Malaria and HIV in pregnancy, and effects on the infant in western Kenya

van Eijk, A.M.

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Human Immunodeficiency Virus Increases the Risk for Malaria in Women of all Gravidities in Kisumu, Kenya
Human Immunodeficiency Virus Increases the Risk for Malaria in Women of all Gravidities in Kisumu, Kenya


From The *Kenya Medical Research Institute, Center for Vector Biology and Control Research, Kisumu, Kenya, the †Department of Infectious Diseases, Tropical Medicine & AIDS, Academic Medical Center, University of Amsterdam, the Netherlands, the ‡Kenya Ministry of Health, Kisumu, Kenya, and the §Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

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Disclaimer: Use of trade names is for identification only and does not imply endorsement by the Kenya Medical Research Institute or the Ministry of Health, Kenya, or by the U.S. Department of Health and Human Services.

Correspondence: A. M. van Eijk, Po Box 1578, Kisumu, Kenya (AvanEijk@kisian.mimcom.net).

Requests for reprints to: AM van Eijk, Po Box 1578, Kisumu, Kenya.
Abstract

Objective: To study the importance of HIV infection for malaria in pregnancy in Kisumu, Kenya.

Subjects and methods: Healthy women with an uncomplicated pregnancy of ≥32 weeks attending the prenatal clinic in the Provincial Hospital between June 1996 and March 1999 were tested for HIV and malaria after consent had been obtained. For participating women who delivered in the same hospital, a blood smear of the mother and the placenta were obtained.

Results: In the third trimester, 5,093 women consented to testing: the prevalence of malaria and HIV was 20.1% and 24.9% respectively. Among the 2,502 screened women who delivered in the hospital, the prevalence of HIV, peripheral parasitemia and placental malaria was 24.5%, 15.2%, and 19.0%, respectively. Compared with HIV-seronegative women, HIV-seropositive women were more likely to be parasitemic, to have higher parasite densities, and to be febrile when parasitemic. Placental infections in HIV-seropositive women were more likely to be chronic, as indicated by the presence of moderate-to-heavy pigment depositions. When adjusted by age, the typical gravidity specific pattern of malaria in pregnancy disappeared in HIV-seropositive women; HIV-seropositive primigravidae had a similar risk of malaria as HIV-seropositive multigravidae. The excess malaria attributable to HIV in the third trimester increased from 34.6% among HIV-seropositive primigravidae, to 41.5% among HIV-seropositive secundigravidae, and 50.7% among HIV-seropositive gravidae with >3 pregnancies.

Conclusion: HIV infection alters patterns of malaria in pregnant women; in areas with both infections, all pregnant women should use malaria prevention.

Keywords: HIV infection, malaria, pregnancy, Africa, women

Introduction

Pregnant women are at increased risk for malaria in sub-Saharan Africa, and this affects more than 20 million pregnant women and their children each year [1]. In highly malaria-endemic areas, Plasmodium falciparum infection is generally not associated with fever, and
therefore remains undetected and untreated. The adverse consequences include maternal anemia, premature delivery, and intrauterine growth retardation, resulting in the delivery of a low birth weight infant [2, 3]. Low birth weight is known to be the most important risk factor for neonatal mortality [4, 5].

During pregnancy, the ability to limit the presence and number of parasites is reduced. This increased risk of malaria is higher in primigravidae than in multigravidae, in teenagers than in older women, and in the second trimester than in the third trimester of pregnancy [2, 3]. There is a gravidity-specific decrease, with the highest prevalence of malaria (and malaria-related morbidity) in primigravidae, rapidly decreasing from the 2nd pregnancy onwards [2, 3].

Two studies in Malawi observed that in rural settings where malaria is highly endemic with seasonal year-round transmission, human immunodeficiency virus (HIV)-seropositive multigravidae had an increased susceptibility to malaria compared with HIV-seronegative multigravidae, but little difference was observed in primigravidae [6, 7]. In a later study conducted in a peri-urban setting in Kenya with similar, although not seasonal, malaria transmission, HIV-seropositive women in their first and second pregnancy were found to be at an increased risk for malaria [8].

