

THE BURDEN OF CO-INFECTION WITH HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 AND MALARIA IN PREGNANT WOMEN IN SUB-SAHARAN AFRICA

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Abstract. In sub-Saharan Africa, human immunodeficiency virus (HIV) and malaria are among the leading causes of morbidity during pregnancy. We reviewed available information collected since the first report 15 years ago that HIV impaired the ability of pregnant women to control malaria parasitemia. Results from 11 studies showed that HIV-infected women experienced consistently more peripheral and placental malaria (summary relative risk = 1.58 and 1.66, respectively), higher parasite densities, and more febrile illnesses, severe anemia, and adverse birth outcomes than HIV-uninfected women, particularly in multigravidae. Thus, HIV alters the typical gravidity-specific pattern of malaria risk by shifting the burden from primarily primigravidae and secundigravidae to all pregnant women. The proportional increase of malaria during pregnancy attributable to HIV was estimated to be 5.5% and 18.8% for populations with HIV prevalences of 10% and 40%, respectively. Maternal malaria was associated with a two-fold higher HIV-1 viral concentrations. Three studies investigating whether placental malaria increased mother-to-child HIV-1 transmission showed conflicting results, possibly reflecting a complex balance between placental malarial immune responses and stimulation of HIV-1 viral replication. Further investigations of interactions between antiretroviral drugs, prophylaxis with cotrimoxazole, and antimalarial drugs in pregnant women are urgently needed. Although much has been learned in the past 15 years about the interaction between malaria and HIV-1 during pregnancy, many issues still require further information to improve our understanding. There is a clear need to strengthen the deployment of existing malaria and HIV prevention and intervention measures for pregnant women.

INTRODUCTION

Recent estimates suggest that in malaria-endemic sub-Saharan Africa, each year approximately 25 million women become pregnant and are at increased risk of infection with *Plasmodium falciparum*, particularly in their first two pregnancies.¹ This results in maternal anemia and reduced neonatal birth weight due to preterm delivery and intrauterine growth retardation (IUGR).^{2,3} The vast majority of these infections are low-grade, frequently sub-patent,^{4,5} and in most women are asymptomatic and therefore undetected and untreated.⁶

The effects of human immunodeficiency virus (HIV) on maternal health have been superimposed on that of malaria in the malaria-endemic regions. In sub-Saharan Africa, 55% of the HIV-infected adults are reproductive age women,⁷ accounting for 80% of the world's HIV-infected women.⁸ Studies in pregnant women suggest that in several parts of Africa the prevalence of HIV now exceeds 25%.^{7,8} Without intervention, it is estimated that ~25–45% of the HIV-infected women will transmit infection to their children. In ~15–30%, this occurs in the intrauterine and intrapartum period and the remainder is due to breastfeeding.⁷

There are several points in the immune system where malaria and HIV can interact.^{9,10} Although there is now accumulating evidence for an effect of HIV-1 infection in adults and children on malaria,^{11–15} initial studies conducted among children and adults failed to show a consistent pattern of a biologic or clinical interaction, with the exception of studies in pregnant women.^{16–19} The first clear indication of an effect of HIV on malaria was reported by Steketee and others who found in 1987–1989 that HIV in multigravid women appeared to impair a pregnant woman's ability to control malaria parasitemia, resulting in more frequent and higher density par-

asitemia than in HIV-uninfected pregnant women.²⁰ Because of the high prevalence of HIV and malaria in sub-Saharan Africa, co-infections are common. This has important implications, since both HIV and malaria are among the leading causes of morbidity in pregnancy in Africa, and even modest effects of one infection on the other could lead to a substantial negative impact on the health of pregnant women and their newborns.^{12,18} Here we review the available information collected in the 15-year period since the study by Steketee and others,²⁰ discuss the effects of HIV and malaria on each other, and suggest programmatic implications.

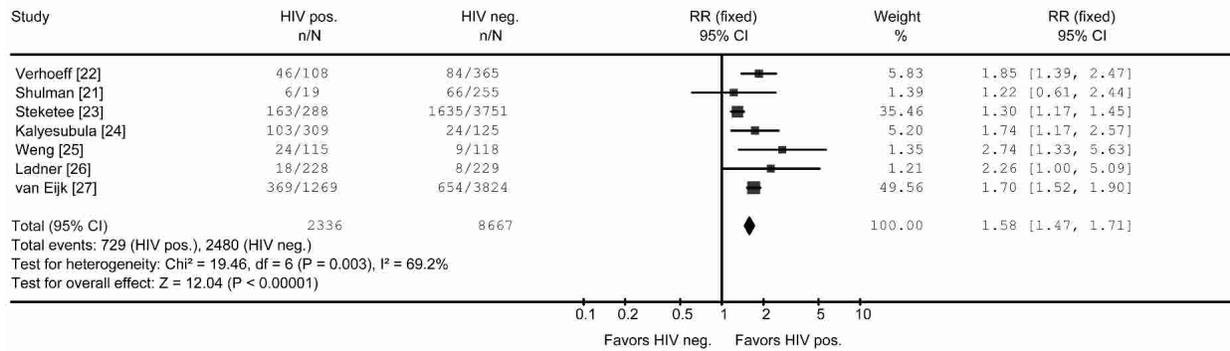
We searched PubMed for English publications using the keywords HIV, malaria, pregnancy, or pregnant, and we obtained further information from abstracts of scientific meetings, the internet, and personal communications with scientists.

EFFECT OF MATERNAL HIV ON MALARIA DURING PREGNANCY

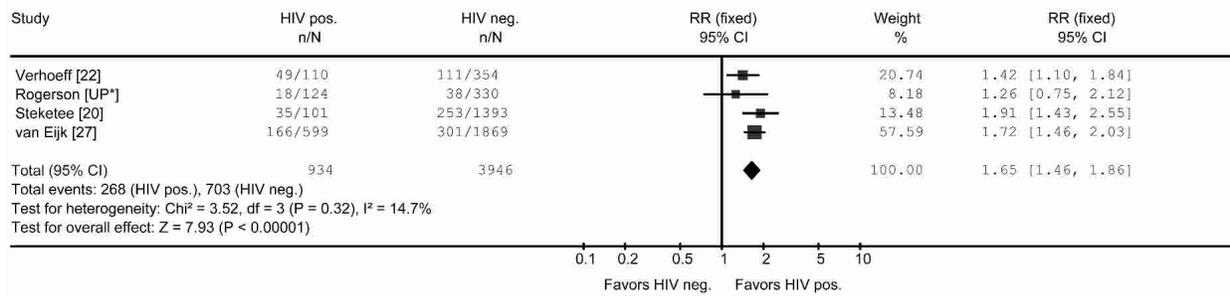
Parasitemia. Figure 1 summarizes the data from 11 of 13 studies (12 published^{20–31} and one unpublished [Rogerson SJ, unpublished data]) identified that determined the prevalence of maternal and placental malaria in HIV-infected and uninfected women in sub-Saharan Africa. These studies show a consistent increased risk of malaria parasitemia in HIV-infected women during pregnancy (risk ratio [RR] = 1.58), at the time of delivery (RR = 1.65), and in the placenta (RR = 1.66). The HIV-infected pregnant women also had higher malaria parasite densities (Table 1).

