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SYSTEMATIC REVIEW AND META-ANALYSIS

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The Effect of Malaria and HIV Co-Infection on Anemia

A Meta-Analysis

Cho Naing, MBBS, PhD, Nisha Kaur Sandhu, BMedSc, and Victor Nyunt Wai, MBBS, PhD

Abstract: Malaria and human immunodeficiency virus (HIV) infections are globally important public health concerns. The objectives of this study were (i) to determine the prevalence of malaria and HIV co-infections in people living in endemic countries, and (ii) to assess the effect of co-infection on anemia.

Studies were searched on electronic databases including PubMed, Embase, Medline, Google Scholar, and African Journals Online. Observational studies, assessing the prevalence of co-infection and reporting its association with anemia, were included. The methodological quality of included studies was assessed using a tool called the risk of bias assessment for non-randomized studies. Heterogeneity among studies was investigated with the *I*-square test. Pooled prevalence of the co-infection and its 95% confidence interval (CI) were estimated using the random-effect model, reflected on heterogeneity among studies. Summary odds ratio (OR), summary standardized mean difference (SMD), and their corresponding 95% CIs were estimated, as appropriate. Subgroup analysis and meta-regression were performed for robustness of results. Publication bias was assessed by visualization of a funnel plot.

Twenty-three studies were included in the present study. Overall, the pooled prevalence of co-infection was 19% (95% CI: 15–23%, I^2: 98.1%), showing 26% (95% CI: 20–32%, I^2: 98.7%) in adults, 12% (95% CI: 7–17%, I^2: 95.0) in pregnant women, and 9% (95% CI: 6–11%, I^2: 68.6%) in children. Anemia was comparable between the monoinfected and co-infected adults (summary OR: 1.49, 95% CI: 0.93–2.37) and increased by 49% in co-infected pregnant women (summary OR: 1.49, 95% CI: 1.14–1.94). The mean hemoglobin concentration was significantly lower in the co-infected group than the monoinfected group (summary SMD: −0.47, 95% CI: −0.61 to −0.33). The results of meta-regression on the prevalence of co-infection using the publication year and total population as covariates showed the I^2 value remained high implying a *de facto* random distribution of heterogeneity. An asymmetrical funnel plot indicated the presence of publication bias. Due to heterogeneity of the studies in this review, the results have to be interpreted with caution.

The findings of this study suggest that the prevalence of malaria and HIV co-infection, particularly in pregnant women, requires special attention from healthcare personnel. Better understanding of the co-infection is crucial for designing treatment strategies. Future well-powered, prospective designs assessing the interaction between malaria and HIV are recommended.

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Abbreviations: AJOL = African Journals Online, ART = antiretroviral therapy, CI = confidence interval, Hb = hemoglobin, HCT = haematocrit, HIV = human immunodeficiency virus, MOOSE = Meta-analyses of Observational Studies in Epidemiology, OR = odds ratio, PCV = packed cell volume, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, PROSPERO = International Prospective Register of Systematic Reviews, RoBANS = Risk of Bias Assessment for Non-randomized Studies, SciELO = Scientific Electronic Library Online, SMD = standardised mean difference, VSA = variant surface antigen, WHO = World Health Organization.

INTRODUCTION

A substantial progress in malaria control has already been achieved in 55 of the 106 endemic countries in the context of target 6 in Millennium Development Goal. However, malaria remains endemic in all 6 World Health Organization (WHO) regions and the heaviest burden is in the African Region which claimed ~ 90% of all malaria deaths.[1] Sub-Saharan Africa also accounted for an estimated 25 million adults and children living with HIV/AIDS. Globally, malaria and HIV are the 2 major health problems and together they contribute to >4 million deaths per year.[2] People residing in regions where HIV and malaria are endemic are prone to develop co-infection. As such, there is a growing interest in whether this dual infection intensifies each other and attributes to complications in the clinical spectra and treatment outcomes.

Anemia is a significant consequence of malaria infection in terms of morbidity. Co-infection with HIV could lead to worsening of anemia through nutritional or immunological interactions. Empirical studies on malaria-HIV co-infection and particularly its effects on anemia showed varied results. Some studies reported this dual infection adversely affects maternal hemoglobin (Hb) concentration,[3] whereas others reported differently.[4–6] There is limited information on the collective impact of malaria-HIV co-infection on the Hb levels in general population.[7] Hence, a better understanding of the impact of co-infections could help in prevention and control of malaria. Earlier reviews in this field were either merely narrative[8,9] or not up-to-date.[10] However, since there has been a continuous flow of publications on the co-infection in endemic areas, it is timely to synthesis evidence by a meta-analysis.[11] Taken together, the objectives of the present study were (i) to determine the prevalence of malaria and HIV co-infections in people living in endemic countries, and (ii) to assess the effect of co-infection on anemia.

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From the School of Postgraduate Studies (CN, NKS); and School of Medicine (VNW), International Medical University, Kuala Lumpur, Malaysia.
Correspondence: Cho Naing, International Medical University, Kuala Lumpur, Malaysia (e-mail: cho3600@gmail.com).
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METHODS

The present study was carried out following the guideline on Meta-analyses of Observational Studies in Epidemiology (MOOSE)[12] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[13] (See supplemental checklist, http://links.lww.com/MD/A853). The protocol of this study is available in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42015020248).

Study Search

Studies on the co-infection between malaria and HIV up to the end of June 2015 were searched in databases such as Embase Medline, Global Health, Google scholar, Scientific Electronic Library Online (SciELO), and African Journals Online (AJOL). To maximize the search, only 2 subject headers were used: malaria and HIV or AIDS and co-infections. Subsequently, specific terms such as plasmodium and HIV/AIDS were used. Only malaria and HIV were used for the search in SciELO and AJOL. Only studies on humans, published in English language were considered. The references of the identified papers and relevant reviews were reviewed to track any study that had not been captured by the electronic search.

Selection of Studies

Studies were included if they were (i) done on participants co-infected with malaria and HIV, and (ii) observational studies which compared the outcomes of anemia between those who were co-infected with malaria and HIV and those with mono-infection. To be eligible, malaria was confirmed by microscopy of Giemsa-stained blood films or rapid-onsite diagnostic test. Subsequent PCR-based analysis for confirmation of the species was advantageous, if done. Severe *falciparum* malaria and anemia were defined according to the WHO guideline.[14,15] Anemia was defined as Hb $<$ 13 g/dL in men and $<$12 g/dL in women, whereas severe anemia as Hb $<$ 7 g/dL in adults and $<$8 g/dL in children.[15] Placental malaria was diagnosed, based on analysis of placenta blood, either by PCR, by blood smear or both. Anemia defined in terms of low packed cell volume (PCV) or hematocrit (HCT) was accepted. If Hb concentration were specified as $<$5 g/dL or 11 g/dL in the same group, then it was collectively grouped under Hb $<$ 11 g/dL. HIV was confirmed by an HIV RNA analysis/concentration, CD4+ cell counts, and rapid-onsite immunochromatographic test (RDT). For case-control studies, controls were not to be co-infected either with HIV or malaria, or vice versa. HIV in this study is HIV-1. Studies which did not meet the inclusion criteria were excluded.

