HIV infection and malaria in pregnancy in western Kenya. Their interaction and effects on maternal and infant health
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Submitted
The effect of dual infection with HIV and malaria on pregnancy outcome in western Kenya

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Running Head: HIV, Malaria, and pregnancy outcome in western Kenya

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Objective: To determine the effect of dual infection with HIV and malaria on birth outcome and maternal anaemia among women delivering at a large public hospital in Kisumu, western Kenya.

Subjects and methods: Data on obstetrical and neonatal characteristics, maternal and placental parasitaemia, and postpartum haemoglobin (Hb) were collected among all women enrolled in a cohort study of the interaction between malaria and HIV during pregnancy.

Results: Between 1996-1999 data were available from 2466 singleton deliveries. The maternal HIV seroprevalence was 24.3%, and at delivery 22.0% of the women had evidence of malaria. Low birthweight (LBW), preterm delivery (PTD), intrauterine growth retardation (IUGR) and maternal anaemia (Hb<8 g/dl) occurred in 4.6%, 6.7%, 9.8% and 13.8% of deliveries respectively. Maternal HIV, in the absence of malaria, was associated with a 99 g (95% CI 52-145) reduction in mean birthweight among all gravidae. Malaria was associated with both IUGR and PTD, resulting in a reduction in mean (95% CI) birthweight of 145g (82-209) among HIV-seronegative and 206g (115-298) among HIV-seropositive primigravidae, but not among multigravidae. Both HIV and malaria were significant risk factors for postpartum maternal anaemia, and HIV-seropositive women with malaria were twice as likely to have Hb < 8g/dl than HIV-seronegative women with or without malaria.

Conclusion: Women with dual infection are at a particular risk of adverse birth outcome. In areas with moderate or high prevalence of HIV and malaria, all pregnant women should be the focus for malaria and anaemia control efforts to improve birth outcomes.

Keywords: Low birth weight, preterm delivery, intrauterine growth retardation, HIV, malaria, Kenya.
Introduction

Malaria during pregnancy is a major problem in sub-Saharan Africa, affecting an estimated 24 million pregnant women each year [1,2]. In malaria endemic areas *Plasmodium falciparum* parasitaemia during pregnancy is associated with anaemia in pregnant women, and low birthweight (LBW) resulting from premature delivery and intrauterine growth retardation [3-5], and LBW is an important risk factors for early infant mortality and morbidity [6].

During the past two decades, HIV/AIDS has emerged as a major problem in many malaria-endemic areas of sub-Saharan Africa where an estimated 28 million people are infected with HIV [7]. Africa south of the Sahara accounts for over two-thirds of the world’s 40 million HIV-infected persons, and 80% of the world’s HIV-infected women [7], with HIV prevalence as high as 25-45% among pregnant women [7-14]. Given the wide geographical overlap between HIV and malaria, the epidemic of HIV/AIDS in areas where *P. falciparum* is endemic has generated serious concern about potential interactions between the two infections [9,11,13,14,15]. Studies among pregnant women in sub-Saharan Africa have shown that HIV-infected women, particularly multigravidae are more likely to be infected with *P. falciparum*, and to have higher parasite densities than HIV uninfected women [9,11,13]. Thus, HIV infection seems to alter the well established parity-specific pattern of malaria susceptibility in areas of stable malaria transmission, where in the absence of HIV, primigravidae and, to a lesser extent, secundigravidae are more affected than are other parities [1,3].

Although it is now well established that HIV-infected pregnant women are more susceptible to malaria, little is known of the adverse consequences of dual infection with maternal HIV and malaria on pregnancy outcome. We report here the effects of dual infections on infant outcomes, including their effect on the two major etiological pathways of
LBW: shortened gestation [preterm delivery (PTD)] and intrauterine growth retardation (IUGR) [i.e., small for gestational age (SGA)] [17]. Because maternal malaria and HIV infections are also associated with an increase in severity of anaemia, a known risk factor for maternal death and poor infant outcomes [18-21], we also report on the effect of dual infections on maternal anaemia at delivery.