Within a large study of maternal malaria and mother-to-child transmission of HIV, in a setting with endemic HIV and malaria transmission, we further evaluated the effect of maternal HIV infection on malaria in pregnancy. Effect of maternal HIV infection and malaria in pregnancy on hemoglobin level have been reported elsewhere [9].

Materials and Methods

Study site

This study was conducted at Nyanza Provincial General Hospital (NPGH) in Kisumu, a town with a population of approximately 300,000, located on the shore of Lake Victoria in western Kenya. Malaria transmission is perennial and P. falciparum accounts for 98% of the malaria
cases. Chloroquine resistance is widespread; in the early 1990s, 75% of persons infected with *P. falciparum* were reported to have an RII/RIII resistance to chloroquine [10]. NPGH is a government-referral hospital with a total of 400 beds; it provides health care mostly to the local low-income population. On average, approximately 90 women attend the prenatal clinic service daily, of whom 33% arrive for their first prenatal visit.

**Study population and enrollment procedures**

This study formed part of an investigation of the interaction between malaria in pregnancy and HIV infection, details of which have been described elsewhere [9]. Briefly, healthy pregnant women with no known underlying disease visiting the prenatal clinic service of the NPGH with an uncomplicated singleton pregnancy of at least 32 weeks gestation and residing in the Kisumu area were invited to participate. After informed consent was obtained, a questionnaire was completed to collect information on socioeconomic status, medical, and obstetrical history. Body weight, height and axillary temperature were measured. After the client received counseling about HIV, blood was obtained by finger prick for HIV testing, a malaria thick smear and Hb levels. Post-test counseling, supportive counseling and haematinics were offered to all participating women. All women with symptomatic malaria (axillary temperature ≥ 37.5°C) were treated with sulfadoxine-pyrimethamine (SP). At delivery blood was again obtained from the mother by finger prick for a malaria smear and Hb level, and a placental blood smear was obtained. The study was completed before the introduction of intermittent protective treatment with SP as the national policy for control of malaria in pregnancy [11].

**Laboratory Procedures**

Blood smears were stained with Giemsa and examined under oil immersion for malaria parasites. A thick smear was considered negative if 100 microscopic fields revealed no parasites. Malaria parasites were counted against 300 leucocytes. Parasite densities were estimated by assuming a count of 8,000 white blood cells per microliter of blood. Placental smears were
treated and counted the same way. Pigment in placental smears was scored on a 1-4+ scale that reflected the proportion of macrophages with pigment (1+: ≤ 10%; 2+: 10-25%; 3+: 26-50%; 4+: ≥ 50%). HIV testing involved the use of 2 rapid test methods: Serostrip HIV-1/2 (Saliva Diagnostic Systems Pte. Ltd., Singapore) and Capillus HIV-1/HIV-2 (Cambridge Diagnostics, Wicklow, Ireland). A Coulter counter (AcT.10: Coulter Corporation, Miami, USA) was used to assess the white blood cell (WBC) count for a subgroup of women, one month postpartum.

Definitions

Malaria was defined as the presence of asexual-stage parasites in thick smears, independent of the presence or absence of clinical signs or symptoms and independent of species. A high-density infection was defined as a parasitemia with a density of ≥ 5000 parasites per mm³. Chronic-active infection of the placenta was defined as parasitemia in the presence of moderate to heavy deposits of pigment (2+ or more) and past infection as the presence of pigment in the absence of parasitemia [12]. Because we were interested in the effect of HIV on malaria during pregnancy overall, maternal peripheral parasitemia at delivery and placental malaria were combined as evidence of active malaria infection at delivery. This is referred to as malaria at delivery in the analyses. Documented fever was an axillary temperature of ≥ 37.5 °C at the time of interview. Clinical malaria was defined as a history of fever (within the last week in third trimester or the last two weeks at the time of delivery) or documented fever in the presence of parasitemia (any density). HIV seropositivity of women was defined as a reactive result on both rapid tests; women not reactive by the Serostrip HIV-1/2 were considered HIV-seronegative. In case of an inconclusive result, a Western blot test was performed. The median age (21 years) was used to define young maternal age (< 21 years). An uncomplicated pregnancy was defined as a pregnancy without evidence of multiple gestation, hypertension, pre-eclampsia, polyhydramnios, an abnormal presentation of the fetus, a history of caesarian section, haemorrhage or repeated abortions (> 2). The absence of electrical supply to the house was considered as low socioeconomic status (SES) [13].
Analysis and statistical methods

Differences in means were compared using the Student $t$ test. The Mann-Whitney U test was used for nonparametric comparison of 2 groups. Differences in proportions were analyzed using the chi-square test or Fisher exact test when appropriate. Risk ratios (RR) were used to calculate gravidity specific attributable fractions (attributable fraction $[AF] = \frac{(RR\ -\ 1)}{RR}\times100$) \[14\].