Data Extraction and Quality Assessment

Two authors independently screened the citations, retrieved articles potentially eligible for the present study and extracted data from the studies, using a piloted data extraction sheet. Any discrepancies were resolved by consensus. The 2 investigators independently determined the quality of studies following the risk of bias assessment for nonrandomized studies (RoBANS) checklist, which consists of 6 domains.[16]

Statistical Analysis

For the variance stabilizing transformation of the proportions in estimating the prevalence of malaria and HIV co-infection, the Freeman–Tukey double arcsine transformation method was used as described elsewhere[17] and *metaprop* command in Stata. Details of this Stata command are available elsewhere.[18] Data were pooled using DerSimonian and Laird random-effect model, according to the results of heterogeneity testing.[19] For pooling of effect estimates for the effect of co-infection on anemia, summary odds ratio (OR) and its 95% CI for dichotomous data, and summary standardized mean difference (SMD) and its standard deviation (SD) for continuous data were used. The heterogeneity between these studies was assessed with the I^2 test. An I^2 value of $>$50% indicated substantial heterogeneity. For pooling of the results, a more conservative random-effect model was used as heterogeneity was substantial.[20]

Sensitivity Analysis

The prevalence of co-infections was stratified into infants, children, adults, and pregnant mothers. Due to paucity of data, stratification by *Plasmodium* species (*P vivax*, *P falciparum,* and mixed infections), CD4 counts in HIV, parasite density, or by gravidae were not possible. To account for within-study heterogeneity, metaregression on the prevalence of co-infection was performed using the publication year and total population as covariates. As a minimum number of 10 studies were available to investigate the publication bias,[20] a funnel plot was drawn with data of the effect size on anemia. This includes the regression line corresponding to the regression test for funnel-plot asymmetry.[21] Data entry was done in spreadsheet and analysis was with STATA 14.0 (Stata Corp, Txt). This study was approved by the Institutional Ethical Review Board ([BMS1–1/2015 [05]).

RESULTS

The study selection process was shown in the flowchart (Figure 1). The initial search yielded 2109 citations, of which 47 potentially met the inclusion criteria. A final of 23 studies (with 24 datasets) (n = 9159) were included in quantitative synthesis. Around one-third (37.5%) of the included studies were published between 2013 and 2015.

Characteristics of the Included Studies

The main characteristics of the 23 included studies[7,21–43] were presented in Table 1. Among the included studies, all but one study were carried out in the African countries. The remaining 1 was from Thailand in the WHO South-East Asia region.[42] A summary of the 24 excluded studies were provided[44–63] (see, Supplemental Table 1, http://links.lww.com/MD/A852). Sixteen of the 23 included studies used cohort designs; of them, 13 studies were prospective cohort designs, 2 studies were longitudinal cohort studies, and 1 study was nested-cohort study. Malaria transmission was high in all these African countries where studies in this review were done. Thailand has low malaria transmission potential. Many studies showed low or unclear risk of bias (see, Supplemental Table 2, http://links.lww.com/MD/A852).

Prevalence of Malaria and HIV Co-Infection

All 23 studies included in the present review provided data on prevalence of co-infection. Among these, 13 studies reported prevalence of HIV in malaria-infected patients,[22–24,27,28,30,35,37–40,42,43] whereas 10 studies on prevalence of malaria in HIV positives.[7,25,26,29,31–34,36,41]

Overall, prevalence of co-infection among individual studies ranged between 2% and 72% and pooled prevalence of co-infection was 19% (95% CI: 15–23%, I^2: 98.1%). The pooled analysis of 13 studies with HIV in malaria yielded a prevalence

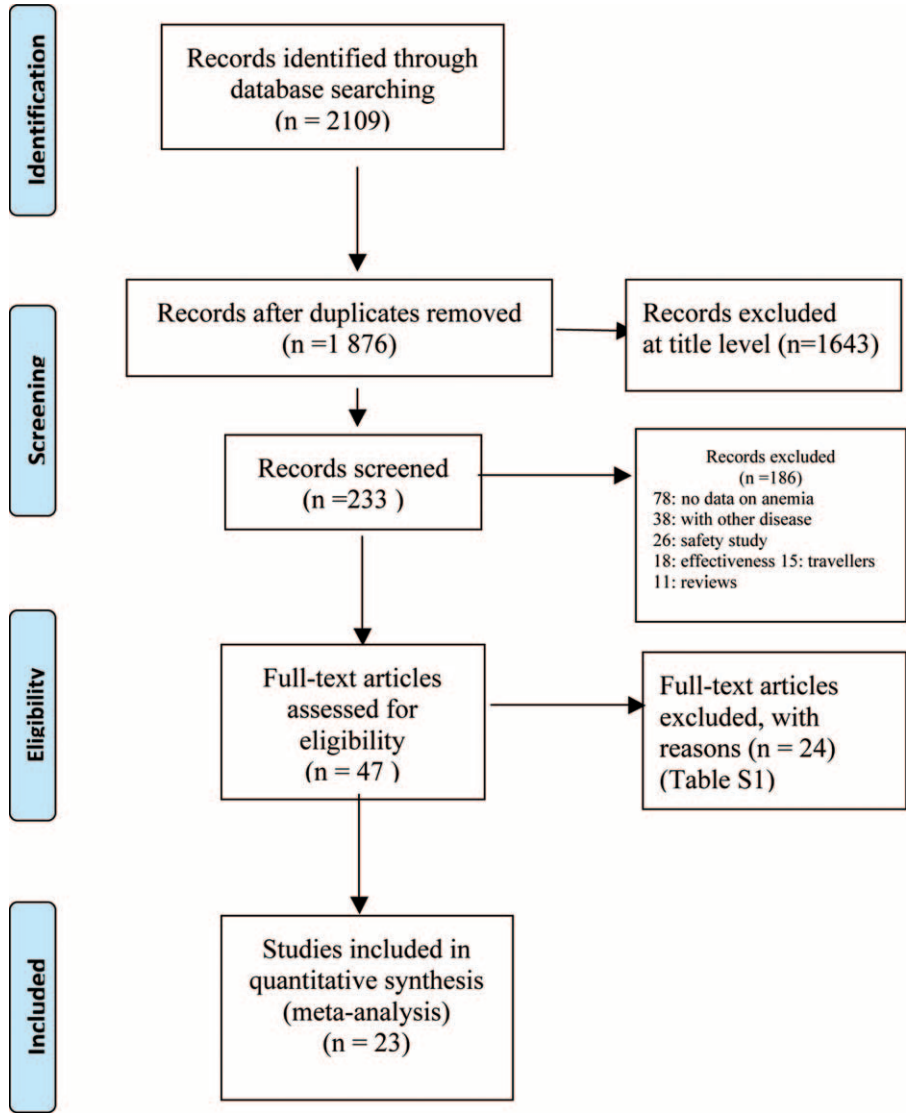


FIGURE 1. PRISMA flow diagram indicating the study selection process.

