes...
associated with pregnancy—increased levels of immunosuppressive corticosteroids, in particular—may be responsible for part of the enhanced susceptibility seen in primigravid women [8]. However, there is also ample evidence that humoral and cellular immune responses play key roles in resistance to or control of PM. For instance, the cytokine interferon-γ, which regulates macrophage-mediated killing of intraerythrocytic parasites, has been associated with protection against infection [9]. Findings on humoral immunity in resistance to PM have been more indirect, such as the observation that primigravidae are less likely to have antibodies that agglutinate chondroitin sulfate A–binding parasites (which sequester in the placenta) than are multigravidae [10].

Monocytes, macrophages, and other leukocytes express Fc receptors for IgG (FcγRs), which provide an important bridge between the humoral and cellular arms of the immune response [11]. Among the 3 classes of FcγRs, class II is the most widely distributed and, on many cells, is the sole FcγR type expressed [11]. A single point mutation at position 131, arginine (Arg131) or histidine (His131), in the gene for the FcγRIIa, a subtype of the FcγRII, is critical for the binding of human IgG subclasses, in which the FcγRIIa-Arg/Arg131 genotype binds to IgG1/3 and the FcγRIIa-His/His131 genotype interacts efficiently with IgG2.

We have previously demonstrated the biological relevance of FcγRIIa polymorphism in malaria in infants from western Kenya; that study showed that the FcγRIIa-Arg/Arg131 genotype, which does not bind to IgG2, was associated with protection from high-density *P. falciparum* infection [12]. Recently, it has been demonstrated that adults homozygous for the FcγRIIa-His131 variant are at increased risk for developing cerebral malaria [13]. It is believed that antibody-dependent cellular inhibition (ADCI) of malarial parasites, mediated by the FcγRIIa, may play a role in these findings. This speculation is supported by in vitro studies that show that binding of IgG1/3 immune complexes with monocytes confers protection [14, 15], whereas IgG2 triggers a less-effective response [16].

To our knowledge, no study has investigated the relationship between FcγRIIa polymorphism and PM. In vitro investigations have shown that the FcγRIIa is present in the human placenta during all trimesters and is expressed by maternal-derived monocytes and macrophages in the intervillous space and tissues [17, 18]. Given the distribution of the FcγRIIa and the importance of FcγRIIa polymorphism for peripheral malaria in children and cerebral malaria in adults, the present study was undertaken to examine the relationship between genetic polymorphism of the FcγRIIa and malaria in the context of the unique immunological milieu of the placenta.

Our study population comprised pregnant women in an area of western Kenya where malaria is holoendemic. HIV infection in women of reproductive age is also a major public-health problem in this area, as it is in many other regions of the world where malaria is endemic. Recent studies conducted in this area have shown that HIV infection in pregnant women enhances susceptibility to PM, likely due to the consequent deterioration of the immune system resulting from HIV infection [19–21]. Therefore, in the present study, the effect that FcγRIIa polymorphism has on PM was explored in both HIV-negative and positive women.

**POPULATION, MATERIALS, AND METHODS**

**Study Site and Population**

The present study was integrated into an epidemiologic investigation of the relationship between PM and perinatal mother-to-child transmission of HIV-1 in western Kenya [22]. Residents of this area are primarily of the Luo ethnic group [23]. Malaria is holoendemic [24], and transmission, although perennial, peaks during and through the end of the short and long rains in this region [25]. *P. falciparum* is the predominant species, accounting for 98% of malaria cases [25]. In HIV-negative women from the population under study, PM occurs in ~22% of first, ~14% of second, and ~9% of later pregnancies. Risk for PM in HIV-infected women is considerably increased, with ~32% of primi-, ~26% of secundi-, and ~23% of multigravid women having PM [20]. HIV-1 prevalence was ~26% in pregnant women in Kisumu at the time of the present study [23, 26]. Maternal anemia is common in western Kenya, especially in primi- or secundigravid women with either malaria or HIV infection [27].

Study design and enrollment criteria for the larger epidemiologic study have been detailed elsewhere [23]. In brief, women were enrolled through the antenatal clinic at the New Nyanza Provincial General Hospital in Kisumu if they had an uncomplicated singleton pregnancy of at least 32 weeks gestation and had no known underlying chronic illness (if HIV positive, no signs of AIDS). At delivery, enrollment priority was given to HIV-positive women. For the HIV-negative women surveyed, enrollment priority was given to women with PM. The epidemiologic study originally enrolled 269 HIV-negative and 829 HIV-positive pregnant women. To investigate the effect that FcγRIIa polymorphism has on PM, blood samples obtained between 1996 and 2001 from 245 HIV-negative and 658 HIV-positive pregnant women were tested. Samples were selected on the basis of both availability of DNA and information on treatment for malaria during the third trimester of pregnancy.