Poisson regression was used to examine gravidity as a risk factor for malaria in HIV-seropositive and HIV-seronegative women in the third trimester and at delivery in multivariable analysis. Gravidity was grouped as primigravidae (G1), secundigravidae (G2), and multigravidae with 3 or more pregnancies (G3+) as reference group. Age was dichotomized at the median age (21 years). Other variables adjusted for included tribe (belonging to the Luo versus non Luo tribe), socioeconomic status as indicated by the presence of electricity in the house, location of residence (peri-urban versus urban location), and the use of SP in pregnancy.

The statistical programs SPSS (SPSS for Windows 9.0, SPSS Inc. Chicago, Illinois) and SAS (SAS system for Windows, version 6.12, SAS Inc. Cary, NC) were used for analyses. For all statistical tests, a two-sided $P$ value $< 0.05$ was considered significant.

Results

Characteristics of women in the third trimester and at delivery

Between June 1996 and March 1999, 5,211 women in their third trimester of pregnancy were interviewed. Forty three women had two consecutive pregnancies during the three year study period; only the first pregnancy was included. Fifty three women with an indeterminate HIV status, and 22 women with no malaria smear result were excluded; the remaining 5,093 women contributed to the analysis of the relationship between malaria and HIV in the third trimester. Of these women, 2,539 (49.9%) delivered in the hospital during the study period; 37 (1.5%) were excluded because no peripheral or placental smear was obtained at delivery, leaving 2502
women in the analysis of data at delivery. Compared to the 2,502 women included in the analysis, women who were not included were significantly older, were more likely to be multigravidae, had less years of education, had a lower socio-economic status and were more likely to live in a peri-urban compared to an urban location (Table 1).

The malaria prevalence in the third trimester was 20.1%, and 21.9% at delivery (15.2% maternal peripheral parasitemia at the time of delivery and 19.0% placental malaria). The overall HIV prevalence among women seen in third trimester was 24.9%; among women seen at delivery the HIV prevalence was 24.5%. The proportion of women with HIV infection among G1, G2 and G3+ women in the third trimester was 22.3%, 29.2% and 25.0% respectively, and this was similar to those delivering in the hospital (21.5%, 27.6% and 26.7% respectively). HIV-seropositive women were more likely to be older and multigravidae than HIV-seronegative women (Table 1).

**HIV and malaria in pregnancy**

Malaria parasitemia in the third trimester was more common in HIV-seropositive women compared with HIV-seronegative women (29.1% versus 17.1%, risk ratio [RR] 1.70, 95% confidence interval [CI] 1.52-1.90, *P* < 0.001); a similar pattern was seen at delivery (30.1% versus 19.3%, RR 1.56, 95% CI 1.34-1.81, *P* < 0.001). This difference in malaria infection rates was most pronounced in multigravidae (Figure 1). Among the HIV-seronegative women, a typical pregnancy specific pattern of malaria risk was observed, with G1 being more at risk than G2, who in turn were at an increased risk compared with the G3+ women. Among HIV-seropositive women, the expected trend of decreasing risk with increasing pregnancy number was less evident. A similar pattern was seen with peripheral parasitemia at delivery, with placental malaria and with the combination of these 2 (data not shown). Calculation of the attributable fraction showed that approximately one third of the malaria infections in HIV-seropositive G1 (37.5% in the third trimester and 31.5% at delivery), more than one third of the infections in G2 (42.9% and 38.7%, respectively) and more than half of the infections in HIV-
seropositive G3+ women (52.2% and 51.5%, respectively) could be attributed to concurrent HIV infection.