of 22% (95% CI: 16–27%, I^2: 98.5%). The pooled analysis of 10 studies with malaria in HIV-infected individuals yielded a prevalence of 16% (95% CI: 10–22%, I^2: 96.8%) (Figure 2).

Anemia in Co-infection

All studies measured anemia in terms Hb except for 2 which measured in terms of PCVs[32] and hematocrit.[22] Nine studies (with 10 datasets) compared mean Hb levels between those who had dual infection and those who had malaria or HIV infection.[7,25,26,30–32,35,36,40] Thirteen studies compared proportions of anemia between those who were co-infected and those who had monoinfected.[22,24,27–29,33,34,37–39,41–43] Anemia was comparable between the monoinfected and co-infected adults (summary OR:1.49,95%CI:0.93–2.37) and increased by 49% in co-infected pregnant women (summary OR:1.49,95%CI:1.14–1.94) (Figure 3). Only 1 study on children reported that anemia was 5.5 times more in the co-infected group.[28]

When stratified by infection groups, studies with malaria in HIV showed significant lower level of Hb concentrations in the co-infected group than in the individuals infected with malaria alone (summary SMD:−0.47, 95% CI:−0.61 to −0.33). On further breakdown, this was (summary SMD: -0.33, 95% CI:-0.51 to -0.14) among adults and (summary SMD: −0.66, 95% CI: -0.87 to -0.45) among pregnant women (Figure 4). As expected, a fall in Hb concentration was more pronounced in pregnant women than in the nonpregnant adults.

Subgroup Analysis on Prevalence of Co-infection

Studies identified for the current analysis were done in different subgroups. By age groups, prevalence of co-infection was 26% (95% CI: 20–32%, I^2: 98.7%) in adults, 12% (95% CI: 7–17%, I^2: 95.0) in pregnant women and 9% (95% CI: 6–11%, I^2: 68.6%) in children (see, Supplemental Figure 1, http://links.lww.com/MD/A852, which shows prevalence of co-infections stratified by age groups). Only 1 study on infants reported

TABLE 1. Characteristics of the Included Studies

No.	Author, y [ref]	Study Duration	Country	Study Setting	Study Design	Study Participants	Malaria Endemicity	Male %	Mean Age ± SD (y)	Co-infected Cases/Total Cases	Malaria Status	Malaria Species	Confirmation of Malaria	Confirmation of HIV	Hb Level (g/dL)	Adjusted Factors[¶]
1.	Tay et al, 2015[7]	Nov 2011–Jan 2012	Ghana	Hp	CS	Children and adults (1–73 y)	High	27	NA	47/400	UCM	Pf	M	ICT, CD4 count	Mean	Age
2.	Niyongabo et al, 1994[22]	Mar 1991–Mar 1992	Burundi	Hp	PC	Adults	High	71	28.6 ± 13.2	2/31	SM	Pf	M	EIA, Wb	Ht < 30%	Age, sex
3.	Ladner et al, 2002[23]	Jul 1992–Aug 1993	Rwanda	Hp	PC	Pregnant women	High	NA	25.8 ± 4.7	18/47	UCM	Pf	M	EIA, Wb	<11	Age
4.	Grimwade et al, 2004[24]	Jan 2000–May 2000	South Africa	Hp	PC	Adults (>14 y)	High	39	30 (22–42)	180/613	UCM	Pf	M	EIA	<5	Duration of illness, PG, previous malaria and Rx
5.	Mount et al, 2004[25]	Dec 2000–Jul 2002	Malawi	Hp	PC	Pregnant women	High	NA	24.1 ± 4.7	44/298	UCM	Pf	M	CD4 count, HIV-1 RNA assay	Mean	Age
6.	Mwapasa et al, 2004[26]	Dec 2000–Jun 2002	Malawi	Hp	PC	Pregnant women	High	NA	23.9 (20.9–27.0)	74/304	UCM	Pf	M	Rapid AB test	Mean	Age
7.	Cohen et al, 2005[27]	Jan–May 2001, Jan–Apr 2002	South Africa	Hp	PC	Adults (15–49 y)	High	77	30 (17–49)[*]	110/336	SM	Pf	M	CD4 count, EIA	Mean	Demographic characteristics, country of origin and the duration of residence
8.	Otieno et al, 2006[28]	NA	Kenya	Hp	PC	Children <2yr	High	12[*]	12 ± 0.11	23/317	UCM	Pf	M, CBC	Rapid AB test, PCR	<5	Age, sex, area of residence
9.	Ned et al, 2008[29]	Jun 1996–Aug 2001	Kenya	Hp	LC	Infants	High	51.9[†]	1.02 ± 0.02[‡]	62/404	UCM	Pf	M	EIA	<11	NA
10.	Van Geertruyden et al, 2009[30]	Oct 2004–Jun 2005	Zambia	HC	Nested cohort in RCT	Adults (15–50yr)	High	37.4	29.5 ± 7.6	115/339	UCM	Pf	M, PCR	EIA, CD4 count, PCR	Mean	NA
11.	Chinedum et al, 2010[31]	NA	Nigeria	Hp	PC	Adults	High	NA	NA	19/101	UCM	Pf	NA	NA	Mean	NA
12.	Ukibe et al, 2010[32]	NA	Nigeria	Cl	PC	Adults (16–72)	High	48.3	44 ± 28	91/207	UCM	Pf	M	ICT	PCV	NA
13.	Idindili et al, 2011[33]	Apr 2008–Apr 2009	Tanzania	Hp, HC	PC	Adults	High	40[§]	35.5 ± 1.3[§]	50/421	UCM	Mixed	M	EIA	<8	Age, PG, severe diseases
14.	Akinbo and Omoregie, 2012[34]	Jul 2010–Jun 2011	Nigeria	Hp	CS	Adults (20–66yr)	High	29.5	NA	6/285	UCM	Pf	M	CD4 count	<13 (mal) <12 (fem)	Age
15.	Hendriksen et al, 2012[35]	Oct 2005–July 2010	Mozambique	Hp	PC	Adults >15yr	High	55	27 (25–38)	74/655	UCM	Pf	M, peripheral blood parasite count	CD4 count, rapid AB test	<5	Age, Rx
						Children <15yr,			5 (3–8)	49/68						
16.	Tchinda et al, 2012[36]	Apr–Jun 2010	Cameroon	Hp	CS	Adults		32.4	NA	59/238	UCM	Pf	M	CD4 count	Mean	Age, gender, CD4 count, ART
17.	Iriemenam et al, 2013[37]	1996–2001	Kenya	Hp	PC	Pregnant women	High	NA	21.6 ± 4.6[‖]	119/728	SM	Pf	M	Rapid AB test, flow cytometry	<11	NA
18.	Sanyaolu et al, 2013[38]	1996–1997	Nigeria	Hp	CS	Adults and children	High	52.8	NA	31/1080	UCM	Pf, Pm	M	Rapid AB test	<11	NA
19.	Berg et al, 2014[39]	Jan–March 2011 Nov 2011–March 2012	Mozambique	Hp	CS	Adults	High	53	44.03 ± 16.754	70/131	UCM	Pf	M, PCR	RT-PCR	<5	PG
20.	Kyeyune et al, 2014[40]	Jul 2002– Jul 2004	Malawi	Hp	CS	Children	High	40	1.7 (0.75–5)	26/356	UCM	Pf	M	Rapid AB test, PCR	<5	Age & study site
21.	Manyanga et al, 2014[41]	Feb–Apr 2013	Tanzania	Hp, HC, Dis	CS	Pregnant women	High	NA	28 ± 5.2	19/420	UCM	Pf	MRDT	CD4 count	<11	NA
22.	Rattanapunya et al, 015[42]	2005–2013	Thailand	Cl	PC	Adults	Low	66.7	NA	16/867	UCM	Pf	M	CMIA, gel particle passive agglutination, PCR	<12	Sex, age, ethnicity,
23.	Wumba et al, 2015[43]	2009–2012	Congo	Hp	PC	Pregnant women	High	NA	28.6 ± 6.1	19/332	UCM	Pf	M, PCR	Rapid AB test	<11	Age