Subjects and methods

Study site

This study was conducted at the Nyanza Provincial General Hospital (NPGH) in Kisumu, a city with a population of approximately 300 000 people, located on the shores of Lake Victoria. Malaria transmission is perennial and *P. falciparum* accounts for 98% of the malaria cases, the remaining 2.0% being caused by *P. malariae* and *P. ovale*. Chloroquine resistance is widespread with 75-80% of *P. falciparum* strains showing RII/RIII resistance [22]. NPGH is a 400-bed government referral hospital providing health care mostly to the local low-income population. On average, about 100 pregnant women present each day to the antenatal care (ANC) clinic, 30 of whom do so for their first visit. As part of the ANC package for this hospital, women are tested for syphilis using the rapid plasma reagin (RPR) card test, (Becton Dickinson microbiological systems, Cockeysville, USA), and those seroreactive for syphilis are treated with 2.4mU intramuscular benzathine penicillin [23]. The study was completed before the introduction of intermittent protective treatment with sulfadoxine-pyrimethamine as the national policy for control of malaria in pregnancy [11].

Enrollment Procedures

Enrollment procedures have been described elsewhere [24]. 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 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, and body weight was measured. After the client received counseling about HIV, blood was obtained by finger prick for HIV testing, a malaria thick smear and haemoglobin levels. Post-test counseling, supportive counseling and haematinics were offered to all participating women, and women with symptomatic malaria were treated. All screened women were encouraged to deliver in NPGH. At delivery, blood was again obtained from the mother for a malaria smear and haemoglobin, and a placental blood smear was obtained. Within 24 hours of birth, infants were weighed on an electronic balance (Ohaus Florham Park, NJ, USA), and their gestational age was assessed by trained study assistants using the modified Dubowitz method [25].

**Ethical review**

The study protocol was approved by the institutional review boards of the Kenya Medical Research Institute (KEMRI), the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia (USA) and the Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands.

**Laboratory Procedures**

Peripheral and placental blood smears were stained with Giemsa and examined for malaria parasites. A thick smear was considered negative if 100 microscopic fields revealed no parasites. Haemoglobin was measured using Hemocue® (Mission Viejo, CA, USA.). HIV testing involved two rapid tests: an initial Serostrip HIV-1/2 (Saliva Diagnostic Systems Pte. Ltd, Singapore) and a confirmatory Capillus HIV-1/HIV-2
(Cambridge Diagnostics, Wicklow, Ireland Ltd) on samples that tested positive. Western blot was performed on discordant samples.

**Definitions**

An *uncomplicated pregnancy* was defined as a pregnancy without the presence of hypertension, pre-eclampsia, polyhydramnios, an abnormal presentation of the foetus, a history of a previous caesarean section, haemorrhage, or repeated spontaneous abortions (>2). Because we were interested in the overall effect of malaria in pregnancy, *malaria infection at delivery* was defined as any evidence of current malarial infection (post-delivery maternal peripheral parasitaemia or placental parasitaemia, either in the presence of asexual stages or malaria pigment), detected on a thick blood smear. Haemoglobin (Hb) < 11g/dl of blood and <8g/dl were considered *anaemia* and *moderate to severe anaemia*, respectively [26,27]. *HIV-seropositivity* was defined as a positive result on both rapid tests; women not reactive with the initial Serostrip HIV-1/2 test were considered *HIV-seronegative*. Women who were HIV-seronegative and had no malaria at delivery were considered to be *uninfected*. Women who were HIV-seronegative but had malaria at delivery were considered to be infected with *malaria-alone*. Women who were HIV-seropositive but had no malaria at delivery were considered to be infected with *HIV-alone*. Women were considered to have *dual infection* if they were HIV-seropositive and had malaria at delivery. Newborns were classified as *low birthweight (LBW)* if they weighed <2500g [28]. *Preterm delivery (PTD)* was defined as any delivery that occurred before 37 completed weeks of gestation. *Small for gestational age (SGA)* was defined as a sex-specific birthweight at or below the 10th percentile for weight-for-gestational age of an international reference population [29]. For the purpose of this analysis normal weight-for-gestational age were children with a birthweights >10th percentile.
of the weight-for-gestational age reference population. *Rainy season* included the months of April, May and June (long rains) and October and November (short rains).