HIV-seropositive women were more likely to have higher parasite densities in the third trimester than HIV-seronegative women (Table 2). Chronic-active infections of the placenta were also significantly more frequent in HIV-seropositive women, but the prevalence of past placental infections was similar (1.8% in HIV-seropositive versus 1.6% in HIV-seronegative women). To exclude an effect of decreased white blood cells (WBC) in HIV-seropositive women on the estimation of parasite densities, we compared the WBC in a subgroup of women, for whom WBC counts one month post partum were available. No significant difference was detected between 297 HIV-seropositive and 122 HIV-seronegative women (geometric mean 6,694 WBC/microliter and 6,855 WBC/microliter respectively, t-test \( P = 0.4 \)).

HIV-seropositive women had more clinical malaria than HIV-seronegative women (Figure 2). Hospitalization during pregnancy was reported by 159 women, and was more frequent among HIV-seropositive women (4.3%) compared with HIV-seronegative women (2.7%, RR 1.59, 95% CI 1.16-2.20, \( P = 0.005 \)). Malaria was reported as the most common reason for admission during pregnancy (39.6%), but among hospitalized women HIV-seropositive women were not more likely to have a malaria diagnosis than HIV-seronegative women (34.5% versus 42.3%, RR 0.82, 95% CI 0.53-1.25, \( P = 0.4 \)).

Use of medication for fever or malaria in pregnancy was common: 43.8% of the study population reported use in the third trimester and 19.2% in the 2 weeks before delivery. HIV-seropositive women reported a higher use of antimalarials (SP, chloroquine, or quinine) in the third trimester (21.7%) than HIV-seronegative women (18.8%, RR 1.16, 95% CI 1.02-1.31, \( P = 0.02 \)). No difference was seen in the use of antipyretics (Table 3). Antimalarial drug use in the third trimester was reported significantly more frequently by G3+ women (27.0% in HIV-seropositive and 23.5% in HIV-seronegative women, compared with G2 women 20.8% and 16.6%, and G1 women 17.5% and 16.1% respectively). At delivery the differences in use of antimalarials and antipyretic between HIV-seropositive and HIV-seronegative women (Table 3)
or by gravidity group were not significant (use of antimalarials: G1 6.0%, G2 6.8% and G3+ 8.7%).

The use of SP was similar among HIV-seropositive and HIV-seronegative women (Table 3), and was associated with a protective effect against malaria in both HIV-seropositive and HIV-seronegative women in the third trimester and at delivery. Among the 81 HIV-seropositive women who reported the use of at least one dose of SP in the third trimester, 13.6% had a peripheral parasitemia, compared with 29.9% in the 1176 HIV-seropositive women who did not report the use of SP in the third trimester (RR 0.45, 95% CI 0.26-0.79, \(P = 0.001\)). Among the 201 HIV-seronegative women who reported the use of SP in the third trimester, 9.5% had a peripheral parasitemia, compared with 17.6% among the 3595 HIV-seronegative women who did not report the use of SP (RR 0.54, 95% CI 0.35-0.83, \(P = 0.002\)). At the time of delivery a similar protective effect of the reported use of SP, although not statistically significant, was seen (RR 0.23, 95% CI 0.04 - 1.54, \(P = 0.08\) (Fisher exact test), and RR 0.53, 95% CI 0.21-1.35, \(P = 0.2\), respectively).

To determine if the effect of gravidity on malaria differed by HIV status when adjusted for potentially confounding variables, we used a multivariate model, stratified by HIV status (Table 4). In HIV-seronegative women, G1 women remained at an increased risk for malaria compared with G3+ women. In HIV-seropositive women, the gravidity specific effect was no longer evident and G1 women were at similar risk compared with G3+ women. Age, tribe, and location of residence were the main confounders of the association between gravidity and malaria. Similar results were seen when grandaie 4+, or grandaie 5+ were taken as the reference group. Thus, HIV changed the epidemiology of malaria in pregnancy, increasing the risk for malaria in women of all gravidities.

Discussion
This study shows that in areas of Africa where malaria is endemic, the growing HIV epidemic has important consequences for malaria in pregnant women. This large hospital-based study was conducted in a setting with a mature HIV epidemic. We saw a marked increase of malaria in HIV-seropositive women in the third trimester and at delivery. Parasite densities were higher in HIV-infected women, who were more likely to experience clinical illness associated with parasitemia and to report self-medication with antimalarials. Between 30% to 50% of the malaria infections in HIV-seropositive pregnant women in this study population could be attributed to HIV. Multigravidae women contributed relatively more to the increase in malaria in HIV-seropositive women, with a doubled risk on malaria compared with HIV-seronegative women, and a prevalence of malaria similar to HIV-seronegative primigravidae. Additionally we observed that the use of SP was associated with a reduced prevalence of malaria in both HIV-seropositive and HIV-seronegative women.