In the study by Steketee and others, the effect of HIV was principally observed in multigravidae, but there was no significant increased risk of malaria prevalence in primigravidae, although parasite densities were significantly higher.²⁰ Now,

a: Maternal malaria during pregnancy



b: Maternal malaria at delivery



c: Placental malaria

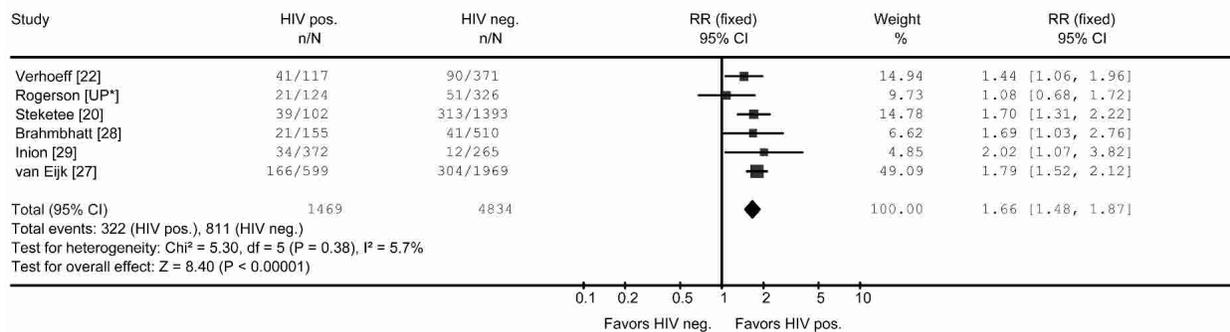


FIGURE 1. Malaria during pregnancy, at delivery, and placental malaria by human immunodeficiency virus (HIV)-infected and uninfected women. A search was conducted in Pubmed for English publications using the keywords, HIV, malaria, pregnancy, or pregnant and we obtained further information from abstracts of scientific meetings, the internet, and personal communications with scientists. Only studies that provided data from all gravidity groups were included in this figure (Rogerson SJ and others, unpublished [UP*] data).²⁰⁻²⁹ We excluded the study by Parise and others⁹⁹ because it included data only from primigravidae and secundigravidae, and that of Ticconi and others³¹ because it was not specified whether the malaria smears were taken during pregnancy or at the time of delivery, and from the mother or from the placenta. Placental malaria was determined by microscopy^{20,27,33} or placental histology (Rogerson SJ and others, unpublished data).²⁹ One study used hematoxylin and eosin stain to meet the original goal of the study (determining the impact of sexually transmitted diseases on HIV transmission).²⁸ pos. = positive; neg. = negative; RR = relative risk; CI = confidence interval; df = degrees of freedom.

TABLE 1

Parasite densities in human immunodeficiency virus (HIV)-infected and uninfected pregnant women*

Study	Geometric mean parasite densities at first ANC visit		
	HIV infected (N)	HIV uninfected (N)	P
Steketee and others, 1996	PG: 4,390 (45)	PG: 1,375 (678)	<0.001
Malawi ²⁰	MG: NA (104)†	MG: NA (1,867)†	<0.05†
Verhoeff and others, 1999, Malawi ³³ and unpublished data	AG: 1,558 (149)	AG: 670 (2,545)	<0.001
van Eijk and others, 2003, Kenya ²⁷	PG: 1,634 (18)‡	PG: 1,048 (46)‡	0.17
	MG: 822 (24)‡	MG: 729 (31)‡	0.43
	AG: 1,143 (46)	AG: 908 (84)	0.23
	PG: 1,463 (81)	PG: 684 (201)	<0.001
	MG: 757 (85)	MG: 323 (100)	<0.001
	AG: 1,031 (166)	AG: 499 (301)	<0.001

* ANC = antenatal clinic; AG = all gravidae; PG = primigravidae; MG = multigravidae.
 † Details of geometric mean parasite densities for multigravidae were not available (NA) from the published manuscript, but reported as "significantly higher in HIV-infected women than in seronegative women."²⁰
 ‡ Excluding women reporting recent antimalarial use.

with the availability of data from three more studies that present details by gravidity, it is clear that HIV-infected primigravidae are also affected (Table 2). Nevertheless, the HIV-associated risk of malaria is consistently greater in multigravidae (Table 2), suggesting that HIV affects the immune memory mechanism responsible for the parity-dependent acquisition of antimalarial immunity in pregnancy.³² Alternatively, multigravid women have longer sexual experience and may be more immunosuppressed because they have been infected with HIV longer than younger primigravid women. Thus, HIV alters the typical gravidity specific pattern of malaria risk by shifting the burden from primarily primigravidae and secundigravidae to all pregnant women, placing HIV-infected multigravidae in western Kenya at similar risk of malaria as HIV-uninfected women in their first and second pregnancies after adjusting for maternal age.²⁷

Maternal morbidity. Clinical malaria. The HIV-infected pregnant women were more likely to develop clinical malaria, defined as documented fever or a history of fever in the presence of microscopically detected malaria parasitemia.²⁷ They were also more likely to have used antimalarials during pregnancy other than those provided as part of intermittent preventive therapy.^{27,33}

Maternal anemia. Both HIV (especially with advanced im-

munosuppression)^{34,35} and malaria³⁶ are known causes of maternal anemia. Several studies describe a negative effect of the combined impact of HIV and malaria on maternal hemoglobin (Hb) concentrations.^{22,31,37,38} Table 3 shows prevalence of anemia for HIV-infected, malaria-infected, and dually infected women in three studies that stratified results by gravidity from western Kenya and Malawi. Women with single infections with HIV or malaria were more at risk than uninfected women. However, dually infected women were at considerably greater risk of having any anemia (Hb < 11 g/dL) or moderate-to-severe anemia (Hb < 8 g/dL) than those with single infections. There was evidence for a synergistic interaction between the effect of malaria and HIV in each study, suggesting that the degree of malaria-associated anemia is worse in HIV-infected women, possibly reflecting the higher parasite densities and longer duration of malaria infection.