AB = antibody; ART = antiretroviral therapy; CL = clinic; CMIA = chemiluminescent microparticle immunoassay; CS = cross-sectional study; Dis = dispensary; EIA = enzyme-linked immunosorbent assay; HC = Health center; Hp = hospital-based study; ICT = immuno-chromatographic rapid test; LC = longitudinal cohort; M = microscopy; MRDT = malaria rapid diagnostic test; NA = not available/not reported; PC = prospective cohort; PCR = polymerase chain reaction; PG = pregnancy; RCT = randomized control trial; Ref = reference number; RT-PCR = reverse transcription polymerase chain reaction; Rx = treatment; SM = severe malaria; UCM = uncomplicated malaria; Wb = western blot technique.

[*] HIV+ cases only.

[†] Percentage of co-infected male infants only.

[‡] Co-infected infants at their first follow-up.

[§] Patients with HIV and malaria parasite only.

[‖] Co-infected mothers only.

[¶] Factors that may affect that relationship.

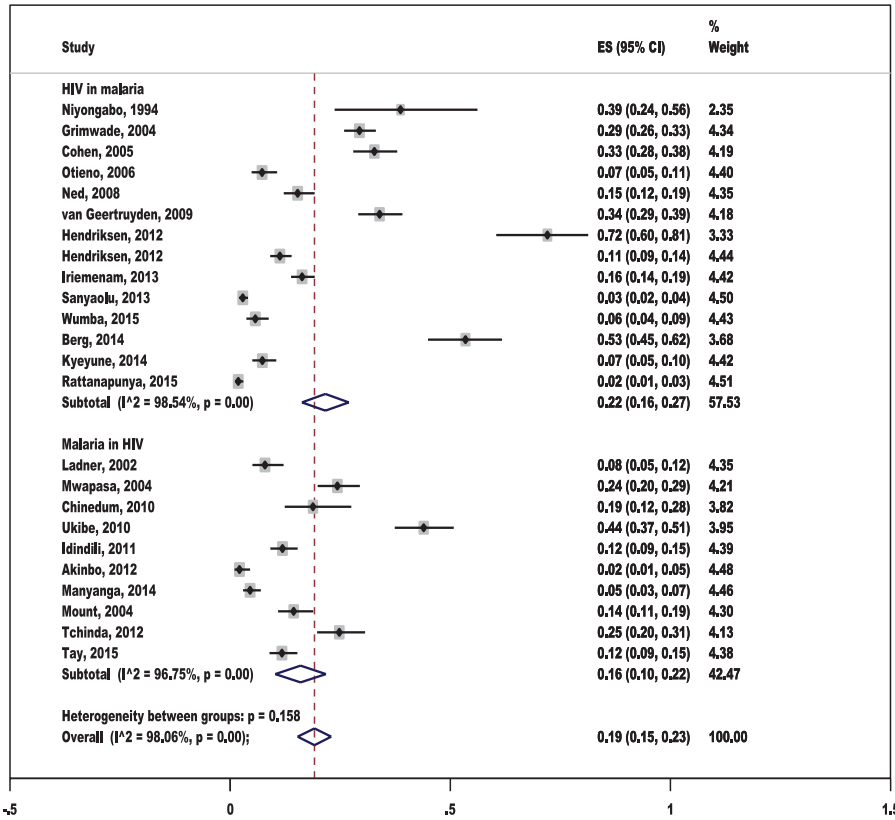


FIGURE 2. Forest plot showing overall prevalence of co-infections.

the prevalence of co-infection was 15% (95%CI:12–19%).[29] The prevalence of co-infection among severe/complicated malaria cases was 28% (95% CI: 14–42%, I^2: 94.5%) and 18% (95% CI: 14–22%, I^2: 98.0%) among uncomplicated malaria cases (data not shown).

The metaregression plots obtained show that the publication year of the included studies could explain only 4.1% of the heterogeneity (figure not shown) and size of the denominator population of the included studies could attribute to 29.2% of the heterogeneity (Figure 5). The funnel plot of studies assessing effect on anemia showed an asymmetrical plot in the presence of publication bias among studies. This might be a result of the smaller studies producing smaller effect size[21] (Figure 6).