Our findings are consistent with previous reports of an increase in malaria prevalence and parasite densities in HIV-seropositive pregnant women [6-8]. In the three previous studies, the number of HIV-seropositive women was approximately 160 per study, the numbers of HIV-seropositive primigravidae were small, and as a consequence the confidence intervals associated with the estimate were large. One of these studies was done in the early stage of the HIV epidemic when the prevalence of HIV was low, and this may have affected the results; no increased risk of parasite prevalence was seen in HIV-seropositive primigravidae, but parasite densities in this group were significantly higher compared to HIV-seronegative women [6]. Consistent with a previous study in Kisumu, we found a significant increase in prevalence of malaria in all gravidity groups, in particular also in primigravidae [8].

As suggested by others, the most likely explanation for the increased risk on malaria in HIV-seropositive women is that HIV infection limits pregnant women's ability to mount an effective immune response to malaria [6]. HIV may have a negative impact on several components of the immune system which have been explored to explain the pregnancy-specific differences in malaria risk, including hormonal regulations, cellular and humoral responses, and cytokine
production [15-18]. For example, recent studies have highlighted the potential importance of local production of cytokines and the risk of placental malaria infection [18]. The cytokine interferon-γ (IFN-γ) responses, in particular, may play a critical role in protection against placental malaria [18], and these responses are impaired in HIV-seropositive pregnant women [19].

The lower risk of malaria in HIV-seronegative multigravidae is believed to be a function of both pregnancy specific immunity acquired over multiple pregnancies and non-pregnancy specific immunity which is acquired over a life time and is strongly correlated with age and cumulative exposure. This hypothesis is supported by the increasing magnitude of the effect of HIV with increasing gravidity seen in the current study. However, the enhanced risk of malaria in HIV-seropositive primigravidae, also suggests that other mechanisms may be important. These may include the pregnancy specific immuno-modulation, which may be stronger in HIV-seropositive primigravidae than in multigravidae (e.g because of higher cortisol levels) [16, 17], or may be related to the further impairment of age-related acquired immunity in HIV-seropositive women, unrelated to pregnancy [20].

Although environmental or behavioral factors may partly explain the difference in malaria between HIV-seropositive and HIV-seronegative women, in this study population HIV-seropositive women did not differ from HIV-seronegative women with regard to socio-economic status, place of residence, house characteristics (data not shown), or employment. The mean age of HIV-seropositive women was slightly older (22.3 vs 22.0 years, \( P=0.054 \)) and they were more likely to be multigravidae, but both these characteristics are generally associated with a decreased risk of malaria in pregnancy, and do not explain the direction and magnitude of the effect of HIV infection on malaria found in this study. This study population was a selected group of relatively healthy women, with a high proportion of G1 and G2 women (65.3% in the third trimester and 70.3% at delivery). Although this proportion is representative of the prenatal clinic population in this referral hospital, it is much higher than expected in the overall population of pregnant women (45%, Kenya demographic survey) [21]. They, however, do
illustrate the potentially large impact of HIV on malaria in pregnancy in this urban population; taking a pregnant population with 45% G1 and G2 women and an HIV prevalence of 25%, the population attributable factor (PAF) of HIV on malaria in the third trimester and at delivery could be approximately 17%. In other words, 17% of the malaria infections in all pregnant women could be due to the effect of HIV-infection on the immunity against malaria. The magnitude of the risk reported is likely to be an underestimate, as women with advanced HIV infection were excluded, and multigravidae, the group most affected, were under represented.