Birth outcome. Seven studies were identified that examined the effect of dual infection with malaria and HIV on birth outcome.^{25,31,33,37,39,40} Although differences in study design limit direct comparisons between the studies, they generally show an increased risk of poor birth outcome in terms of low birth weight (LBW < 2,500 grams), preterm birth, and IUGR with both HIV and malaria, with the greatest risk in women with dual infection. Table 4 summarizes the effect of malaria alone, HIV alone, and dual infections in two studies that provided data by gravidity group. Although the risk of LBW was consistently greatest in women with dual infection, it was less clear than with the effect on anemia if the effect of HIV and malaria on birth weight were additive or synergistic. Studies that reported on gestational age suggest that the effect on birth weight reflects a combined effect of shortened gestational age and IUGR.^{31,37,39,40}

The impact of HIV on the burden of maternal malaria. The magnitude of the impact of the HIV epidemic on maternal malaria in sub-Saharan Africa can be expressed as the proportional increase in malaria during pregnancy in a population that is due to HIV (the population attributable fraction [PAF]). The PAF is a function of the HIV-associated increased risk of malaria during pregnancy and increases with increasing prevalence of HIV-1 in a population (Figure 2). The mean HIV prevalence among pregnant women visiting antenatal clinics in 39 sub-Saharan countries was 8.6% during 1985–2000.⁴¹ The PAF for malaria during pregnancy associ-

TABLE 2

Prevalence, relative risk, and proportion of maternal and placental malaria attributable to human immunodeficiency virus (HIV) in primi-, secundi-, and grand-multigravidae*

	Prevalence (N)		RR (95% CI)	AF (95% CI)
	HIV-infected	HIV-uninfected		
Maternal malaria				
Primigravidae	34.3 (359)	25.2 (1,590)	1.36 (1.14–1.62)	26.5 (12.3–38.3)
Secundigravidae	30.6 (241)	16.0 (778)	1.91 (1.47–2.49)	47.6 (32.0–59.8)
Grandmultigravidae	21.2 (383)	10.2 (1,691)	2.09 (1.63–2.69)	52.2 (38.7–62.8)
Placental malaria				
Primigravidae	34.5 (359)	27.2 (1,589)	1.27 (1.06–1.51)	21.3 (5.7–33.8)
Secundigravidae	30.4 (241)	17.9 (774)	1.70 (1.30–2.23)	41.2 (23.1–55.2)
Grandmultigravidae	24.6 (382)	10.3 (1,686)	2.39 (1.87–3.07)	58.2 (46.5–67.4)

* Grand multigravidae is defined as ≥third pregnancy. Published^{27,30,33} and unpublished (Rogerson SJ and others, unpublished data) data were used from four different studies conducted in Malawi and western Kenya that presented results by gravidity. Maternal malaria at delivery represents malaria detected using peripheral smears collected from the mother at the time of delivery or within 24 hours thereafter. Placental malaria was determined using malaria microscopy of the maternal side of the placenta^{20,27,33} or placental histopathology (Rogerson SJ and others, unpublished data). The attributable fraction (AF) was calculated using the weighted relative risk (RR) of malaria in HIV-infected women and uninfected women [AF = 100 × (RR – 1/RR)]. The RR and 95% confidence interval (CI) were obtained by the Mantel-Haenszel method for combining trials in fixed effect models.¹⁵⁹ Proportions in the second and third column represent the weighted prevalence and numbers in parentheses represent the number of pregnant women. The effects of HIV on the risk of malaria differed significantly between the three gravidity groups (tests for heterogeneity between gravidity groups: maternal malaria at delivery: P = 0.03, placental malaria: P = 0.004).

TABLE 3
Effect of malaria and human immunodeficiency virus (HIV) on anemia in pregnant women

	van Eijk and others ³⁸ (Hemoglobin < 8 g/dL) third trimester*				Ayisi and others ³⁷ (Hemoglobin < 8 g/dL) delivery†				Rogerson and others, unpublished data (Hemoglobin < 11 g/dL) delivery‡§			
	Primi gravidae		Multi gravidae§		Primi gravidae		Multi gravidae§		Primi gravidae§		Multi gravidae¶	
	N	%	N	%	N	%	N	%	N	%	N	%
No infection	1,233	11.8	1,889	13.6	607	10.7	708	12.1	89	20.3	175	13.1
HIV alone	286	18.9	601	21.8	147	19.0	229	14.0	51	34.2	114	26.3
Malaria alone	368	18.2	273	14.3	206	13.6	119	14.3	80	35.6	69	23.2
Dual infection	172	23.8	194	34.0	81	23.5	76	32.9	19	72.7	28	35.7

* Hemoglobin and maternal malaria assessed at ≥ 32 weeks gestation as part of antenatal care.

† Malaria defined as positive placental or peripheral blood smear (microscopy). Hemoglobin taken during or within 24 hours of delivery. Constitutes a sub-sample of the women seen in the third trimester by van Eijk and others.³⁸

‡ Malaria defined as positive placental blood smear (microscopy). Hemoglobin taken during or within 24 hours of delivery.

§ Statistically significant ($P < 0.05$) interaction between the effect of malaria and HIV on anemia.

¶ $P = 0.09$ for the interaction between the effect of malaria and HIV on anemia.

ated with this HIV prevalence is 4.8% (95% confidence interval [CI] = 3.9–5.8). In settings where HIV prevalence in pregnant women is 25% or 40%, 12.7% (95% CI = 10.5–15.1) and 18.8% (95% CI = 15.8–22.1) of the maternal malaria infections will be attributable to HIV-1, respectively (Figure 2).

The PAF can also be used to estimate the annual excess number of malaria cases during pregnancy that is due to HIV using a three-step process. First, the total number of pregnant women exposed each year to malaria in areas with stable transmission in sub-Saharan is estimated to be 24.6 million (in 2002).¹ Second, previous estimates from 20 studies from 8 countries in sub-Saharan Africa conducted between 1985 and 2000 involving 24,451 pregnant women showed the weighted prevalence of maternal malaria during pregnancy to be 42.8% HIV.⁴² Combining these figures suggests that annually at least 10.5 million women have malaria in the second or third trimester. Third, with an average HIV prevalence of 8.6%⁴¹ (PAF = 4.8%), it can be estimated that the HIV-1 epidemic results in an additional 505,382 women per year who have malaria during pregnancy. This number would increase to 1.34 million pregnancies per year if the average HIV seroprevalence among pregnant women reached 25% (PAF = 12.7%). This reflects the minimum effect of HIV on malaria in pregnancy because the 42.8% estimate is based on single point prevalence data, and does not take into account women who may have had malaria before or after the time of the point estimate.

Why are HIV-infected pregnant women more susceptible to malaria? The increased susceptibility of pregnant women

to malaria is not well understood, but is presumed to be related to modifications in systemic and placental immunologic parameters. There have been a limited number of studies of the cellular and humoral immune responses to malaria that may allow further understanding of the impact of HIV on these malaria and pregnancy specific immune responses.