DISCUSSION

The current meta-analysis provides information on the prevalence of malaria and HIV co-infections and its impact on anemia in endemic countries.

Prevalence of Co-infection

As shown, the prevalence of HIV in malaria cases was higher (16–27%) than that of the malaria in HIV-infected patients (15–23%). This implies that the 2 pathogens could interact synergistically in human hosts.[64] Thus, the communities in these regions suffer a double burden of these 2 infections, with the higher burden being the HIV infections. HIV infection could impair immune responses to malaria parasites, leading to a decreased ability to control parasitemia,[27] whereas malaria infection can modulate HIV progression[65] and HIV RNA replication.[29,64,66]

It has been established that both humoral and cellular immune responses play protective roles against malaria infection.[65] During a humoral response the HIV-associated decline in antibody responses to variant surface antigens (VSAs) could partially explain the increased susceptibility of HIV-infected pregnant women to malaria. Hence, HIV infection impairs antimalarial immunity, most notably in immunosuppressed women. This increases the susceptibility of women to malaria during pregnancy. Studies have documented that the placenta provide a unique and hospitable niche for HIV-1 replications.[63,67]

Effect on Anemia

The cause of anemia is multifactorial, involving a number of mechanisms. Both malaria and HIV could individually cause anemia; the present analysis has documented that anemia was comparable between the monoinfected and co-infected adults. Both infections can lead to loss of appetite. Furthermore, advanced HIV/AIDS cases may cause diseases of the gastrointestinal tract, leading to malabsorption of nutrients necessary for the formation of Hb, which subsequently results in anemia.[58] Also, the ability of HIV to infiltrate the bone marrow[68] could accentuate the progression of anemia in co-infected individuals.

It has been well established that the primary target of human plasmodium species is the red blood cells (RBCs). In both *vivax* and *falciparum* malaria, parasitized and possibly

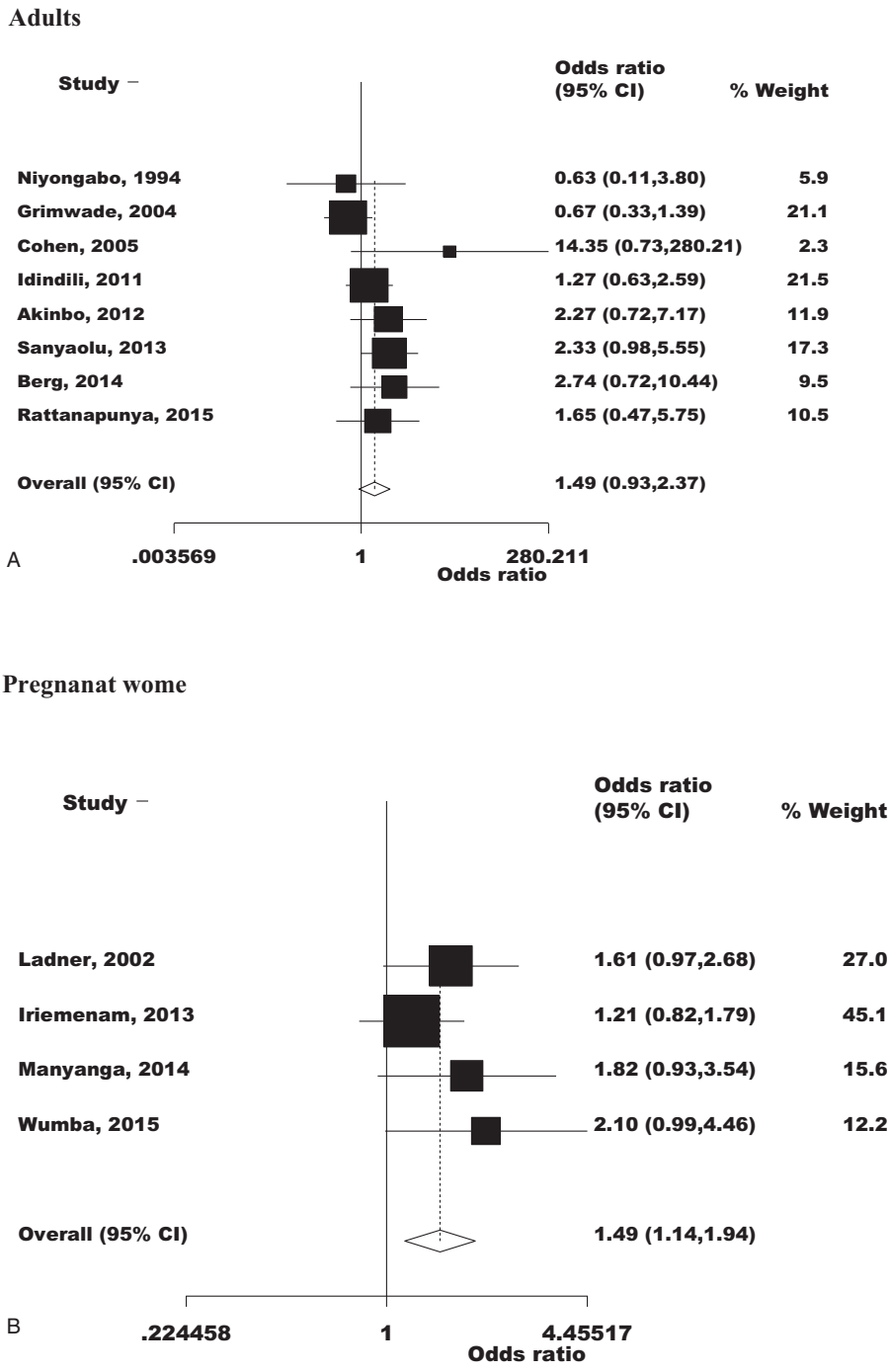
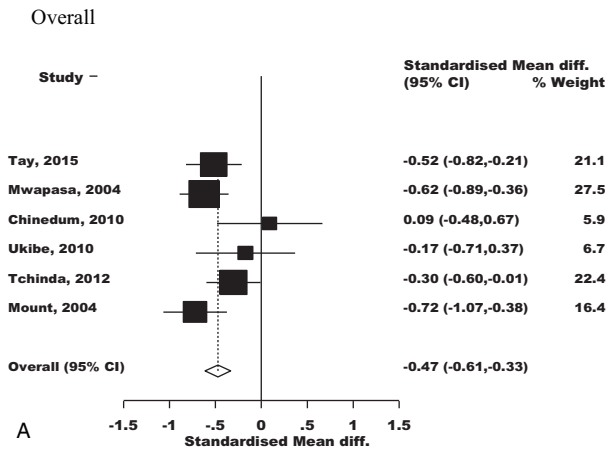
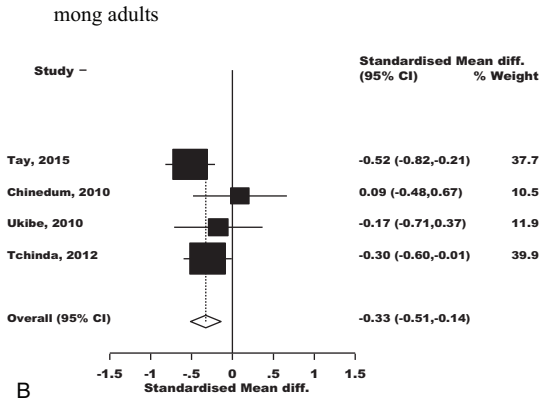