**Data analysis and statistical methods**

Differences in means were compared using the Student *t* test, and differences in proportions were analyzed using the chi-square test. Risk ratios (RR) were computed with 95% confidence intervals (CI) to measure the strength of the associations. The relationship between malaria at delivery, maternal HIV infection and demographic and obstetric factors on adverse birth outcome (defined as a LBW, PTD or SGA infant, or moderate to severe maternal anaemia at delivery) were investigated by bivariate analysis, stratified by gravidity (primigravidae versus multigravidae). Adjusted risk ratios were computed using Poisson log-linear model of grouped data, with each person in the group assumed to have the same time at risk [30-33]; models were adjusted for maternal weight (< 25 percentile versus ≥25 percentile, kg), maternal age (< 20 versus ≥20 years), years of education (< 8 versus ≥8 years), ethnicity (Luo versus non Luo), season of delivery (rainy versus dry), hospitalization in current pregnancy, and gender of the child. The models for postpartum anaemia were also adjusted for type of delivery (caesarean section or assisted delivery versus normal delivery) and use of haematinics. The covariates were included in the models if they were significantly associated with any of the four outcomes measures in the bivariate analyses, or if they were known to be associated with these outcomes based on prior studies. Multiple linear model [34] was used to assess the effect of HIV, malaria, and dual infection on birth weight, gestational age and maternal haemoglobin. We assessed interaction between malaria and HIV in separate models, but no statistically significant interaction was evident. We then repeated the analyses using the infection categories: no infection, HIV-alone, malaria alone or dual infection. Analysis was done using EPI INFO 6.01 (Centers for Disease Control and
Prevention, Atlanta, GA, USA) and SAS (Version 6.12, SAS Institute, Cary, North Carolina, USA).

Results

Study population

Between June 1996 and March 1999, 5,168 women were screened of whom 75 (1.5%) did not have complete laboratory results. Of the remaining 5093 women, and consistent with patterns of home versus health facility delivery, 2539 (49.9%) delivered at the study hospital (Figure 1). Women with twins (36), and women without malaria result (37) were excluded from analysis (Figure 1).

Compared to women who were included in the analysis, those who were excluded (i.e., home delivery or incomplete laboratory data) were more likely to be older, to have < 8 years of education, to be married, to be multigravidae, to be of Luo ethnicity, to reside in the peri-urban rather than urban area of Kisumu, and to have moderate-to-severe anaemia in the third trimester. Prevalence of HIV, syphilis and malaria in the third trimester was similar between the two groups (data not shown).

Of the 2466 women included in the analysis, 1169 (47.4%) were primigravidae. Compared to multigravidae, primigravidae women were more likely to be younger [mean age, standard deviation (SD) 18.8 (2.5) versus 24.3 (4.7) years; P<0.001]. Among the 2466 women, 599 (24.3%) were HIV-seropositive and 543 (22.0%) had evidence of malaria infection at delivery. Malaria infection at delivery occurred in 179 of 599 HIV-seropositive women (29.9%) compared to 364 of 1867 HIV-seronegative women (19.5%) [risk ratio (RR), 1.5; 95% Confidence Interval (CI), 1.3-1.8; P < 0.001], and was more common among primigravidae in whom 323 out of 1169 (27.6%) had malaria at delivery compared to 220 out of 1297 (17.0%) among multigravidae (RR, 1.6; 95% CI, 1.4-1.9; P
Comparing women who had and who did have malaria at delivery, women who had malaria at delivery were more likely to have had malaria in the third trimester 45.1% (245 out of 543) versus 11.8% (227 out of 1923), (RR, 3.8; 95% CI, 3.3-4.5, P< 0.001).

Of the 34 stillbirths, 17 (1.1%) were recorded among 1503 women without HIV and malaria infection, 4 (1.0%) among 420 women infected with HIV-alone, 9 (2.5%) among 364 women with malaria-alone, and 4 (2.2%) among 179 women with dual infection. Compared to women without malaria, stillbirths were more common in women with malaria infection at delivery, irrespective of HIV status [1.1% (21 of 1923) versus 2.4% (13 of 543); P = 0.02]; stillbirth rates were similar in women with and without HIV infection regardless of malaria infection status [1.3% (8 of 599) versus 1.4% (26 of 1867); P = 1.00]. Because of the small numbers, all stillborn infants were removed from the further analysis, leaving 2432 live singleton infants with maternal HIV and malarial infection status available for analysis (Figure 1). Cigarette smoking, a well-known risk factor for low birthweight, was not common in this population (reported by less than 1% of the women) and was not included in the analysis. Characteristics of the women studied stratified by outcome at delivery are shown in Table 1. Third trimester anaemia, HIV infection, malaria at delivery and dual infection had the strongest association with an adverse birth outcome.