Cellular immune responses. Intervillous blood mononuclear cells (IVBMCs) produce interferon- γ (IFN- γ), which has been implicated in protection against placental malaria.⁴³ In HIV-infected pregnant women with *P. falciparum* malaria, this production is reduced in response to malarial antigen stimulation⁴⁴ due to severe impairment of the interleukin-12 (IL-12), but not IL-18-mediated IFN- γ pathway.⁴⁵ This impairment was more pronounced with low CD4 counts,^{44,45} and highlights the shift in the cytokine responses as infection with HIV progresses. Not all the cytokine responses were

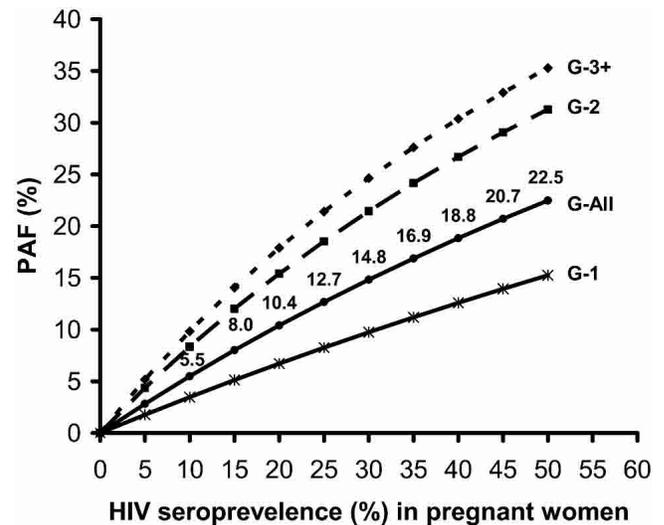


FIGURE 2. Proportion of overall malaria prevalence during pregnancy that can be attributed to human immunodeficiency virus type 1 (HIV-1) HIV-1 in the population as a function of HIV seroprevalence in pregnant women and by pregnancy order. G-All = all gravidae; G-1 = primigravidae; G-2 = secundigravidae; G-3+ = grandmultigravidae. The population attributable fraction (PAF) was calculated as $100 \times [p(RR - 1)/(1 + p(RR - 1))]$ where p is the HIV seroprevalence and RR is the summary risk ratio for malaria parasitemia associated with HIV infection (1.58, see Figure 1). For example, 12.7% of the malaria during pregnancy can be attributed to HIV-1 alone in areas with an antenatal HIV seroprevalence of 25%.

TABLE 4

Effects of malaria and human immunodeficiency syndrome (HIV) on the frequency of low birth weight*

	Ayisi and others ^{37†}				Rogerson and others, unpublished data‡			
	Primi gravidae		Multi gravidae		Primi gravidae		Multi gravidae§	
	N	%	N	%	N	%	N	%
No infection	676	4.1	809	2.7	30	21.0	79	5.1
HIV alone	160	7.5	256	3.9	38	23.7	176	8.0
Malaria alone	226	9.3	129	2.3	59	25.4	54	13.0
Dual infection	91	14.3	84	4.8	14	35.7	24	16.7

* Low birth weight (LBW) was defined as < 2,500 grams in singleton live births.

† Positive placental or peripheral blood smear (microscopy).

‡ Positive placental blood smear (microscopy).

§ Statistically significant ($P < 0.05$) interaction between the effect of malaria and HIV on LBW.

affected, indicating that there is no generalized suppression of immune response in these pregnant women.^{44–46} Given that *P. falciparum* is an intracellular parasite whose clearance requires an active cellular immune mechanism involving macrophages, it is understandable that impairment of the IL-12-mediated IFN- γ pathway due to HIV is a potential cause for increased malaria.

Humoral immune responses. Two recent studies conducted in Kenya and Malawi also show partial impairment of the humoral immune response to malaria in HIV-infected pregnant women.^{32,47} Although the anti-malarial antibody responses were unaltered for most of the antigen or epitopes tested,^{32,47} responses were impaired to the pre-erythrocytic stage circumsporozoite protein (NANP-5),⁴⁷ apical merozoite antigen 1 (AMA-1), and variant surface antigens (VSA) expressed on infected erythrocytes that bind to chondroitin sulfate A,³² a key receptor for placental sequestration.⁴⁸ This impairment is greatest in women with more advanced HIV disease, and occurs across all gravidities and in women with and without current malaria infection.³² What is not presently clear is whether T cell, B cell, or macrophage functional impairments, or a combination of all three, best explain the predisposition to malaria described in infections with HIV.

EFFECT OF MATERNAL MALARIA ON HIV

HIV-1 viral load. The role of immune-activation by coinfecting pathogens has long been postulated as a factor influencing the severity and rate of disease progression in HIV-infected individuals in developing countries.^{18,49} Two studies in non-pregnant adults with *P. falciparum* malaria showed that plasma HIV-1 RNA concentrations are transiently in-

creased and this higher HIV viral load is in part reversible with successful antimalarial therapy.^{50,51} More recently, three of four studies confirmed that this also occurs in pregnant women (Table 5).^{29,52–54} The magnitude of the effect (approximately two-fold increase in viral load) appears smaller than the seven-fold increase seen in adults with symptomatic malaria,⁵¹ perhaps because few pregnant women are symptomatic. One study also assessed the relationship between placental malaria and placental viral load, and found a similar two-fold increase in placental HIV-1 RNA concentrations, with the greatest increase in women with highest placental parasite densities.⁵³ Importantly, these observations were independent of the degree of immunosuppression as assessed by CD4 cell counts and can thus not be explained by an increased risk of malaria in subjects with more advanced immunosuppression and potentially greater HIV-1 viral load.⁵³

As in non-pregnant adults, *P. falciparum* can increase HIV-1 replication by activating both the lymphocyte and macrophage cell pool^{55,56} through up-regulating pro-inflammatory cytokine production, particularly TNF- α . Similarly, rodent *P. chabaudi* malaria induces virus expression in HIV-infected transgenic mice.⁵⁷ In addition, parasite sequestration in the placenta results in inflammatory increases in IVBMCs, predominantly monocytes and macrophages, the degree of which is correlated with the density of placental parasitemia, resulting in high levels of local proinflammatory cytokine responses such as TNF- α .^{46,58–63} Placental malaria is also associated with increased expression on placental macrophages and fetal Hofbauer cells of CC chemokine receptor 5 (CCR5),^{64,65} a major fusion co-receptor for HIV-1 cell-entry.^{64,66} The HIV-1 viruses that are transmitted from mother to child are predominantly CCR5 trophic.⁶⁷ Thus, there are several pathways that combined could result in in-

TABLE 5
Effect of maternal and placental malaria on human immunodeficiency virus 1 (HIV-1) viral load*

Study	Design		Peripheral viral load		Placental viral load
			Peripheral malaria at delivery	Placental malaria	Placental malaria
Kapiga and others, 2002 ⁵²	Cohort	Malaria	63,299 (13,461, 105,459)†	NA	NA
		No malaria	17,291 (3,336, 64,719)†	NA	NA
		Difference‡	Ratio 3.66, <i>P</i> = 0.01		
Mwapasa and others, 2004 ⁵³	Cross-sectional	Malaria	42,727 (25,745–70,892)§	62,359 (41,706–93,218)§	11,733 (7,091–19,413)
		No malaria	29,833 (23,421–38,001)§	24,814 (18,785–32,772)§	4,919 (3,533–6,849)
		Difference‡	Ratio 1.43, <i>P</i> = 0.21#	Ratio 2.51, <i>P</i> = 0.0007#	Ratio 2.39, <i>P</i> = 0.008#
Ayisi and others, 2004 ⁵⁴	Cross-sectional	Malaria	2,979 (1,795–4,942)§	2,399 (1,550–2,399)§	NA
		No malaria	1,725 (1,393–2,137)§	1,774 (1,426–2,208)§	NA
		Difference‡	Ratio 1.73, <i>P</i> = 0.03#	Ratio 1.35, <i>P</i> = 0.20#	
Inion and others 2003 ²⁹	Cross-sectional	Malaria¶	NA	13,029§	NA
		No malaria	NA	12,419§	NA
		Difference‡		Ratio 1.05, <i>P</i> = 0.921#	

* NA = not assessed/available. Malaria was diagnosed by microscopy unless indicated otherwise. The average increase in peripheral HIV-1 RNA concentration was 1.9-fold for peripheral malaria and 2.08-fold for placental malaria (weighted by sample size).

