Uncovering HIV and malaria interactions: the latest evidence and knowledge gaps

Antía Figueroa-Romero, Anna Saura-Lázaro, Sheila Fernández-Luis, Raquel González

The geographical distribution of malaria and HIV infections widely overlap in sub-Saharan Africa, constituting a complex global health challenge. The interplay between both infections raises concerns about potential immunological, clinical, and therapeutic interactions. Both diseases have been reported to exacerbate the transmission of the other, including the possible vertical transmission of HIV in pregnant individuals with malaria. Co-infection also increases the risk of adverse outcomes such as severe malaria and death. In addition, interactions between antiretroviral and antimalarial drugs have been reported, potentially reducing the efficacy of these drugs. We review the current knowledge of the epidemiological, clinical, immunological, and therapeutic interactions of both infections. We focus on the latest available data and identify key knowledge gaps that should be addressed to guide policy makers in providing optimal HIV and malaria prevention, care, and treatment in vulnerable populations.

Lancet HIV 2024; 11: e255–67

Published Online
March 5, 2024
https://doi.org/10.1016/S2352-3018(24)00035-3

Barcelona Institute for Global Health (ISGlobal), Hospital Clínic-Universitat de Barcelona, Barcelona, Spain (A Figueroa-Romero MSc, A Saura-Lázaro MD, S Fernández-Luis PhD, R González PhD)**; Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain** (A Figueroa-Romero, R González)**; Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique** (S Fernández-Luis, R González)**; Pediatrics Department, Pediatric Research and Clinical Trials Unit (UPIC), Fundación para la Investigación Biomédica del Hospital 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (IMAS12), Madrid, Spain** (S Fernández-Luis)

Correspondence to:
Dr Raquel González, Barcelona Institute for Global Health (ISGlobal), Hospital Clínic-Universitat de Barcelona, Barcelona 08036, Spain
raquel.gonzalez@isglobal.org

Introduction

Malaria and HIV infections constitute two of the most important global health concerns, as they are leading causes of morbidity and mortality worldwide.[1] The geographical distribution and social determinants of both diseases greatly overlap in tropical regions, particularly in sub-Saharan Africa.[1] Consequently, malaria and HIV co-infection is common in this region, leading to opportunities for complex disease interactions at both the individual and population level.[2]

Available evidence suggests that malaria and HIV have a synergistic effect, with co-infection exponentially exacerbating the adverse effects of one infection on the other, thus adversely affecting prognoses and complicating the prevention and treatment of both diseases (figure 1).[2,3] Moreover, malaria and HIV co-infection has been shown to speed up the spread of both diseases in sub-Saharan Africa, and the treatment of individuals living with HIV and malaria has raised concerns about potential drug interactions.[4,5]

Therefore, gaining comprehensive understanding of the interaction of these two infections is imperative for effective control, particularly in sub-Saharan Africa, where the burden of the two diseases is concentrated. This Review summarises the latest evidence on the burden of malaria and HIV co-infection, the effect of one infection on the transmission of the other, and the implications of co-infection on biological, clinical, and immunological outcomes. This Review also discusses therapeutic strategies for managing individuals living with both malaria and HIV, concluding with some knowledge gaps and policy implications.

The overlapping burden of HIV and malaria

In 2022, there were an estimated 249 million cases of malaria worldwide, resulting in 0·61 million related deaths.[1] Sub-Saharan Africa accounted for approximately 94% of all malaria cases and 95% of all malaria-related deaths.[1] *Plasmodium falciparum* was the most prevalent malarial parasite in the region, and children younger than 5 years and pregnant women were the most affected groups.[6] Globally, there were an estimated 39 million people living with HIV in 2022, approximately 1·3 million new diagnoses, and 0·63 million HIV-related deaths.[7] More than half of people living with HIV were adolescent girls and women (53%), and children younger than 15 years accounted for approximately 10% of all newly acquired HIV.[7] Similarly to malaria, the global HIV epidemic has the greatest impact in sub-Saharan Africa, with an estimated 67% of people living with HIV worldwide residing in this region.[7]

The distribution of HIV and malaria overlaps in many regions, including in southeast Asia, Latin America and the Caribbean, and particularly in sub-Saharan Africa (figure 2).[6–8] The most severely affected countries include Zambia, Zimbabwe, Mozambique, Malawi, and the Central African Republic. In these countries, HIV prevalence exceeds 10%, and 90% of the population is exposed to malaria.[6] Besides the geographical overlap in distribution, there is also social overlap. Both diseases disproportionately affect people in the lowest income bracket in these populations, who do not have access to quality education, information, and state services, all of which are especially relevant in sub-Saharan Africa.[2]

The prevalence of malaria and HIV co-infection has been estimated to be 19% overall in sub-Saharan Africa, with values of 26% in non-pregnant adults, 12% in pregnant women, and 9% in children.[9] Furthermore, a 2018 review[2] reported varying prevalences of malaria and HIV co-infection across different populations and regions in sub-Saharan Africa, ranging from 0·7% to 72%, with values of 0·7% to 47·5% in non-pregnant adults, 0·94% to 37% in pregnant women, and 1·2% to 27·8% in children.