Birthweight:

Birthweight was recorded for 2431 infants (99.9%). The overall mean (SD) birthweight was 3235 g (450), and 113 of 2431 babies (4.6%) had LBW. An increase in LBW prevalence was seen among firstborns of mothers with HIV-alone, malaria-alone, or dual infection compared to those with neither infection (P = 0.09, 0.006 and <0.001, respectively) (Table 2). However, no difference was seen in prevalence of low
birthweight and maternal infection status among multigravidae ($P = 0.3$, $P = 0.4$, and $P = 1.0$, respectively). Women who had parasitaemia in the third trimester and also had malaria at delivery were at a higher risk of delivering a LBW baby compared to aperasitaemic women in the third trimester who had malaria at delivery [10.5% (25 out of 239) versus 5.5% (16 out of 291), RR, 1.9; 95% C, 1.0-3.5; $P = 0.04$]. In a Poisson model among the primigravidae, malaria-alone and dual infection were associated with a 2-fold and a 3-fold increased risk of LBW ($P = 0.008$ and $P < 0.001$) respectively, with no significant effect seen in women with similar status among the multigravidae ($P = 0.7$ for both groups; Table 3).

In a linear model, maternal HIV infection was associated with a 99 g (95% CI, 52-145) reduction in mean birthweight among all gravidae ($P < 0.001$). Among primigravidae, the mean (SD) birthweight of infants of uninfected women was 3186 g (416) (Figure 2). After adjusting for other covariates in the linear model, this mean (95% CI) birthweight was 40g (-32 to 112; $P = 0.3$) lower in primigravidae women with HIV-alone, 145 g (82-209; $P = 0.001$) lower in primigravidae women with malaria-alone, and 206 g (115-298; $P = 0.001$) lower in primigravidae with dual infection. The mean (SD) birthweight of infants of uninfected multigravidae women was 3373g (447). Maternal HIV-alone and dual infection lowered this mean birthweight by 138g (78-199) and 161g (63-259), respectively ($P < 0.001$ for each), but malaria infection alone had no effect (8g, 95% CI -71 to 88; $P = 0.80$).

Gestational age:

Gestational age was determined for 2397 infants (98.6%). The mean (SD) gestational age was 38.6 weeks (1.3 weeks) and 160 infants (6.7%) were PTD. Higher rates of preterm
delivery were seen with maternal malaria infection \( (P = 0.027) \) or dual HIV/malaria infection \( (P < 0.0001) \), but only in the primigravidae (Table 2).

In a Poisson model, primigravidae women infected with malaria-alone had increased risk of PTD when compared with uninfected women, but this risk was only marginally significant \( (P = 0.06) \), while dual-infection in the same group increased the risk of PTD by 3-fold \( (P < 0.001) \); none of the infections had any effect on PTD among the multigravidae (HIV-alone \( P = 0.5 \), malaria-alone \( P = 0.3 \) and dual-infection \( P = 0.2 \), Table 3).

The mean (SD) gestational age of infants of uninfected primigravidae women was 38.6 (1.3) weeks. In a linear model, malaria and dual infection had a minimal, but significant effect on mean gestational age among primigravidae, but not among multigravidae (data not shown).

**Small for gestational age:**

Overall, the prevalence of small-for-gestational age (SGA) was 9.8% (236 out of 2397) and like PTD, the prevalence of SGA was higher among primigravidae with malaria-alone \( (P = 0.008) \) or primigravidae and multigravidae with dual-infection \( (P = 0.02) \), and \( (P = 0.01) \) respectively (Table 2). Women who had parasitaemia in the third trimester and also at delivery were at higher risk of delivery of SGA infant compared to aparasitaemic women in the third trimester who had malaria at delivery [18.2% (43 out of 236) \textit{versus} 11.4% (33 out of 290), RR, 1.6; 95% CI, 1.1-2.4; \( P = 0.03 \)], but no effect was observed on prematurity [8.5% (20 out of 236) \textit{versus} 9.0% (26 out of 290), RR, 0.9; 95% CI, 0.5-1.7; \( P=0.8 \)]. In a Poisson model, primigravidae women infected with malaria-alone \( (P = 0.01) \) or dual infection \( (P = 0.03) \) were at increased risk of delivery of a SGA infant when compared with uninfected women (Table 3). Multigravidae with dual infection had a borderline significant increase in the risk of SGA \( (P = 0.06) \).
Maternal anaemia:

A haemoglobin was available for 2173 women (89.4%). The mean (SD) hemoglobin was 10.5 (2.4) g/dl and 1243 out of 2173 women (57.2%) had anaemia (Hb < 11 g/dl), and 300 women (13.8%) had moderate to severe anaemia (Hb < 8 g/dl). A higher prevalence of moderate to severe anaemia was seen among primigravidae with HIV-alone (P = 0.008) and in both gravidae with dual infection (P = 0.003 for primigravidae) and (P < 0.001 for multigravidae) (Table 2). In a Poisson model, primigravidae with HIV-alone had a 1.8-fold increased risk of postpartum moderate to severe anaemia (P = 0.01; Table 3), and this risk was more than 2-fold among dually infected primigravidae or multigravidae (P = 0.002 and P < 0.001 respectively).

Mean hemoglobin levels, stratified by maternal infection status and gravidity are shown in Figure 3. The mean (SD) haemoglobin of uninfected primigravidae was 10.8 (2.4) g/dl. After adjusting for other covariates in the multiple linear model, this mean (95% CI) haemoglobin was 0.9 (0.4-1.3) g/dl lower in primigravidae women with HIV-alone (P < 0.001), 0.8 (0.4-1.2) g/dl lower in primigravidae women with malaria-alone (P < 0.001), and 1.5 (0.9-2.0) g/dl lower in women with dual infection (P < 0.001) (Figure 3). Among uninfected multigravidae women, the mean (SD) haemoglobin was 10.7 (2.4) g/dl. Multiple linear model among multigravidae women, showed that infection with HIV-alone lowered the mean (95% CI) Hb levels by 0.4 (0.05-0.7) g/dl (P = 0.03), but malaria-alone had no effect, mean reduction 0.4 (0.0-0.8) (P = 0.1). Dual infection significantly lowered the mean (95% CI) Hb by 1.3 (0.7-1.8) g/dl (P< 0.001) (Figure 3).

Adverse birth outcome in relation to single versus dual infection

Compared to primigravidae women infected with HIV-alone, those with dual infection had a marginally increased risk of delivery of LBW baby (P = 0.06) and
significantly increased the risk of PTD \( P = 0.03 \); and, anemia \( P = 0.002 \) among the multigravidae (Table 3). Similarly, dual infection increased the risk of maternal anaemia among the primigravidae \( P = 0.05 \) and multigravidae \( P = 0.03 \) over and above the risk due to infection with malaria-alone (Table 3).

**Discussion**

Compared to uninfected women (with no malaria or HIV), maternal HIV infection was associated with a 99 g reduction in mean birthweight, which is consistent with findings of other studies in the region [35,36]. This effect was greatest among the multigravidae (138 g), although this reduction did not translate into a greater risk of LBW. Neither PTD nor SGA was associated with HIV-infection alone, a finding consistent with a Ugandan study among asymptomatic HIV-seropositive women [35], but in contrast to findings from Kinshasa, Zaire [37]. The latter study included women with symptomatic HIV-infection and a significantly higher prevalence of PTD and LBW was reported among infants in that study [37].

Infection with HIV-alone nearly doubled the risk of postpartum moderate to severe anaemia in primigravidae, and was associated with a reduction in mean haemoglobin levels in multigravidae, and is consistent with a previous report [21]. Postpartum haemorrhage has been found to be associated with HIV infection [38] and could have lowered the postpartum Hb levels in our study, however, this pregnancy outcome was reported in less than 1% of our study population and could not be further evaluated in our study. In addition, time between delivery and taking blood for Hb could affect the maternal postpartum Hb levels due to volume redistribution resulting from the effects of labour. However, blood sample for Hb estimation in our study was taken soon after delivery in a consistent manner for all the women in the four groups. Thus the
observed trend in Figure 3 is likely a true trend reflecting the direct effect of HIV [39] and/or its co-infection with malaria on postpartum anaemia.

As expected, maternal malaria infection identified at delivery was associated with a reduction in mean birth weight resulting from a combination of reduced gestational age and an increased risk of intrauterine growth retardation among the primigravidae [40]. Women who had parasitaemia during the third trimester and also had malaria at delivery had increased risk of both LBW and SGA, when compared to women with malaria at delivery but had no detectable parasitaemia in third trimester. This may reflect the effect of chronic malaria infection on foetal growth.