† Values are the median (interquartile range).

‡ Ratio of median or geometric means.

§ Values are the geometric mean (95% confidence interval).

¶ Placental histology.

Comparison of log₁₀ viral load.

creased systemic and/or placental replication of HIV-1 and viral reservoir in placentas of dually infected women, and thus increased mother-to-child transmission (MTCT) of HIV-1.

Mother-to-child transmission of HIV-1. The question of whether malaria during pregnancy enhances the risk of MTCT is pivotal for sub-Saharan Africa, where few women take anti-retroviral drugs and uptake of MTCT preventive services has been low.⁷ Although maternal HIV-1 viral load is the single most important risk factor for MTCT of HIV-1,^{68–70} the available evidence suggests that placental malaria may not necessarily increase the risk of MTCT (Table 6).^{28,29,54,71} Among three recently published studies that provided sufficient detail to allow comparison, significant heterogeneity ($P = 0.01$) was found in the risk of MTCT associated with placental malaria, ranging from an increased risk in Uganda (RR = 2.89, 95% CI = 1.12–7.52),²⁸ to no effect in Mombasa, Kenya,²⁹ and a significant protective effect in Kisumu in western Kenya (RR = 0.44, 95% CI = 0.27–0.72, $P < 0.001$).⁵⁴

The apparent discrepancies may reflect a complex relationship between maternal immune responses to malaria that on the one hand may stimulate HIV viral replication in the placenta thereby increasing the local viral load, and on the other hand may potentially control the severity of malarial infection and HIV replication. The balance of these can tip either in the direction of enhanced risk of MTCT or a protective effect, depending on the degree of immune suppression, and on the severity of the malaria and thus the degree of placental monocyte infiltrates and proinflammatory cytokine and chemokine responses (Figure 3).

Although the precise mechanism needs to be established, it has been suggested that the family of CC-chemokines (β -chemokines) such as macrophage inflammatory protein (MIP)-1 α , MIP-1 β ; and “regulated-upon activation normal T-cell expressed and secreted” (RANTES) protein may play a potential protective role in this relationship.^{54,72} The CC-chemokines have a broad spectrum of action, including lymphocyte and monocyte homing and migration. These three CC-chemokines are also ligands for the co-receptor CCR5 and competitively inhibit HIV-1 entry into macrophages. Individuals with high concentrations of these three chemokines remain uninfected despite repeated exposure to HIV.⁷³ Furthermore, infants born to HIV-infected women who have

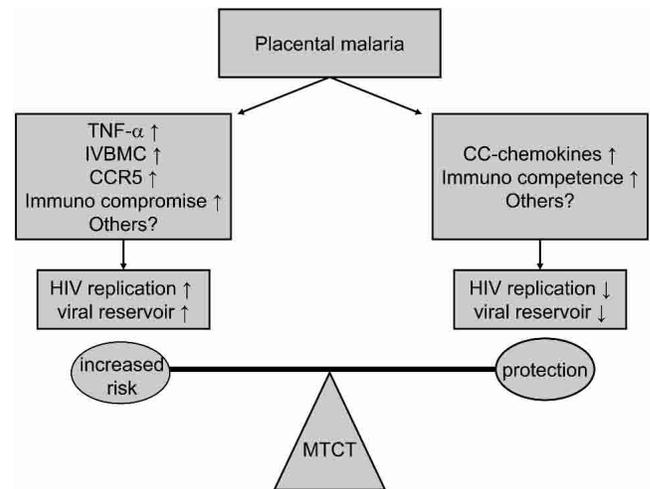


FIGURE 3. Model of immune interactions during placental malaria and human immunodeficiency virus type 1 (HIV-1) co-infection and their putative impact on mother-to-child transmission of HIV-1. Infection of the placenta with *Plasmodium falciparum* activates the immune system and results in up-regulation of placental proinflammatory cytokines, especially tumor necrosis factor- α (TNF- α), which in turn could increase HIV-1 replication. Placental malaria also results in the increased infiltration of mononuclear cells in the intervillous spaces of the placenta (IVBMC) and increased expression of CC chemokine receptor 5 (CCR5) on placental macrophages and fetal Hofbauer cells. These changes may further increase the placental HIV-1 viral load. With a healthy immune status, tightly regulated proinflammatory response, and CC-chemokine responses to malaria (which block HIV-1 entry through the CCR5 receptor) may successfully control malaria parasite densities and favor protection against mother-to-child transmission (MTCT) by controlling viral load and promoting other as yet undefined protective factors. Conversely, these putative protective factors may be overwhelmed in women with high-density malaria infections and/or HIV-related immunosuppression associated with high placental HIV-1 viral load and sub-optimal immune response to malaria. This could result in a local environment that favors MTCT of HIV-1.

high plasma concentrations of CC-chemokines and strong anti-HIV cytotoxic/suppressor T cell responses at birth have a reduced risk of HIV-1 infection.⁷⁴ Although some differences exist between different studies, it has been generally found that the concentrations of one or more of these chemokines

TABLE 6
Placental malaria and mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1)*

Study	Method used	Results
St Louis and others, 1993 ⁷¹	Placental histology	No data given "No association between placental malaria and perinatal HIV-1 transmission"
Brahmbhatt and others, 2003 ²⁸	Placental histology (hematoxylin and eosin stain)†	Placental malaria
		No malaria
		Crude RR
		Adjusted RR
Inion and others, 2003 ²⁹	Placental histology	Placental malaria
		No malaria
		Crude RR
		Adjusted RR
Ayisi and others, 2004 ⁵⁴	Microscopy	Malaria
		No malaria
		Crude RR
		Adjusted RR

* The weighted summary relative risk (RR) (95% confidence intervals) for mother-to-child transmission (MTCT) of the three studies that provided numerator and denominator details was 0.79 (0.55–1.15) and was obtained with the Mantel-Haenszel method for combining trials in fixed effect models¹⁵⁹ (HIV-infected women with [n = 170] and without [n = 759] placental malaria.^{28,29} The effects of placental malaria on MTCT of HIV-1 differed significantly between the three recent studies (tests for heterogeneity: $P = 0.01$).