**Clinical Procedures**

At enrollment, information was collected on reproductive history, demographics, and clinical status. Malaria blood smears, hemoglobin concentrations, and blood samples for HIV-antibody testing were obtained. At delivery, blood samples were obtained from the mother, placenta, and cord, to measure ma-
larial infection and HIV-1 load. One month after birth, additional blood samples were obtained from the women for CD4 cell counts and for assessment of hemoglobin and malaria.

**Ethics Issues**

The study methods were reviewed and approved by the Kenya Medical Research Institute Ethical Review Committee and the Institutional Review Board of the Centers for Disease Control and Prevention. The human-experimentation guidelines of the US Department of Health and Human Services were followed. Written, informed consent was obtained from women at enrollment. Patient identifiers on all information were coded to maintain privacy. From 1996 to 1998, those women found to have malaria with fever (axillary temperature of \( \geq 37.5^\circ C \)) were offered a single dose of sulfadoxine-pyrimethamine; in 1999, presumptive intermittent treatment was introduced into the study, according to Kenya Ministry of Health guidelines [28]. Pre- and post–HIV test counseling was provided to all women. At the time of the study (1996–2001), treatment with zidovudine or nevirapine was neither recommended by the Kenya Ministry of Health nor available.

**Laboratory Procedures**

**Malaria-related tests.** PM was assessed on blood samples obtained from a shallow incision on the maternal side of the placenta. Thick smears made from maternal and placental blood were examined by microscopy. The number of asexual parasites/300 leukocytes was counted. Parasite density was estimated on the assumption of 8000 leukocytes/\( \mu L \). Placental-smear readings were further categorized on the basis of presence of malarial pigment in placental intervillous macrophages [29]. Peripheral-blood hemoglobin concentrations (grams per deciliters) were quantified by use of the HemoCue system (HemoCue).

**HIV-related tests.** A primary Serostrip HIV-1/2 (Saliva Diagnostic Systems) and a confirmatory Capillus HIV-1/2 test (Cambridge Diagnostics) were used to determine maternal HIV status [23]. CD4 cell counts in HIV-positive women were determined by use of commercial monoclonal antibodies (Becton Dickinson) and standard fluorescent-activated cell-sorting analysis on whole blood, as recommended by the manufacturer (FACScan). Maternal HIV-1 load was measured by use of the Roche Amplicor HIV-1 monitor (test version 1.0; Roche Diagnostics).

**Determination of FcγRIIa genotypes.** Genomic DNA was extracted from peripheral-blood mononuclear cells, and a 366-bp section of the variable region of the FcγRIIa gene was amplified by use of the 9600 GeneAmp polymerase chain reaction (PCR) system. Allele-specific restriction-enzyme (BstUI; New England Biolabs) digestion of the PCR products, followed by electrophoresis on a 3% (wt/vol) agarose gel, allowed for determination of genotype. The FcγRIIa-Arg/Arg131 genotype produced a 322-bp fragment, and the FcγRIIa-His/Arg131 genotype produced a 343-bp fragment, and the FcγRIIa-His/His131 genotype produced both fragments [30].

**Definitions**

Peripheral parasitemia was defined as any asexual blood-stage parasites seen, by microscopy, on a thick smear. Thick smears were deemed to be negative if inspection of 100 fields revealed no parasites. PM was similarly defined, and placentas with malarial pigment, in the absence of parasitemia, were also classified as negative for PM. Malaria-transmission season comprised the months of April–June and October–December, which roughly correspond with the long and shorts rains, respectively. The season of the beginning of the third trimester of pregnancy corresponded with the transmission season 3 months before delivery. By use of a modified Dubowitz method, newborns were classified as “preterm” if delivery occurred before 37 weeks gestation [31]. Low birth weight (<2500 g) was based on weight measured to the nearest gram within 24 h of birth [32]. CD4 cell counts were compared with cutoffs of 350 and 500 cells/\( \mu L \) [33], and gravidity was divided into primi- versus secundi- or multigravid, because the immunological milieu of early pregnancies, particularly with regard to malaria in areas where it is holoendemic, differs from that of later pregnancies [2]. Maternal HIV-positive status was determined on the basis of antibodies to HIV-1, detected by 2 sequential rapid tests [23]. Virus loads below the limit of quantitation of the test kits (400 copies/mL) were assigned the value of 200 copies/mL of plasma.