FIGURE 3. Overall anemia comparing between the co-infection and the monoinfection groups.

nonparasitized RBCs are hypothesized to be more fragile than RBCs in noninfected individuals and more prone to damage from shear stress.[69] Malaria causes anemia through increased destruction of infected RBCs as well as uninfected RBCs.[70]

Studies had documented multiple factors that can contribute to ineffective erythropoiesis in severe malaria anemia including (i) hemozoin-induced repression of macrophage function, (ii) secretion of proinflammatory cytokines from macrophages, and (iii) perturbation of erythroblast metabolism with the resultant decrease in RBC output from the bone marrow.[71] Details of these mechanisms are described elsewhere.[70,71] An empirical study showed that HIV-infected multigravidae were less likely to clear infection than primigravidae. The altered immune-recognition in the setting of HIV could have contributed to it.[59] This implies that in malaria endemic regions, anemia could be more pronounced in multigravidae women co-infected with HIV/AIDS.





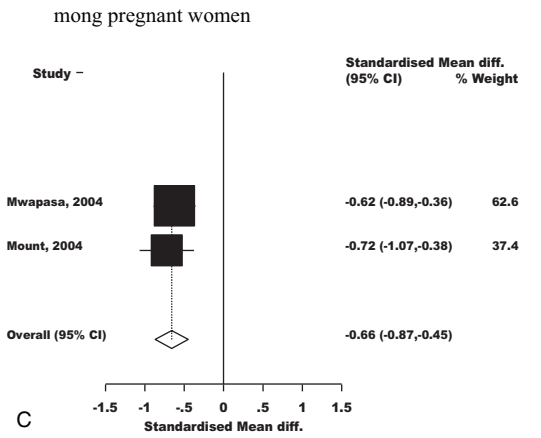


FIGURE 4. Forest plot indicating the overall effect of malaria in HIV on anemia.

Study Limitations

A small number of participants in some studies identified for this review may not be adequately powered to reach the statistically significant level between the co-infected group and the mono-infected group. Sampling bias could occur if the participant groups, whether HIV-positive and HIV-negative

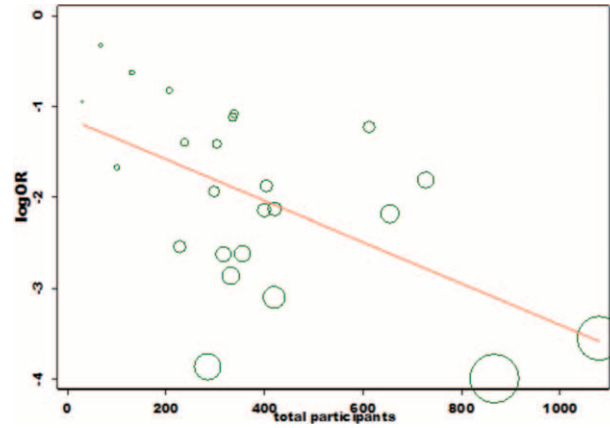


FIGURE 5. Meta-regression plot on prevalence of co-infection and size of denominator population.

or malaria positive and malaria negative were recruited at different times of the year. It is also important to note antiretroviral therapy (ART) such as zidovudine may cause anemia in HIV/AIDS patients as well as malaria and HIV co-infected patients. Other confounding factor includes the possibility of co-medication effects and other comorbidity conditions (e.g., tuberculosis, hepatitis B, hepatitis C, diabetes mellitus, renal failure, and chronic liver disease) in the participants in primary studies. These factors should be kept in mind when interpreting the findings. Furthermore the quality of included studies varied because many of these studies were not primarily aimed to assess the effect of anemia in co-infections. This could have attributed to ascertainment bias among these studies. As there was publication bias, findings in the current analysis should be interpreted with caution.

Public Health Implications

Anemia caused by *P falciparum* remains the frequent indication for blood transfusion in Sub-Saharan Africa.[72] As HIV can affect the course of malaria infection in many ways, screening of HIV for blood transfusion is important. Moreover, routine screening of pregnant women for both HIV and malaria at the first antenatal visits and education on malaria prevention

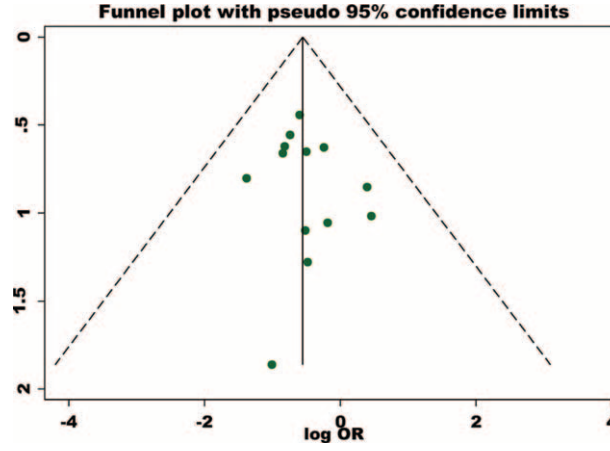


FIGURE 6. Asymmetrical funnel plot in the presence of publication bias.

(e.g., insecticide-treated nets and intermittent prophylactic treatment) should be initiated.

CONCLUSION

The findings of this study suggest that the prevalence of malaria and HIV co-infection, particularly in pregnant women, requires special attention from healthcare personnel. Better understanding of the co-infection is crucial for designing treatment strategies. Future well-powered, prospective designs assessing the interaction between malaria and HIV are recommended.