† Hematoxylin and eosin stain was used to meet the original goal of the study (determining the impact of sexually transmitted diseases on HIV transmission).

are significantly elevated in women with placental malaria, irrespective of their HIV status.^{63,72,75} Preliminary results from the MTCT study in western Kenya that found a protective effect of placental malaria on MTCT suggest that concentrations of MIP-1 α and MIP-1 β , but not RANTES, were lower in malaria-infected placentas from women who transmitted the virus to their infants than in malaria-infected placentas from non-transmitting women (Chaisavaneeyakorn S, Udhayakumar V, unpublished data). Based on these findings, one could speculate that these chemokines may play some protective role in MTCT of HIV-1. The half-lives of the CC-chemokines, however, are short and a causal role remains to be established. Alternatively, it is also possible that elevated levels of chemokines may be simply an immune marker for protection.

The immunocompetence of the host may be another important determinant in the MTCT of HIV outcome. The majority of women in the same study in western Kenya had CD4 counts > 400/ μ L and peripheral HIV-1 RNA concentrations were low (Table 5).⁵⁴ No details were given of the viral load or CD4+ counts from the Ugandan study that found an increased risk of MTCT.²⁸ Although individual studies adjusted for viral load and/or CD4 counts, large differences between the studies in immunocompetence of HIV-infected women cannot be excluded as an explanation for the differences in the effect of placental malaria on MTCT (Table 6).

Although further studies are needed to provide an explanation for the apparent heterogeneous effects of placental malaria on MTCT of HIV-1, we hypothesize that immune factors play an important balancing act in this relationship (Figure 3). Other potential explanations for the apparent difference between the three studies may include variation in the sensitivity of the techniques used for the determination of placental malaria (Table 6).

Future studies should also include assessment of the role of severity and the timing of malaria (acute versus chronic placental infection), viral phenotypes⁷⁶ and potential host genetic factors that could provide a mechanism of resistance against transmission of HIV-1.⁷⁷ Furthermore, children who develop T cell responses to HIV peptides *in utero* are less likely to acquire HIV-1,⁷⁸ but no studies have systematically examined the effect of maternal or fetal malaria on the reactivity or susceptibility of fetal leukocytes to HIV-1.

IMPLICATIONS OF MATERNAL CO-INFECTION WITH HIV AND MALARIA FOR INFANT HEALTH

Transfer of maternal antibodies to the fetus. The materno-fetal transfer of antibodies forms an important protection against infectious diseases in the first months of life. Maternal HIV-1 infection can cause placental pathologic changes that might interfere with transfer of antibodies to some malarial antigens, including against the pre-erythrocytic stage circumsporozoite protein NANP-5, the synthetic blood stage peptides merozoite surface protein 3 (MSP-3), AMA-1, and VSA.^{32,47} Immunoglobulin transfer across the placenta is an active process, with IgG being primarily taken up by FcRN receptors on the syncytiotrophoblast.⁷⁹ How HIV-1 interferes with this process is presently unknown and it is also unclear whether this leads to an increased susceptibility to malaria in infants.

Malaria and anemia in infants. Several published^{80–85} and

unpublished studies (van Eijk AM and others, unpublished data) have shown that newborns of mothers who had malaria during pregnancy are at an increased risk of malaria and anemia during infancy, particularly in the first six months of life. Early immune priming/sensitization *in utero* and the development of immunologic tolerance could possibly explain the susceptibility of infants born the mothers with malaria.^{84,86–88} Very few studies have addressed the effect of maternal HIV-1 on cord blood parasitemia and infant malaria. The available evidence does not suggest that maternal HIV-1 has a consistent effect on congenital malaria^{20,89,90} or affects the relationship between maternal and infant malaria (Table 7)(van Eijk AM and others, unpublished data).^{91,92}

Mother-to-child transmission of HIV-1 places their children at risk of severe anemia.⁹³ Maternal HIV also has an indirect, albeit small, effect on infant anemia. The HIV-exposed but HIV-uninfected children born to Kenyan mothers with advanced HIV immunosuppression were at increased risk of severe anemia compared with HIV-uninfected children from HIV-uninfected mothers (RR = 1.14, 95% CI = 1.03–1.26),⁸⁰ although in Malawi, no such increased risk of anemia was seen in infants of HIV-infected mothers.⁸⁵

Infant mortality. Previous data from Malawi showed that dual exposure to both placental malaria and maternal HIV-1 increased the risk of post-neonatal mortality 3–8 fold (depending on the birth weight) compared with infants born to mothers with HIV alone, suggesting an increased risk of MTCT or increased rate of HIV-1 disease progression in infants.⁹⁴ This was not confirmed by two subsequent studies in southern Malawi and western Kenya where lower mortality rates were observed among infants born to HIV-infected women with placental malaria than those without placental malaria (Table 8).^{89,95} The protective effect in western Kenya is consistent with the reduced MTCT found in women with dual infection compared with women without placental malaria.⁵⁴

TREATMENT ISSUES AND PROGRAMMATIC IMPLICATIONS

Response to treatment, chemoprophylaxis, and intermittent preventive treatment (IPT). The World Health Organization (WHO) currently recommends a three-pronged approach for malaria control during pregnancy in sub-Saharan Africa: intermittent preventive treatment (IPT), insecticide-

TABLE 7

Association between placental malaria or maternal human immunodeficiency virus (HIV) infection and infant parasitemia during the first three months of life

	Univariate odds ratio (95% confidence interval)
Taha and others, 1994 ⁸²	
Maternal HIV infection	0.78 (0.43–1.40)
Slutsker and others, 1996 ⁹¹	
Maternal HIV infection	0.47 (0.21–1.02)
Placental malaria	0.91 (0.54–1.53)
van Eijk and others, unpublished ⁹⁷	
Maternal HIV infection	0.94 (0.67–1.32)
Placental malaria	1.48 (1.08–2.01)

* Placental malaria status was not known in this study.

† No evidence for interaction in multivariate model (*P* interaction term = 0.3).

TABLE 8

Maternal human immunodeficiency status (HIV) status and placental malaria as risk factors for post-neonatal infant mortality in Malawi and Kenya*

HIV status	Placental malaria	RR (95% CI) Verhoeff and others, 2000† ⁹⁵	RR (95% CI) van Eijk and others, unpublished‡ ⁸⁹	RR (95% CI) Bloland and others, 1995§ ⁹⁴
Negative	Negative	Reference	Reference	Reference
Positive	Negative	8.4 (3.3–21.6)	7.1 (1.7–29.1)	3.89 (1.17–12.91)
Negative	Positive	3.5 (1.1–10.8)	3.1 (0.63–14.8)	2.28 (0.94–5.53)
Positive	Positive	4.7 (1.2–19.1)	4.5 (1.0–19.6)	9.38 (3.85–22.84)

* RR = risk ratio; CI = confidence interval. Among infants of HIV-uninfected women, placental malaria was a consistent risk factor for post-neonatal infant mortality, and 56–71% of post-neonatal infant deaths may be attributed to placental malaria.