**Data Analysis**

Univariate analysis was performed for each variable, to determine which variables were associated with outcomes of interest in HIV-positive and -negative women. The effect that FcγRIIa genotype has on the odds for PM and other malaria-related factors was assessed by multivariate logistic regression. Although some variables considered in the univariate analyses had missing values, this issue was not as relevant in the multivariate analysis, because all of the variables in the final model were fully represented. Because not all HIV-negative women who qualified for the study were enrolled (more PM-positive than -negative women were selected), statistical models were adjusted to account for this selection bias. In HIV-infected women, the effect that virus load and CD4 cell count have on the relationship between FcγRIIa genotype and PM was assessed by multivariate logistic regression, with the inclusion of an interaction term for the HIV parameter of interest with FcγRIIa genotype. The FcγRIIa-His/Arg131 group was used as a reference in analyses, because this allotype is the most prevalent in human populations [34]. Two-sided \( P < .05 \) was considered to be statistically significant. Data analyses were performed by use of SPSS software (version 10.0) and SAS software (version 8.02).
RESULTS

Characteristics of women by PM status. The characteristics of the HIV-positive and -negative women were assessed separately, because potential confounding variables associated with PM may differ by HIV status. Univariate analyses of the HIV-negative women (n = 245) showed PM to be associated with younger maternal age, primigravidity, maternal peripheral malaria, malarial pigment in the placenta, and delivering a newborn of low birth weight (table 1). Similar to the HIV-negative women, the HIV-positive women (n = 698) with PM had an increased likelihood of having peripheral malaria and malarial pigment in the placenta and were more likely to be younger, primigravid, and deliver a newborn of low birth weight than those with PM-negative women (table 1). Additionally, compared with the HIV-negative women with PM, the HIV-positive women with PM were less likely to have received treatment for malaria during their third trimester and were more likely to become anemic during pregnancy (table 1).

Overall, there was no difference in FcγRIIa genotype frequencies and FcγRIIa allele distributions between the HIV-positive and -negative women (P = .80, Hardy-Weinberg equilibrium test; P = .43, χ² test [data not shown]). There was no statistically significant association between FcγRIIa genotype and PM in HIV-negative women (table 1). However, in HIV-positive women, there was a borderline statistically significant difference in FcγRIIa polymorphism between the women with and without PM in univariate analysis (P = .06) (table 1).

Table 1. Characteristics of HIV-1–negative and HIV-1–positive women, by placental malaria (PM) status.