The geometric means of WBC counts were similar in HIV-seropositive and HIV-seronegative women, making a systematic overestimation of parasite density in HIV-seropositive women unlikely. Although the WBC in this study was obtained 1 month postpartum, a previous study in a malarious area confirmed no difference in mean WBC between HIV-seropositive and HIV-seronegative women in a group of women seen in the third trimester and at 6 weeks postpartum [22]. A recent report from Uganda showed an increased risk of high density parasitemia and clinical malaria among HIV-infected adults, and this risk increased with decreasing CD4-cell counts [20]. In the subgroup of women for whom we had CD4 counts obtained 1 month post partum, no association was seen between CD4 count and parasite prevalence, density, or clinical malaria in HIV-seropositive women in third trimester or at delivery (data not shown).

The increased risk of malaria in HIV-infected pregnant women is likely to have considerable public health implications in areas where both diseases are prevalent. In this study population, dual infection with malaria and HIV is associated with a significant reduction of birth weight and maternal hemoglobin levels at delivery in both primi- and multigravidae (unpublished data). Kenya has recently adopted a policy of using intermittent protective treatment (IPT) with SP in pregnancy. The reported use of SP was beneficial in reducing malaria in both HIV-seropositive and HIV-seronegative women in our study. This is encouraging and consistent with a recent study in which monthly doses of SP in HIV-seropositive women showed substantial protection against malaria [8]. In addition, results of this study confirm that HIV-seropositive multigravidae
have a similar risk of malaria as HIV-seronegative primigravidae and indicate that in areas with a high prevalence of HIV, programs to control malaria in pregnancy should not be limited to primigravidae but should target women of all gravidities. In addition, it will be important that these control strategies to prevent or decrease the morbidity of malaria, like IPT with antimalarials and insecticide-impregnated bed nets, be evaluated in HIV-seropositive women to assess their benefit and appropriate deployment in this very vulnerable population.

Acknowledgments

We thank the project staff at the prenatal clinic service and the labor ward, counselors, and staff at the laboratories in the provincial hospital and in Kisian for contributing to this work. Our special thanks go to all the pregnant women who participated in this study. We appreciate the help of Dr. Kevin de Cock. We thank the director of the Kenya Medical Research Institute for his support and approval of publication of this paper.

References


Figure 1: Parasitemia in third trimester and at delivery, stratified by HIV status and gravidity, Kisumu, Kenya, June 1996-March 1999

HIV+: HIV-seropositive women; HIV-: HIV-seronegative women; G1: primigravidae; G2: secundigravidae; G3+: gravidae 3 or more; high density: malaria infection with a density ≥5000 parasites per microliter; RR: risk ratio. Numbers on top of the bars are percentages for total parasitemia (all densities).

* P < 0.05, comparing prevalence parasitemia (all densities) in HIV-seropositive and HIV-seronegative women (Chi-square test).
Figure 2: Clinical malaria in third trimester and at delivery, stratified by HIV status and gravidity, Kisumu, Kenya, June 1996-March 1999

HIV+: HIV-seropositive women; HIV-: HIV-seronegative women; G1: primigravidae; G2: secundigravidae; G3+: gravidae 3 or more; RR: risk ratio. Clinical malaria: parasitemia in the presence of a complaint of fever in the last week (third trimester), or the last 2 weeks (delivery) and/or documented fever. At delivery: maternal peripheral parasitemia and/or placental malaria.

*P < 0.05 (Chi-square test)
<table>
<thead>
<tr>
<th>Maternal characteristic</th>
<th>Third trimester</th>
<th>In analysis at delivery</th>
<th>Excluded</th>
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<tr>
<td></td>
<td>N=5093</td>
<td>HIV+ $^|$ &amp; HIV- $^|$</td>
<td>N=2502</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 20 years (%)</td>
<td>34.5</td>
<td>28.7</td>
<td>36.4$^|$</td>
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<td>20-29 years (%)</td>
<td>56.1</td>
<td>63.0</td>
<td>53.8</td>
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<td>≥30 years (%)</td>
<td>9.4</td>
<td>8.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Gravidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1 (%) $$</td>
<td>40.9</td>
<td>36.6</td>
<td>42.4$^|$</td>
</tr>
<tr>
<td>G2 (%)</td>
<td>24.4</td>
<td>28.6</td>
<td>23.0</td>
</tr>
<tr>
<td>G3+ (%)</td>
<td>34.7</td>
<td>34.8</td>
<td>34.6</td>
</tr>
<tr>
<td>&lt; 8 years of education (%)</td>
<td>36.4</td>
<td>35.7</td>
<td>36.6</td>
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<tr>
<td>Unemployed (%)</td>
<td>75.4</td>
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<td>75.8</td>
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<tr>
<td>Low SES (%) $$</td>
<td>79.3</td>
<td>79.0</td>
<td>79.4</td>
</tr>
<tr>
<td>Peri-urban (versus urban) residence (%)</td>
<td>21.0</td>
<td>19.1</td>
<td>21.5</td>
</tr>
<tr>
<td>Luo tribe (versus other tribe) (%)</td>
<td>79.2</td>
<td>84.6</td>
<td>77.4$^|$</td>
</tr>
</tbody>
</table>