† Adjusted for low birth weight and fetal anemia. Adapted from Verhoeff and others⁹⁵ after exclusion of twins.

‡ Adjusted for low birth weight.

§ Adjusted for low birth weight (Mantel-Haenszel summary risk ratio).

treated bed nets, and effective case management of malaria illness.⁹⁶

The IPT involves the administration of full treatment doses of an effective antimalarial drug at predefined gestational intervals; currently at least two doses of sulfadoxine-pyrimethamine are recommended after quickening, given at routine antenatal clinic (ANC) visits.^{96–100} One clinical trial conducted in western Kenya demonstrated that HIV-infected primigravidae and secundigravidae had a suboptimal response to IPT, requiring at least three doses of sulfadoxine-pyrimethamine to achieve similar reductions in placental parasitemia as HIV-uninfected women who received two doses.⁹⁹ Although both HIV-infected and uninfected women had an excellent parasitologic treatment response by day 14,⁹⁹ HIV-infected women subsequently had a higher prevalence of placental parasitemia that was likely due to late recrudescence of parasitemia and reinfections in women with compromised immunity. Verhoeff and others noted a highly significant reduction in the frequency of LBW in both HIV-infected and HIV-uninfected Malawian women receiving the recommended two doses of IPT with sulfadoxine-pyrimethamine under program conditions (compared with women receiving just one dose), although HIV-infected women were twice as likely to give birth to LBW babies.⁹⁰ This reduction in the frequency of LBW occurred despite high rates of placental parasitemia in women of either HIV serostatus.⁹⁰ Further studies are in progress in Malawi and Zambia to address the issue of IPT frequency in HIV-infected women in more detail.

While the WHO recommends that women receive at least two doses of IPT, if doses are linked to the most recent WHO-recommended schedule of four ANC visits with three after quickening,^{96,101,102} this would potentially deliver three doses to each woman that, based on the limited data available, should be efficacious in areas with high HIV prevalence. Sixty-eight percent of women in sub-Saharan Africa make at least one ANC visit. Of those who attend an ANC, 95% make at least two visits and nearly 60% make at least four visits.¹⁰³

In a clinical study comparing different chloroquine prophylaxis or IPT regimens in Malawi, HIV-infected women had higher rates of persistent and breakthrough parasitemia, and peripheral and placental parasitemia at delivery, indicating a poorer response to both prophylaxis and treatment.²⁰

There are currently no published data on whether HIV-infected pregnant women exhibit an impaired response to the treatment of clinical malaria. Scarce data available from non-pregnant populations have shown variable results.^{104–108}

Prevention of opportunistic infections and malaria. UNAIDS recommends opportunistic infection (OI) prophylaxis with cotrimoxazole for certain groups of HIV-infected persons (or potentially infected infants), including all pregnant women after the first trimester.¹⁰⁹ While WHO does not recommend a specific drug for IPT, the only available data are for sulfadoxine-pyrimethamine^{97–100} and chloroquine.^{40,110,111} Sulfadoxine-pyrimethamine is increasingly being used because chloroquine efficacy is limited by drug resistance.^{96,112,113} Thus, OI prophylaxis with cotrimoxazole and malaria prevention with sulfadoxine-pyrimethamine involve two similar sulfa drugs for HIV-infected pregnant women, which is inadvisable in view of the potential risk of increased adverse drug reactions (ADRs). Because sulfadoxine-pyrimethamine is not as effective against bacterial pathogens,^{114,115} cotrimoxazole might be used to prevent both bacterial infections and malaria. Cotrimoxazole has been shown to effectively treat malaria in children.^{116,117} Cotrimoxazole prophylaxis in HIV-infected persons has been shown to decrease malaria morbidity.¹¹⁸ Data are urgently needed on the efficacy of cotrimoxazole prophylaxis on reducing rates of placental malaria and anemia in HIV-infected pregnant women.

In addition, there is *in vitro* evidence for cross-resistance between trimethoprim and pyrimethamine.¹¹⁹ Widespread use of cotrimoxazole in prophylaxis programs for HIV-infected persons could potentially provide substantial drug pressure that could accelerate the development of *P. falciparum* resistance to sulfadoxine-pyrimethamine. Conversely, expanding use of sulfadoxine-pyrimethamine might further the development of resistance to cotrimoxazole by other pathogens, such as *Streptococcus pneumoniae*.¹¹⁴ The effectiveness of these drugs should be carefully monitored in HIV-1 and malaria control programs.

Interactions and commonalities between antimalarial and antiretroviral drugs. As programs are put into place for the administration of antiretroviral therapy, potential interactions between antiretroviral drugs and antimalarial drugs must be considered. The use of quinidine (and thus, possibly quinine) is contraindicated because of potential cardiotoxicity among persons receiving a number of antiretroviral agents, including nelfinavir and ritonavir,^{120,121} and should be used only with caution and careful monitoring with amprenavir, delaviridine, and lopinavir/ritonavir in combination.^{122–124} The co-administration of cotrimoxazole and lamivudine results in decreased clearance of lamivudine;¹²⁵ there are no reported studies on the interaction of sulfadoxine-pyrimethamine with lamivudine. There is also recent evidence that protease inhibitors may impair CD-36 mediated cytoadherence and non-opsonic phagocytosis of parasitized erythrocytes, which may contribute to altered malaria disease outcomes in co-infected patients.^{126–128}

Chloroquine and hydroxy-chloroquine are antimalarial drugs that have been shown to have antiretroviral activity *in vitro*^{129–132} and *in vivo*,^{133,134} thought to be due to inhibition of post-translational modification of gp120.^{135–137} They have been proposed as potentially useful components of antiretroviral combination therapy in resource-poor settings,^{138,139} including for MTCT of HIV-1 because of their effect on reducing production of infectious virions¹²⁹ and because they accumulate in breast milk cells.¹⁴⁰ However, even if these drugs were used in antiretroviral programs (at much higher doses, i.e., 800 mg of hydroxy-chloroquine/day, than are used

for malaria),^{133,134} their usefulness in preventing the adverse effects of malaria in HIV-infected women would likely be limited because of high levels of chloroquine resistance in sub-Saharan Africa.

Anemia prevention and HIV. Iron deficiency, malaria, and HIV are among the major causes of anemia in pregnant women in sub-Saharan Africa. However, anemia prevention and treatment may be complicated by HIV. Friis and others have reported that relatively asymptomatic HIV-infected pregnant women have slightly reduced iron stores,¹⁴¹ while increased iron stores have been reported in those with more advanced disease.¹⁴² However, in a recent trial in Kenyan adults, iron supplementation was associated with reduced Hb, which was thought to be due to HIV progression.¹⁴³ While iron is important for immune function, it is also required by enzymes involved in HIV replication and, because of its pro-oxidant properties, may even stimulate HIV replication.^{144,145} Epidemiologic studies have shown that supplemental iron,^{146,147} inadequate chelation of iron overload,¹⁴⁸ and the size of iron stores¹⁴⁹ are associated with the progression of HIV.¹⁴¹ Studies are urgently needed to clarify this further because a detrimental effect of iron supplementation on HIV infection would have major implications for antenatal care policies.¹⁴³ Because pregnant women are one of the highest risk groups for anemia, prevention and treatment, especially of severe anemia, is paramount during pregnancy to minimize the potential need for transfusion of blood that may not be adequately screened for HIV.