<table>
<thead>
<tr>
<th>Category, characteristic</th>
<th>HIV-1–negative women</th>
<th></th>
<th>HIV-1–positive women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PM (n = 134)</td>
<td>n = 111</td>
<td>P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>With PM (n = 151)</td>
</tr>
<tr>
<td>Maternal FcγRIIa genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>His/His131</td>
<td>18.7</td>
<td>22.5</td>
<td>.66</td>
<td>31.1</td>
</tr>
<tr>
<td>His/Arg131</td>
<td>56.4</td>
<td>51.4</td>
<td>...</td>
<td>45.7</td>
</tr>
<tr>
<td>Arg/Arg131</td>
<td>24.6</td>
<td>26.1</td>
<td>...</td>
<td>23.2</td>
</tr>
<tr>
<td>Maternal peripheral malaria&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present during third trimester</td>
<td>35.5</td>
<td>11.5</td>
<td>&lt;.01</td>
<td>50.9</td>
</tr>
<tr>
<td>Present at delivery</td>
<td>72.9</td>
<td>4.6</td>
<td>&lt;.01</td>
<td>69.8</td>
</tr>
<tr>
<td>Malarial pigment present</td>
<td>88.1</td>
<td>1.8</td>
<td>&lt;.01</td>
<td>86.8</td>
</tr>
<tr>
<td>Mother’s age, mean ± SD, years</td>
<td>19.6 ± 3.7</td>
<td>22.2 ± 4.6</td>
<td>&lt;.01</td>
<td>21.6 ± 4.5</td>
</tr>
<tr>
<td>Primigravida</td>
<td>64.9</td>
<td>36.9</td>
<td>&lt;.01</td>
<td>45.0</td>
</tr>
<tr>
<td>Secundigravida</td>
<td>19.4</td>
<td>29.7</td>
<td>...</td>
<td>23.2</td>
</tr>
<tr>
<td>Multigravida</td>
<td>15.7</td>
<td>33.3</td>
<td>...</td>
<td>31.8</td>
</tr>
<tr>
<td>Preterm delivery&lt;sup&gt;c&lt;/sup&gt; &lt;37 weeks</td>
<td>7.5</td>
<td>7.3</td>
<td>.96</td>
<td>9.9</td>
</tr>
<tr>
<td>Newborn birth weight&lt;sup&gt;d&lt;/sup&gt; &lt;2500 g</td>
<td>7.5</td>
<td>0</td>
<td>&lt;.01</td>
<td>11.9</td>
</tr>
<tr>
<td>Maternal anemia at delivery&lt;sup&gt;e&lt;/sup&gt; 4 g/dL</td>
<td>61.2</td>
<td>52.8</td>
<td>.19</td>
<td>72.1</td>
</tr>
<tr>
<td>&lt;7</td>
<td>7.0</td>
<td>3.7</td>
<td>.39</td>
<td>12.9</td>
</tr>
<tr>
<td>Antimalarial use, treated during third trimester</td>
<td>18.7</td>
<td>27.9</td>
<td>.09</td>
<td>17.2</td>
</tr>
<tr>
<td>Place of living, semiurban (vs. urban)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>32.8</td>
<td>22.9</td>
<td>.09</td>
<td>28.7</td>
</tr>
<tr>
<td>Season of third trimester, malaria-transmission season</td>
<td>61.2</td>
<td>49.5</td>
<td>.07</td>
<td>52.3</td>
</tr>
<tr>
<td>Maternal CD4 cell count&lt;sup&gt;g&lt;/sup&gt; 9 cells/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350</td>
<td>6.8</td>
<td>17.9</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>&lt;500</td>
<td>37.4</td>
<td>38.9</td>
<td>.77</td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>39.4</td>
<td>47.8</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>1000–9999</td>
<td>33.9</td>
<td>35.1</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>26.6</td>
<td>17.1</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>1884 (200–13,339)</td>
<td>1122 (200–5145)</td>
<td>.07</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are percentage of women, unless otherwise noted. FcγRIIa, Fc receptor IIa for IgG.

<sup>a</sup> P values for univariate analysis are based on either the χ² test; the t test, to compare means; or the Wilcoxon rank sum test, to compare medians for nonnormal data. P values from an exact test are given for malarial pigment, newborn birth weight, and maternal anemia (<7 g/dL).
<sup>b</sup> For HIV-1–negative women, n = 197 for peripheral malaria during the third trimester, and n = 237 for peripheral malaria at delivery; for HIV-1–positive women, n = 504 for peripheral malaria during the third trimester, and n = 643 for peripheral malaria at delivery.
<sup>c</sup> For HIV-1–negative women, n = 244, for HIV-1–positive women, n = 658.
<sup>d</sup> For HIV-1–negative women, n = 244, for HIV-1–positive women, n = 507.
<sup>e</sup> For HIV-1–negative women, n = 237; for HIV-1–positive women, n = 638.
<sup>f</sup> For HIV-1–negative women, n = 243; for HIV-1–positive women, n = 652.
<sup>g</sup> For HIV-1–positive women, n = 482.
Table 2. Univariate and multivariate analysis of the effect that maternal Fc receptor IIa for IgG (FcγRIIA) genotype has on the risk for placental malaria in HIV-1–positive women.

<table>
<thead>
<tr>
<th>FcγRIIA genotype</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>His/His131</td>
<td>1.60 (1.04–2.47)</td>
<td>.032</td>
<td>1.72 (1.11–2.69)</td>
<td>.016</td>
</tr>
<tr>
<td>His/Arg131</td>
<td>1.00</td>
<td>...</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Arg/Arg131</td>
<td>0.95 (0.60–1.50)</td>
<td>.833</td>
<td>0.93 (0.59–1.48)</td>
<td>.766</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; OR, odds ratio.

* Derived from multivariate logistic regression, controlling for treatment of malaria, gravidity, and malaria-transmission season.

Assessment of the effect that FcγRIIA genotypes have on PM.