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REFERENCES

1. Global technical strategy for malaria 2016–2030. World Health Organization [Online]. 2015 [cited 2015 Sept 12]; Available at: http://www.who.int/malaria/areas/global_technical_strategy/en/ (accessed on 12 September 2015).
2. Malaria and HIV interactions and their implications for public health policy. World Health Organization [Online]. 2004 [cited 2015 Sept 12]; Available at: http://www.who.int/hiv/pub/prev_care/malaria-hiv.pdf (accessed September 12, 2015).
3. Guyatt HL, Snow RW. The epidemiology and burden of *Plasmodium falciparum*-related anemia among pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg.* 2001;64(1–2 Suppl):36–44.
4. Nguyen-Dinh P, Greenberg AE, Mann JM, et al. Absence of association between *Plasmodium falciparum* malaria and human immune-deficiency virus infection in children in Kinshasa, Zaire. *Bull World Health Organ.* 1987;65:607–613.
5. Cuadros DF, Branscum AJ, García-Ramos G. No evidence of association between HIV-1 and malaria in populations with low HIV-1 prevalence. *PLoS One.* 2011;6:e23458.
6. Mouala C, Houzé S, Guiguet M, et al. Imported malaria in HIV-infected patients enrolled in the ANRS CO4 FHDH study. *J Acquir Immune Defic Syndr.* 2008;49:55–60.
7. Tay SCK, Badu K, Mensah AA, et al. The prevalence of malaria among HIV seropositive individuals and the impact of the co-infection on their hemoglobin levels. *Ann Clin Microbiol and Antimicrob.* 2015;14:10.
8. Hewitt K, Steketee R, Mwapasa V, et al. Interactions between HIV and malaria in non-pregnant adults: evidence and implications. *AIDS.* 2006;20:1993–2004.
9. Blumberg L, Frean J. Malaria control in South Africa—challenges and successes. *S Afr Med J.* 2007;97:1193–1197.
10. Ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in Sub-Saharan Africa. *Am J Trop Med Hyg.* 2004;71:41–54.
11. Petitti DB. Meta-analysis, Decisions Analysis and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine. 2nd ed. New York: Oxford University Press; 2000.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA.* 2000;283:2008–2012.
13. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PloS Med.* 2009;6:e1000097.
14. World Health Organization (WHO). Severe falciparum malaria. *Trans R Soc Trop Med Hyg.* 2000;94:1–31.
15. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. World Health Organisation [Online]. 2011 [cited 2015 Sept 12]. Available at: http://apps.who.int/iris/bitstream/10665/85839/3/WHO_NMH_NHD_MNM_11.1_eng.pdf (accessed September 12, 2015).
16. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol.* 2013;66:408–414.
17. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist.* 1950;21:607–611.
18. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health.* 2014;72:39.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–188.
20. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. West Sussex, England: Wiley-Blackwell; 2011.
21. Egger M, Smith GD, Schneider M, et al. Bias in meta-anaysis detected by a simple, graphical test. *BMJ.* 1997;315:629–634.
22. Niyongabo T, Deloron P, Aubry P, et al. Prognostic indicators in adult cerebral malaria: a study in Burundi, an area of high prevalence of HIV infection. *Acta Trop.* 1994;56:299–305.
23. Ladner J, Leroy V, Simonon A, et al. HIV infection, malaria and pregnancy: a prospective cohort study in Kigali, Rwanda. *Am J Trop Med Hyg.* 2002;66:56–60.
24. Grimwade K, French N, Mbatha DD, et al. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS.* 2004;18:547–554.
25. Mount AM, Mwapasa V, Elliott SR, et al. Impairment of humoral immunity to *Plasmodium falciparum* malaria in pregnancy by HIV infection. *Lancet.* 2004;363:1860–1867.
26. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of *Plasmodium falciparum* malaria onperipheral and placental HIV-1 RNA concentrations in pregnant Malawian women. *AIDS.* 2004;18:1051–1059.
27. Cohen C, Karstaedt A, Frean J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis.* 2005;41:1631–1637.
28. Otieno RO, Ouma C, Ong'echa JM, et al. Increased severe anemia in HIV-1-exposed and HIV-1-positive infants and children during acute malaria. *AIDS.* 2006;20:275–280.
29. Ned RM, Price AE, Crawford SB, et al. Effect of placental malaria and HIV infection on the antibody responses to *Plasmodium falciparum* in infants. *J Infect Dis.* 2008;198:1609–1619.
30. van Geertruyden JP, van Eijk E, Yosaatmadja F, et al. The relationship of *Plasmodium falciparum* humeral immunity with HIV-1 immunosuppression and treatment efficacy in Zambia. *Malar J.* 2009;8:258.
31. Chinedum CO, Chidiebere FE, Adamma RA, et al. Serum iron markers in HIV and HIV-malaria infected participants residing in malaria endemic area of South-Eastern Nigeria. *Int J Biol Chem Sci.* 2010;4:2409–2414.
32. Ukibe NR, Onyenekwe C, Ahaneku J, et al. Packed cell volume and serum iron in subjects with HIV-malaria co-infection in Nnewi, South-Eastern Nigeria. *Int J Biol Chem Sci.* 2010;4:471–478.