Adverse drug reactions and pharmacovigilance. Reports among non-pregnant persons indicate that the rate of ADRs to sulfonamides may be higher among HIV-infected than HIV-uninfected persons.^{150–152} Parise and others reported that 3.2% and 0.4% of HIV-infected and HIV-negative women in Kisumu, respectively, experienced ADRs after the first treatment dose ($P = 0.08$).¹⁰⁶ Two (2%) of 94 HIV-infected and none of 230 HIV-uninfected women had sulfadoxine-pyrimethamine withheld because of ADRs.⁹⁹

During one year of data collection in a district-wide surveillance study monitoring severe cutaneous reactions associated with sulfonamide use in pregnant and non-pregnant persons in Malawi (where HIV seroprevalence is approximately 25% among pregnant women in urban areas),¹⁵³ rates of severe cutaneous adverse reactions were consistently greater among HIV-infected than among HIV-uninfected persons: 5.1/100,000 versus 1.4/100,000 (sulfadoxine-pyrimethamine only), 14.1/100,000 versus 1.5/100,000 (cotrimoxazole only), and 42.2/100,000 versus 0.4/100,000 (sulfadoxine-pyrimethamine plus cotrimoxazole). Estimated rates among pregnant women were 4.2/100,000 drug exposures; there were insufficient numbers to generate stable estimates comparing rates between HIV-infected and HIV-uninfected pregnant women (Gimnig J, unpublished data). The etiology of the increased rate of ADRs to sulfonamides among HIV-infected compared with HIV-uninfected persons is unclear and is likely multifactorial. Sulfonamide-induced ADRs have been linked to a slow acetylator phenotype¹⁵⁴ and genotype.¹⁵⁵ During acute periods of illness, patients with acquired immunodeficiency syndrome often express glutathione deficiency.¹⁵⁶ The combination of these two acquired deficiencies could potentially lead to high levels of hydroxylamine metabolites, which have been associated with a higher rate of cutaneous ADRs.^{151,154,155} It has also been suggested that in

some cases, the use of high doses of drugs may be a factor, given that there is some evidence for an abnormal accumulation of drug in toxic epidermal necrolysis.^{151,157}

Programs for both non-pregnant and pregnant women must incorporate surveillance systems to monitor for severe ADRs. The apparent dramatic increase in the risk of severe cutaneous reactions among HIV-infected women receiving both cotrimoxazole and sulfadoxine-pyrimethamine also points to the need for both a greater understanding of the efficacy of cotrimoxazole alone in preventing malaria during pregnancy, and a greater integration of HIV prevention and ANC services.

CONCLUSIONS

Although much has been learned in the 15 years since the initial identification of interactions between malaria and HIV in pregnant women, many issues still require further information to improve our understanding. It is now clear that among pregnant women, the majority of co-infections with HIV and malaria occur in sub-Saharan Africa. The HIV-infected pregnant women experience more malaria and higher density malaria parasitemia, and dually infected pregnant women have more febrile illnesses, more anemia, and more adverse birth outcomes (LBW, prematurity, and IUGR) than women with single infections with malaria or HIV. There are caveats about each of these factors and although there is evidence for synergistic interactions exacerbating malarial anemia, present evidence does not allow us to exclude a simple additive effect on birth outcome.

Malaria also increases HIV viral replication and viral load and with inadequate antimalarial treatment this may worsen HIV disease progression, although the latter remains to be determined. The role of malaria as a contributing factor in MTCT of HIV is particularly important. Unfortunately, there are limited studies addressing this and existing findings are inconsistent. The sum of the current data suggests that malaria contributes little to MTCT, but more studies are needed, particularly in light of increasing efforts to prevent both MTCT and maternal malaria.

Similarly, there is limited information on the effects of HIV or malaria on the treatment and prevention interventions directed at the other infection/disease. As described here, there are drug-drug interactions that could be problematic and there is concern that each infection might alter the benefits achieved with drugs for treatment. Again, given the global push to extend the use of antiretroviral drugs and the advent of new and combination antimalarial treatments, further investigation into such interactions will be increasingly important.

While there has been some progress made in examining the human immune response to both HIV and malaria during pregnancy, there remain substantial gaps in our knowledge about how pregnant women respond to these two infections at a time when the immune responses required to maintain a healthy pregnancy are themselves complex. This is an area in which clearly reproductive immunologists and infectious disease immunologists could both make important contributions.

Finally, notwithstanding the present gaps in our knowledge, there is a clear need to strengthen the deployment of existing malaria and HIV prevention and intervention measures. For

pregnant women who are HIV-infected, malaria prevention (with insecticide-treated nets and IPT) should be a priority to reduce the frequency of malaria associated maternal anemia and LBW. For women found to be dually infected, appropriate management of both infections is a priority both for the woman and for her developing fetus. Given that a high proportion of pregnant women do attend antenatal clinics for care, and that there are new resources available globally to tackle HIV and malaria,¹⁵⁸ the global health community has a clear responsibility and opportunity to limit the scourge of these two diseases in this vulnerable population.

Received January 12, 2004. Accepted for publication February 27, 2004.

Acknowledgments: We thank the many colleagues that contributed to these ideas, discussion, and field studies. We are particularly grateful to the following colleagues for providing details or unpublished results for this review: Dr. Steven Meshnick (University of North Carolina, Chapel Hill, NC); Dr. Victor Mwapasa (College of Medicine, Blantyre, Malawi and University of Michigan, Ann Arbor, MI); and Dr. Ingrid Inion and Professor Marleen Temmerman (University of Ghent, Ghent, Belgium).

Financial support: Feiko O. ter Kuile is grateful to Roll Back Malaria/World Health Organization and the Centers for Disease Control and Prevention for support as part of a collaboration between the Liverpool School of Tropical Medicine and the Malaria Branch of the Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention. Francine H. Verhoeff was supported by funds from PREgnancy Malaria and Anemia European Union (PREMA-EU), which received financial support from the European Commission Research Directorate Fifth Framework Program (contract no PREMA-EU-ICA4-CT4-2001-10012). Stephen J. Rogerson is supported by the Wellcome Trust, United Kingdom, through an Overseas Senior Research Fellowship. Anne M. van Eijk is supported by the Oak Ridge Institute for Science and Education, Tennessee.

Disclaimer: Use of trade names is for identification only and does not imply endorsement by U.S. Public Health Service or Department of Health and Human Services.

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