When compared to uninfected women, dual infection among primigravidae was associated with a 3-fold increased risk of LBW, almost a 3-fold increased risk of prematurity, and about a 2-fold increased risk of SGA. In addition, dual infection more than doubled the risk of moderate to severe anaemia (Hb < 8 g/dl) in both primigravidae and multigravidae. Comparison of dually infected women with women infected with HIV-alone showed that the risks of LBW and prematurity among primigravidae, and moderate to severe anaemia among the multigravidae were exacerbated by co-existent malaria. Similarly, when compared to women infected with malaria-alone, dual infection substantially increased the risk of moderate to severe anaemia over and above that among primigravidae and multigravidae women infected with malaria-alone. We are currently also investigating whether children born from women dually infected with HIV and placental malaria are more likely to be infected with HIV, due to increased transmission of HIV from mother to infant in the presence of placental infections with P. falciparum as was postulated in a study from Malawi [41].

Our study has several limitations and may not be fully generalizable to other populations. In our study population, only 4.6% of the infants had LBW, compared to
15.0% reported by a previous study from the same hospital [42]. This is likely to have resulted from the different entry criteria used in the current study: as opposed to the previous study that included all women attending delivery at our study hospital, women in the current study were eligible for screening only if they had no known underlying disease and, had attained a gestational age of 32 weeks or more, and had an uncomplicated pregnancy. Therefore, our study sample is not representative of the overall ANC population in this hospital and represents a selection of otherwise “healthy” women. Because of our study design, we only collected data on women who had met the inclusion criteria, and no pre-enrollment data was documented at the recruitment stage on women who were not eligible for enrollment. Because we only included women with a gestational age $\geq$ 32 weeks, the effects of HIV and malaria infection on early events of pregnancy outcome, such as abortions, and very premature delivery could not be evaluated. In addition, the number of perinatal deaths in our study was small (2.0% $n = 2466$), likely due to the same reasons noted above.

Our study demonstrates that women with dual infection are at a particular risk of adverse birth outcome. In areas with moderate or high prevalence of HIV and malaria, all pregnant women should be the focus for malaria control efforts to improve birth outcomes. It is important to assess if treatments of anaemia that have proven to be beneficial in HIV-seronegative pregnant women offer the same benefits in HIV-seropositive women.
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References


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Figure 1. Flowchart of inclusion and exclusion of study women for analysis

5168
Screened at ANC

75
No lab results, excluded

5093
Had HIV results

2554
Delivered elsewhere, excluded

2539
Delivered at NPGH

36
Multiple deliveries, excluded

37
No PM results, excluded

2466
Singletons

34
Stillbirths, excluded

2432
Live singletons

Abbreviations:
ANC: Antenatal Care Clinic
HIV: human immunodeficiency virus
PM: Placental malaria
NPGH: Nyanza Provincial General Hospital
Figure 2. The effect of single and dual infections with HIV and malaria on mean birth weight adjusted potential confounding covariates* by gravidity, Kisumu, western Kenya, June 1996-March, 1999

*Adjusted for maternal weight (< 25 percentile versus ≥ 25 percentile, kg), maternal age (< 20 vs ≥ 20 years), years of education (< 8 vs ≥ 8 years), ethnicity (Luo vs non Luo), season of delivery (rainy vs dry), a hospitalization in pregnancy and gender of the child and Hb at delivery.

Error bars indicate the 95% confidence interval for mean estimates.

Abbreviation: HIV: human immunodeficiency virus
Figure 3. The effect of single and dual infections with HIV and malaria on mean haemoglobin adjusted potential confounding covariates 
by gravidity. Kisumu.

<table>
<thead>
<tr>
<th>Maternal status</th>
<th>No infection</th>
<th>HIV-alone</th>
<th>Malaria-alone</th>
<th>Dual infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primigravidae</td>
<td>□</td>
<td>×</td>
<td>△</td>
<td>□</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>△</td>
<td>□</td>
<td>×</td>
<td>△</td>
</tr>
</tbody>
</table>

*Adjusted for maternal weight (<25 percentile versus ≥25 percentile, kg), maternal age (<20 vs ≥20 years), years of education (<8 vs ≥8 years), ethnicity (Luo vs non Luo), season of delivery (rainy vs dry), a hospitalization in pregnancy, gender of the child, type of delivery (caesarean section or assisted delivery vs normal delivery) and use of haematinics.

Error bars indicate the 95% confidence interval for mean estimates.