33. Idindili B, Jullu B, Hattendorft J, et al. HIV and parasitic co-infections among patients seeking care at health facilities in Tanzania. *Tanzan J Health Res.* 2011;13:75–85.
34. Akinbo FO, Omoregie R. *Plasmodium falciparum* infection in HIV-infected patients on highly active antiretroviral therapy (HAART) in Benin City, Nigeria. *J Rest Health Sci.* 2012;12:15–18.
35. Hendriksen IC, Ferro J, Chhanganlal KD, et al. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-co-infected children and adults in Mozambique. *Clin Infect Dis.* 2012;55:1144–1153.
36. Tchinda GG, Atashili J, Achidi EA, et al. Impact of malaria on hematological parameters in people living with HIV/AIDS attending the Laquintinie Hospital in Douala, Cameroon. *PLoS One.* 2012;7:e40553.
37. Iriemenam NC, Pandey JP, Williamson J, et al. Association between immunoglobulin GM and KM genotypes and placental malaria in HIV-1 negative and positive women in western Kenya. *PLoS One.* 2013;8:e53948.
38. Sanyaolu AO, Fagbenro-Beyioku AF, Oyibo WA, et al. Malaria and HIV co-infection and their effect on haemoglobin levels from three health-care institutions in Lagos, Southwest Nigeria. *Afr Health Sci.* 2013;13:295–300.
39. Berg A, Patel S, Aukrust P, et al. Increased severity and mortality in adults co-infected with malaria and HIV in Maputo, Mozambique: a prospective cross-sectional study. *PLoS One.* 2014;9:e88257.
40. Kyeyune FX, Calis JC, Phiri KS, et al. The interaction between malaria and human immunodeficiency virus infection in severely anaemic Malawian children: a prospective longitudinal study. *Trop Med Int Health.* 2014;19:698–705.
41. Manyanga VP, Minzi O, Ngasala B, et al. Prevalence of malaria and anaemia among HIV infected pregnant women receiving co-trimoxazole prophylaxis in Tanzania: a cross sectional study in Kinondoni Municipality. *BMC Pharmacol Toxicol.* 2014;15:24.
42. Rattanapunya S, Kuesap J, Chaijaroenkul W, et al. Prevalence of malaria and HIV co-infection and influence of HIV infection on malaria disease severity in population residing in malaria endemic area along the Thai–Myanmar border. *Acta Trop.* 2015;145:55–60.
43. Wumba RD, Zanga J, Aloni MN, et al. Interactions between malaria and HIV infections in pregnant women: a first report of the magnitude, clinical and laboratory features, and predictive factors in Kinshasa, the Democratic Republic of Congo. *Malar J.* 2015;14:82.
44. Simooya OO, Mwendapole RM, Siziya S, et al. Relation between falciparum malaria and HIV seropositivity in Ndola, Zambia. *BMJ.* 1988;297:30–31.
45. Greenberg AE, Nsa W, Ryder RW, et al. *Plasmodium falciparum* malaria and perinatally acquired human immunodeficiency virus type 1 infection in Kinshasa, Zaire. *New Engl J Med.* 1991;325:105–109.
46. Kalyesubula I, Musoke-Mudido P, Marum L, et al. Effects of malaria infection in human immunodeficiency virus type-1 infected Ugandan children. *Pediatr Infect Dis J.* 1997;16:876–881.
47. Chandramohan D, Greenwood BM. Is there an interaction between human immunodeficiency virus and *Plasmodium falciparum*? *Int J Epidemiol.* 1998;27:296–301.
48. Bastos FI, Barcellos C, Lowndes CM, et al. Co-infection with malaria and HIV in injecting drug users in Brazil: a new challenge to public health? *Addiction.* 1999;94:1165–1174.
49. French N, Gilks CF. Fresh from the field: some controversies in tropical medicine and hygiene. HIV and malaria, do they interact? *Trans R Soc Trop Med Hyg.* 2000;94:223–237.
50. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet.* 2000;356:1051–1056.
51. Rowland-Jones SL, Lohman B. Interactions between malaria and HIV infection—an emerging public health problem? *Microbes Infect.* 2002;4:1265–1270.
52. Ayisi JG, Branch OH, Rafi-Janajreh A, et al. Does infection with human immunodeficiency virus affect the antibody responses to *Plasmodium falciparum* antigenic determinants in asymptomatic pregnant women? *J Infect.* 2003;46:164–172.
53. Kassa D, Petros B, Messele T, et al. Parasito-haematological features of acute *Plasmodium falciparum* and *P. vivax* malaria patients with and without HIV co-infection at Wonji Sugar Estate, Ethiopia. *Ethiop J Health Dev.* 2005;19:132–139.
54. Kublin JG, Patnaik P, Jere CS, et al. Effect of *Plasmodium falciparum* malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet.* 2005;365:233–240.
55. Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis.* 2005;192:984–991.
56. Bronzan RN, Taylor TE, Mwenechanya J, et al. Bacteremia in Malawian children with severe malaria: prevalence, etiology, HIV co-infection, and outcome. *J Infect Dis.* 2007;195:895–904.
57. Jaworowski A, Kamwendo DD, Ellery P, et al. CD16+ monocyte subset preferentially harbors HIV-1 and is expanded in pregnant Malawian women with *Plasmodium falciparum* malaria and HIV-1 infection. *J Infect Dis.* 2007;196:38–42.
58. Mehta S, Manji KP, Young AM, et al. Nutritional indicators of adverse pregnancy outcomes and mother-to-child transmission of HIV among HIV-infected women. *Am J Clin Nutr.* 2008;87:1639–1649.
59. Newman PM, Wanzira H, Tumwine G, et al. Placental malaria among HIV-infected and uninfected women receiving anti-folates in a high transmission area of Uganda. *Malar J.* 2009;8:254.
60. Imani PD, Musoke P, Byarugaba J, et al. Human immunodeficiency virus infection and cerebral malaria in children in Uganda: a case-control study. *BMC Pediatr.* 2011;11:5.
61. Wariso KT, Nwauche CA. The prevalence of malaria antigen in the serum of HIV seropositive patients in Port Harcourt. *Nigerian Health Journal.* 2011;11.
62. Laar AK, Grant FE, Addo Y, et al. Predictors of fetal anemia and cord blood malaria parasitemia among newborns of HIV-positive mothers. *BMC Res Notes.* 2013;6:350.
63. Turner AN, Tabbah S, Mwapasa V, et al. Severity of maternal HIV-1 disease is associated with adverse birth outcomes in Malawian women: a cohort study. *J Acquir Immune Defic Syndr.* 2013;64:392–399.
64. Orlov M, Vaida F, Finney OC, et al. *P. falciparum* enhances HIV replication in an experimental malaria challenge system. *PLoS One.* 2012;7:e39000.
65. Ned RM, Moore JM, Chaisavaneeyakorn S, et al. Modulation of immune responses during HIV-malaria co-infection in pregnancy. *Trends Parasitol.* 2005;21:284–292.
66. Ismaili J, van der Sande M, Holland MJ, et al. *Plasmodium falciparum* infection of the placenta affects new-born immune responses. *Clin Exp Immunol.* 2003;133:414–421.
67. Kumar SB, Handelman SK, Voronkin I, et al. Different regions of HIV-1 subtype C env are associated with placental localization and in utero mother-to-child transmission. *J Virol.* 2011;85:7142–7152.
68. Moses AV, Williams S, Heneveld ML, et al. 1996. Human immunodeficiency virus infection of bone marrow endothelium

reduces induction of stromal hematopoietic growth factors. *Blood.* 1996;87:919–925.

69. Douglas NM, Anstey NM, Buffet PA, et al. The anaemia of *Plasmodium vivax* malaria. *Malar J.* 2012;11:135.
70. Lamikanra AA, Brown D, Potocnik A, et al. Malarial anemia: of mice and men. *Blood.* 2007;110:18–28.
71. Lamikanra AA, Merryweather-Clarke AT, Tipping AJ, et al. Distinct mechanisms of inadequate erythropoiesis induced by tumor necrosis factor alpha or malarial pigment. *PLoS One.* 2015;10:e0119836.
72. Idemyor V. Human immunodeficiency virus (HIV) and malaria interaction in sub-Saharan Africa: the collision of two Titans. *HIV Clin Trials.* 2007;8:246–253.