The unadjusted odds for PM in the HIV-positive women with the FcγRIIA-His/His131 genotype were significantly higher than those in the women in the FcγRIIA-His/Arg131 reference group (unadjusted odds ratio [OR], 1.60 [95% confidence interval [CI], 1.04–2.47]) (table 2). When stratified by gravidity, this trend remained. FcγRIIA polymorphism had no effect on maternal anemia, low infant birth weight, gestational age, or PM density (data not shown). By multivariate logistic regression, we controlled for treatment for malaria during pregnancy, malaria-transmission season of third trimester, and gravidity, because these factors were associated with PM in the univariate analyses (table 1). Age, peripheral malaria, and malarial pigment were not included in the analysis, because they were highly correlated with other variables in the model. The results of the multivariate analysis further confirmed that the HIV-positive women with the FcγRIIA-His/His131 genotype were more likely to have PM, compared with the women in the FcγRIIA-His/Arg131 reference group (adjusted OR, 1.72 [95% CI, 1.11–2.69]) (table 2).

We subsequently explored whether CD4 cell count and virus load affected the relationship between the FcγRIIA-His/His131 genotype and susceptibility to PM in the HIV-infected women. The interaction term of FcγRIIA genotype with CD4 cell count or FcγRIIA genotype with virus load was not statistically significant; however, the adjusted odds for PM in the women with the FcγRIIA-His/His131 genotype, compared with those in the women in the FcγRIIA-His/Arg131 reference group, were increased in women with lower CD4 cell counts or higher HIV-1 loads (table 3).

DISCUSSION

The association between malaria during pregnancy and detrimental outcomes in both women and newborns has been well established [1, 3]. However, the biological mechanisms behind increased susceptibility to malaria and resultant health consequences remain unclear [35]. The present study was undertaken to examine the relationship between polymorphism in the gene for the primary cellular IgG receptor, FcγRIIA, and PM. We have provided evidence that the IgG2–binding FcγRIIA-His/His131 genotype is associated with increased susceptibility to PM in HIV-positive women in western Kenya.

Because malaria is caused by an intracellular pathogen with extracellular stages, both cellular and humoral immune responses are vital in combating infection. The importance of the FcγRIIA with regard to malaria comes from its role as a link between the humoral and cellular branches of the immune system [11]. In the present study, the FcγRIIA genotype was not related to PM in HIV-negative women. However, the HIV-positive women homozygous for FcγRIIA-His131 had increased susceptibility to PM. Because the FcγRIIA-His131 variant is the only receptor with high affinity for the Fc of IgG2 (the arginine allelic variant binds well to IgG1 and IgG3 but poorly to IgG2 [36]), this finding suggests that protection against PM may be partially mediated via the FcγRIIA in relation to antibodies [12, 13]. We speculate that IgG possibly binds to parasites that accumulate in the intervillous space of the placenta [29] and that maternal blood, containing a leukocyte population primarily composed of monocytes and macrophages, fills this intervillous space [4], which creates the opportunity for ADCI.

Table 3. Odds ratios (ORs) for placental malaria (PM) in HIV-1–positive women with the Fc receptor IIa for IgG (FcγRIIA)–His/His131 genotype vs. HIV-1–positive women with the FcγRIIA-His/Arg131 genotype, by HIV-1–related parameters.

<table>
<thead>
<tr>
<th>Parameter, level</th>
<th>No. of women (no. with the FcγRIIA-His/His131 genotype)</th>
<th>PM frequency, %</th>
<th>Adjusted OR for FcγRIIA-His/His131 vs. -His/Arg131 (95% CI)</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, cells/µL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350</td>
<td>85 (24)</td>
<td>21</td>
<td>3.57 (0.99–12.8)</td>
<td>.052</td>
</tr>
<tr>
<td>&gt;350</td>
<td>397 (91)</td>
<td>22</td>
<td>1.60 (0.89–2.89)</td>
<td>.118</td>
</tr>
<tr>
<td>HIV-1 load, copies/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10,000</td>
<td>366 (84)</td>
<td>22</td>
<td>0.50 (0.16–1.61)</td>
<td>.245</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>88 (21)</td>
<td>33</td>
<td>2.36 (1.28–4.38)</td>
<td>.006</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; FcγRIIA, Fc receptor IIa for IgG.