Abbreviation: HIV: human immunodeficiency virus. Error bars indicate the 95% confidence interval for mean estimates.
Table 1. Characteristics of women, with a singleton delivery, with and without an adverse outcome at delivery, Provincial hospital, Kisumu, Kenya, June 1996-March 1999

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adverse event* (N=670)</th>
<th>No adverse event (N=1796)</th>
<th>Risk Ratio (95% confidence interval)</th>
<th>Total (N=2466)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No with factor %</td>
<td>No with factor %</td>
<td>Risk Ratio</td>
<td>No with factor %</td>
</tr>
<tr>
<td>Age &lt; 20 years</td>
<td>291 43.4</td>
<td>630 35.1 †</td>
<td>1.24 (1.11-1.38)</td>
<td>921 37.3</td>
</tr>
<tr>
<td>Primigravidae</td>
<td>358 53.4</td>
<td>811 45.2 †</td>
<td>1.18 (1.09-1.29)</td>
<td>1169 47.4</td>
</tr>
<tr>
<td>≥ 8 years of education</td>
<td>437 65.2</td>
<td>1247 69.4 †</td>
<td>0.94 (0.88-1.00)</td>
<td>1684 68.3</td>
</tr>
<tr>
<td>Unemployed</td>
<td>531 79.3</td>
<td>1348 75.1 †</td>
<td>1.06 (1.01-1.11)</td>
<td>1879 76.2</td>
</tr>
<tr>
<td>Married</td>
<td>497 74.2</td>
<td>1384 77.1</td>
<td>0.96 (0.91-1.01)</td>
<td>1881 76.3</td>
</tr>
<tr>
<td>Luo ethnicity</td>
<td>539 80.4</td>
<td>1368 76.2 †</td>
<td>1.06 (1.01-1.11)</td>
<td>1907 77.3</td>
</tr>
<tr>
<td>Urban residence</td>
<td>591 88.2</td>
<td>1551 86.4</td>
<td>1.02 (0.99-1.06)</td>
<td>2142 86.9</td>
</tr>
<tr>
<td>Syphilis (RPR)+ ‡</td>
<td>18 2.9</td>
<td>37 2.2</td>
<td>1.33 (0.76-2.32)</td>
<td>55 2.4</td>
</tr>
<tr>
<td>3 rd trimester malaria</td>
<td>162 24.2</td>
<td>310 17.3 †</td>
<td>1.40 (1.18-1.66)</td>
<td>472 19.1</td>
</tr>
<tr>
<td>Hb &lt; 8 g/dl 3 rd trimester ‡</td>
<td>169 25.5</td>
<td>192 10.8 †</td>
<td>2.36 (1.96-2.85)</td>
<td>361 14.8</td>
</tr>
<tr>
<td>HIV+</td>
<td>209 31.2</td>
<td>390 21.7 †</td>
<td>1.44 (1.25-1.66)</td>
<td>599 24.3</td>
</tr>
<tr>
<td>Malaria at delivery</td>
<td>200 29.9</td>
<td>343 19.1 †</td>
<td>1.56 (1.35-1.82)</td>
<td>543 22.0</td>
</tr>
<tr>
<td>Dual infection</td>
<td>81 12.1</td>
<td>98 5.5 †</td>
<td>2.22 (1.67-2.93)</td>
<td>179 7.3</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>631</td>
<td>94.2</td>
<td>1720</td>
<td>95.8</td>
</tr>
<tr>
<td>------------------</td>
<td>-----</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>

(unassisted)

† Breach or transverse presentation, assisted deliveries (forceps/vacuum extraction), caesarean sections, and intrapartum medical complications such as placental abruption, placenta previa and pre-eclampsia and postpartum haemorrhage (all combined) were uncommon, occurring less than 5%.

*Adverse outcome: Either a still birth, a premature, low birth weight infant, or small-for-gestational-age infant, or maternal moderate to severe anaemia at the time of delivery. For 269 women (10.9%) no haemoglobin was available at the time of delivery, for 2, 64 (2.6%) and 62 (2.5%) infants there was no information on low birth weight, small for gestational age or prematurity respectively.