*Excluded: excluded from the analysis at delivery, either because they did not deliver in the Provincial hospital, or because no malaria result was available at the time of delivery.

§ HIV: human immunodeficiency virus; HIV+: HIV-seropositive women; HIV-: HIV-seronegative women; G1: primigravidae; G2: secundigravidae; G3+: gravidae 3 or more; SES: socio-economic status.

$^\|$ P < 0.05 HIV-seropositive versus HIV-seronegative women (Chi-square test)
** P < 0.05 comparing women included versus women excluded at the time of delivery (Chi-square test).
Table 2: Parasite density in HIV-seropositive and HIV-seronegative women, stratified by gravidity, Kisumu, Kenya, June 1996-March 1999.*

<table>
<thead>
<tr>
<th>Density ≥ 5000 parasites/µl $</th>
<th>Third trimester parasitemia</th>
<th>Placental parasitemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+ $ (%)</td>
<td>HIV- $ (%)</td>
</tr>
<tr>
<td>G1</td>
<td>45 (26.0)</td>
<td>41 (10.8)</td>
</tr>
<tr>
<td>G2</td>
<td>22 (23.4)</td>
<td>12 (9.2)</td>
</tr>
<tr>
<td>G3+</td>
<td>13 (12.7)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>All</td>
<td>80 (21.7)</td>
<td>60 (9.2)</td>
</tr>
<tr>
<td>GMPD (parasites/µl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>1,463</td>
<td>684</td>
</tr>
<tr>
<td>G2</td>
<td>914</td>
<td>431</td>
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<tr>
<td>G3+</td>
<td>637</td>
<td>250</td>
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<tr>
<td>All</td>
<td>1,031</td>
<td>499</td>
</tr>
</tbody>
</table>

Chronic-active infection placenta

<table>
<thead>
<tr>
<th></th>
<th>HIV+ (%)</th>
<th>HIV- (%)</th>
<th>RR (95% CI)</th>
<th>$</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>36 (44.4)</td>
<td>45 (22.3)</td>
<td>2.00 (1.40-2.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>G2</td>
<td>10 (25.0)</td>
<td>7 (12.5)</td>
<td>2.00 (0.83-4.81)</td>
<td>0.2</td>
</tr>
<tr>
<td>G3+</td>
<td>5 (11.1)</td>
<td>3 (6.5)</td>
<td>1.70 (0.43-6.71)</td>
<td>0.5</td>
</tr>
<tr>
<td>All</td>
<td>51 (30.7)</td>
<td>55 (18.1)</td>
<td>1.70 (1.22-2.36)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*For this table only smears positive for malaria were used. Significant risk ratio’s are printed in bold.

§ HIV: human immunodeficiency virus; HIV+: HIV-seropositive women; HIV-: HIV-seronegative women; RR: risk ratio; CI: confidence interval; µl: micro liter; G1: primigravidae; G2: secundigravidae; G3+: gravidae 3 or more; GMPD: geometric mean parasite density.

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Table 3: Reported use of medication for fever in pregnancy and the association with malaria, stratified by HIV-status, Kisumu, Kenya, June 1996-March 1999