* For CD4 cell count, n = 482; for HIV-1 load, n = 454.

b Derived from multivariate logistic regression, controlling for treatment of malaria, gravidity, and malaria-transmission season.
to take place, via the FcγRIIa. In vitro studies have shown that cross-linking of IgG1 and IgG3, directed to surface antigens of malarial parasites, with the FcγRI expressed on monocytes or macrophages can trigger ADCI [14, 15]. Soluble factors are then released that inhibit replication of surrounding intra-erythrocytic parasites [37]. Although there are no data from previous studies indicating that IgG2 is unable to mediate ADCI in the presence of FcγRII-His131–expressing macrophages, in vitro studies of serum samples from subjects residing in areas where malaria is endemic have suggested that IgG2 is comparatively ineffective in triggering ADCI and actually inhibits the ADCI activity of IgG1 and IgG3 in competition experiments [16]. Although there is no direct evidence indicating that antibodies directed to malarial surface antigens play a role in susceptibility to or protection against PM, the importance of antibody subclass has been indicated in areas where malaria is endemic, where IgG1 and IgG3 predominate in individuals protected from clinical malaria and IgG2 is associated with increased risk of infection in susceptible adults [14]. It is important to further study the relationship between susceptibility to PM and FcγRIIa polymorphism in relation to antibodies in in vitro studies.

Our results have shown that, in HIV-infected women, FcγRIIa polymorphism has an effect on the presence or absence of PM but not on PM density. The reason for this may lie in the way PM density was quantified (i.e., the number of parasites in relation to the number of leukocytes). Because some women with PM may have had intervillositis, with resultant high levels of monocytes, whereas some HIV-positive women may have decreased leukocyte counts, it is possible that the discrepancy in total leukocyte counts in placenta masked any possible trend regarding FcγRIIa polymorphism and PM density.

In the present study, FcγRIIa genotype in HIV-positive, but not in HIV-negative, women had a statistically significant association with PM status. The reasons for the differing effects of FcγRIIa genotype on PM in women depending on HIV status remain to be elucidated. That FcγRIIa-His131 and -Arg131 allelic and genotypic frequencies were equivalent in the HIV-positive and -negative women assessed suggests that genotype-related susceptibility to PM is driven by HIV infection and not purely by genetic background. It is likely that, in HIV-positive women, the interaction of a combination of factors—such as differences in cellular FcγRIIa expression [38] and general immunological alterations, with resultant changes in quantity and quality of antibody levels [19, 39, 40] associated with HIV—plays a role in the effect of FcγRIIa polymorphism on susceptibility to PM.

A previous study indicated that FcγRII (including FcγRIIa) expression on CD14+ monocytes, which is the most-prevalent monocyte type, is greatly enhanced in individuals infected with HIV [38]. Thus, increased quantity of the FcγRIIa in HIV-positive individuals may enhance its relative importance in relation to immune responses against malaria. In the present study, the relative influence of FcγRIIa genotype on susceptibility to PM in HIV-positive women may also be related to immunological alterations associated with HIV infection. Our finding that the strength of the association between the FcγRIIa-His/His131 genotype and susceptibility to PM in HIV-positive women tended to increase with higher HIV-1 load and lower CD4 cell count supports this assertion. It is known that there is decreased antibody production and reduced antibody response to certain malarial antigens during malaria in HIV-positive, compared with HIV-negative, pregnant women [19, 39]. Along these lines, a vaccination study of HIV-infected individuals showed that IgG1 expression is more-severely dampened by low CD4 cell count than is IgG2 expression [40]. In addition, it has been shown that IgG2 levels increase during PM in HIV-positive women [41]. Taken together, the unbalance of antibody levels, with a relative increase of IgG2 in comparison with IgG1/3, could have a synergistic effect with increased FcγRIIa expression during HIV infection, whereby the influence of FcγRIIa polymorphism, especially in relation to the IgG2-binding FcγRIIa-His/His131 genotype, is increased.

To our knowledge, the present investigation is the first to examine FcγRIIa polymorphism in relation to PM. We have found that the FcγRIIa-His/His131 genotype is associated with susceptibility to PM in HIV-positive women and that the effect of genotype is enhanced with decreased CD4 cell count or increased HIV-1 load. Results from the present study not only support previous findings of an association between FcγRIIa polymorphism and malaria [12, 13] but also provide a possible biological basis for previous epidemiologic observations that HIV infection increases susceptibility to malarial infection during pregnancy [42]. Clearly, our results suggest the need to further study the effect of this genetic polymorphism on malaria/HIV interaction during pregnancy as well as in children, to gain a deeper understanding of the mechanisms behind our findings.

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