‡ P < 0.05, comparing women with and without an adverse event at delivery

‡ Haemoglobin 3rd trimester missing for 28 women (1.1%), syphilis test result not available for 178 women

(7.2%)
Table 2. Prevalence of low birth weight (LBW), small for gestational age (SGA), preterm delivery (PTD) among infants and maternal anaemia at delivery by maternal status and gravidity, Kisumu, western Kenya, June 1996-March, 1999

<table>
<thead>
<tr>
<th>Infection</th>
<th>Low birth weight&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Preterm delivery&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Small for gestational age&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Hemoglobin &lt; 8 g/dl postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primigravidae</td>
<td>Multigravidae</td>
<td>Primigravidae</td>
<td>Multigravidae</td>
</tr>
<tr>
<td>Status</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>LBW</td>
<td>LBW</td>
<td>PTD</td>
<td>PTD</td>
</tr>
<tr>
<td>No infection</td>
<td>676</td>
<td>809</td>
<td>668</td>
<td>792</td>
</tr>
<tr>
<td>HIV-alone</td>
<td>160</td>
<td>256</td>
<td>158</td>
<td>253</td>
</tr>
<tr>
<td>Malaria-alone</td>
<td>226</td>
<td>129</td>
<td>225</td>
<td>129</td>
</tr>
<tr>
<td>Dual infection</td>
<td>91</td>
<td>84</td>
<td>88</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>1</sup>Low birthweight: a birthweight < 2500 g.

<sup>1</sup>Classified as any delivery that occurred before 37 completed weeks' gestation, using a standardized Ballard method [27].

<sup>1</sup>Defined as sex-specific birth weight at or below the 10<sup>th</sup> percentile weight-for-gestational age of an international reference group [31].

n: refers to number in each category.

HIV, human immunodeficiency virus.
Table 3. The effect of infection with HIV-alone, malaria at delivery alone and the dual infection on birth outcome (multivariable Poisson models*), Kisumu, western Kenya, June 1996-March, 1999

<table>
<thead>
<tr>
<th>Infection status</th>
<th>Low birth weight</th>
<th>Preterm delivery</th>
<th>Small for gestational age</th>
<th>Hb &lt; 8 g/dl post delivery†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primigravidae</td>
<td>Multigravidae</td>
<td>Primigravidae</td>
<td>Multigravidae</td>
</tr>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Uninfected</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>HIV-alone</td>
<td>1.7 (0.8-3.3)</td>
<td>1.4 (0.6-2.9)</td>
<td>1.2 (0.6-2.3)</td>
<td>1.2 (0.7-2.2)</td>
</tr>
<tr>
<td>Malaria-alone</td>
<td>2.2 (1.2-3.8)</td>
<td>0.8 (0.2-2.6)</td>
<td>1.7 (0.9-2.8)†</td>
<td>0.6 (0.2-1.5)</td>
</tr>
<tr>
<td>Dual-infection</td>
<td>3.1 (1.6-6.1)</td>
<td>1.2 (0.4-3.6)</td>
<td>2.9 (1.6-5.2)</td>
<td>0.4 (0.1-1.7)</td>
</tr>
<tr>
<td>P-value interaction §</td>
<td>0.8</td>
<td>0.9</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>HIV-alone</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Dual-infection</td>
<td>2.2 (0.9-4.9)†</td>
<td>0.9 (0.3-3.1)</td>
<td>2.3 (1.1-5.0)</td>
<td>0.3 (0.1-1.5)</td>
</tr>
<tr>
<td>Malaria-alone†</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Dual-infection</td>
<td>1.5 (0.7-3.0)</td>
<td>1.8 (0.4-8.4)</td>
<td>1.8 (0.9-3.4)</td>
<td>0.5 (0.1-3.5)</td>
</tr>
</tbody>
</table>

*All the four models for LBW (low birth weight); SGA (small for gestational age); PTD (preterm delivery) and anaemia at delivery [haemoglobin (Hb) < 8 g/dl] adjusted for maternal weight (< 25 percentile versus ≥ 25 percentile, kg), maternal age (< 20 vs ≥ 20 years), years of education (< 8 vs ≥ 8 years), ethnicity (Luo vs non Luo), season of delivery (rainy vs dry), a
hospitalization in pregnancy and gender of the child. \(^1\)Model for anaemia at delivery [haemoglobin (Hb) < 8 g/dl] also adjusted for type of delivery (caesarean section or assisted delivery vs normal delivery) and use of haematinics. Abbreviations: HIV, human immunodeficiency virus, \(^4\)malaria-alone refers to any evidence of current malarial infection (maternal peripheral parasitaemia or placental malaria); RR, adjusted risk ratio; CI, confidence interval. Bold-faced results were statistically significant (p<0.05). \(^5\)Borderline significant: P = 0.06. §None of the interaction terms between HIV and malaria at delivery were significant for any of the models.