<table>
<thead>
<tr>
<th></th>
<th>Reported in third trimester *</th>
<th>Reported for 2 weeks preceding delivery *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(HIV+: n=1257; HIV-: n=3796 §)</td>
<td>(HIV+: n=603; HIV-: n=1873)</td>
</tr>
<tr>
<td></td>
<td>% with characteristic (n)</td>
<td>% parasitemic (n)</td>
</tr>
<tr>
<td>SP use §</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-seropositive women</td>
<td>6.4 (81)</td>
<td>13.6 (11)</td>
</tr>
<tr>
<td>HIV-seronegative women</td>
<td>5.3 (201)</td>
<td>9.5 (19)</td>
</tr>
<tr>
<td>Chloroquine (CQ) use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-seropositive women</td>
<td>14.5 (182)</td>
<td>25.8 (47)</td>
</tr>
<tr>
<td>HIV-seronegative women</td>
<td>12.8 (484)</td>
<td>14.5 (70)</td>
</tr>
<tr>
<td>Antipyretic use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-seropositive women</td>
<td>25.5 (320)</td>
<td>26.3 (84)</td>
</tr>
<tr>
<td>HIV-seronegative women</td>
<td>23.8 (902)</td>
<td>21.6 (195)</td>
</tr>
<tr>
<td>No use of SP, CQ or Antipyretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-seropositive women</td>
<td>52.7 (662)†</td>
<td>33.1 (219)</td>
</tr>
<tr>
<td>HIV-seronegative women</td>
<td>57.4 (2180)</td>
<td>16.6 (362)</td>
</tr>
</tbody>
</table>

*In the third trimester, drug use was reported during pregnancy so far, 42 missing values. At the time of delivery, drug use was reported for the two weeks preceding delivery, 26 missing values. Malaria at delivery: any parasitemia (maternal peripheral parasitemia and/or placental malaria). Significant risk ratios are printed in bold.
§HIV+: HIV-seropositive women; HIV-: HIV-seronegative women; RR: Risk ratio; CI: confidence interval; SP: sulfadoxine-pyrimethamine.

†P < 0.05 (Chi-square test)
Table 4: Crude and adjusted estimates of the association between gravidity and malaria by HIV status in the third trimester and at delivery, Kisumu, Kenya, June 1996-March 1999*

<table>
<thead>
<tr>
<th>Gravidity</th>
<th>HIV-seropositive women</th>
<th>HIV-seronegative women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Third trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Malaria (%)</td>
</tr>
<tr>
<td>G1</td>
<td>464</td>
<td>173 (37.3)</td>
</tr>
<tr>
<td>G2</td>
<td>363</td>
<td>94 (25.9)</td>
</tr>
<tr>
<td>G3+</td>
<td>442</td>
<td>102 (23.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>n</td>
<td>Malaria (%)</td>
</tr>
<tr>
<td>G1</td>
<td>254</td>
<td>93 (36.6)</td>
</tr>
<tr>
<td>G2</td>
<td>160</td>
<td>43 (26.9)</td>
</tr>
<tr>
<td>G3+</td>
<td>198</td>
<td>48 (24.2)</td>
</tr>
</tbody>
</table>

* Significant risk ratios are printed in bold.

§ RR: risk ratio; CI: confidence interval; G1: primigravidae; G2: secundigravidae; G3+: gravidae 3 or more.

¶ Adjustment for age, tribe, socio-economic status, location of residence, and the use of sulfadoxine-pyrimethamine in pregnancy.

**P = 0.05
Figure 1

![Bar chart showing malaria parasitemia percentages in third trimester and delivery (placenta) for HIV+ and HIV- individuals with low and high density.](image)

- **Third trimester**
  - HIV+, low density: 37.3%
  - HIV+, high density: 23.4%
  - HIV-, low density: 25.9%
  - HIV-, high density: 14.8%

- **Delivery (placenta)**
  - HIV+, low density: 32.4%
  - HIV+, high density: 22.0%
  - HIV-, low density: 25.8%
  - HIV-, high density: 13.5%

Number of participants:
- G1: 464
- G2: 1621
- G3+: 363
- G3+: 880
- G1: 442
- G2: 1323
- G1: 250
- G2: 916
- G1: 155
- G2: 415
- G1: 194
- G2: 538

Risk ratios:
- HIV+ in third trimester: RR 1.60*
- HIV+ in delivery (placenta): RR 1.47*
- HIV- in third trimester: RR 1.75*
- HIV- in delivery (placenta): RR 1.91*
- HIV- in third trimester: RR 2.09*
- HIV- in delivery (placenta): RR 2.73*
Figure 2

Delivery

Third trimester

Gravidaity

Clinical malaria (%)

HIV+ women □ HIV- women □