Pathophysiology and clinical implications of HIV and malaria co-infection

Clinical implications of HIV and malaria co-infection

Previous studies have reported that children with both malaria and HIV have an increased prevalence of severe clinical malaria, which presents with severe acidosis, anaemia, respiratory distress, convulsions and increased

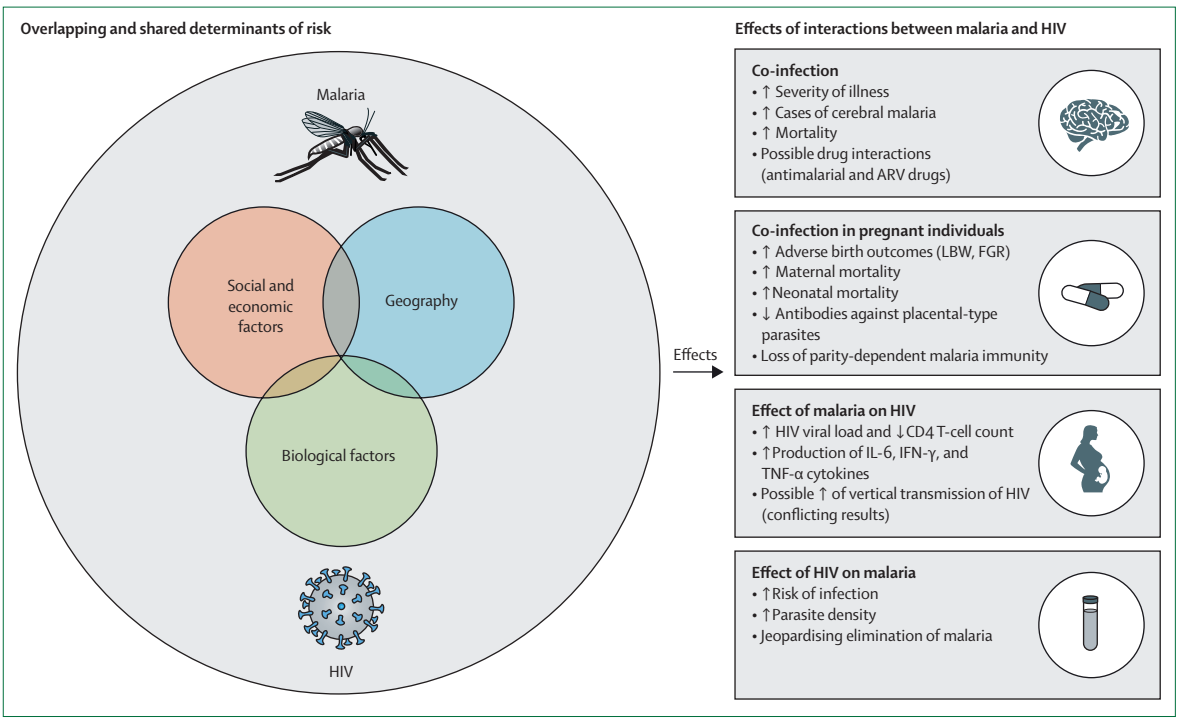

Figure 1: **The most relevant interactions between HIV and malaria**
FGR=fetal growth restriction. IFN=interferon. IL=interleukin. LBW=low birthweight. TNF=tumour necrosis factor.

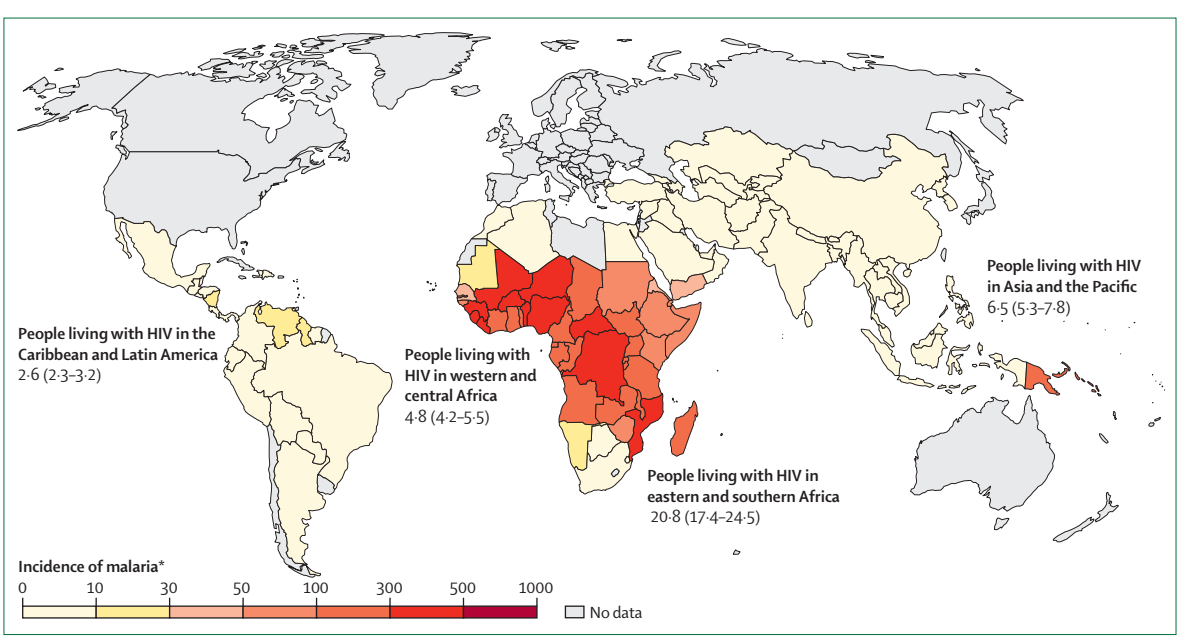

Figure 2: **Map of the incidence of malaria in 2020 showing the number of people living with HIV (in millions) in 2022 in areas where malaria is transmitted**
HIV data are point estimates (range). Map reproduced from OurWorldinData.org (under the CC BY 4.0 license).[8] HIV data are from UNAIDS.[7] *Incidence is the number of new cases of malaria in a year per 1000 people at risk.

peripheral blood parasitaemia, and mortality.[10,11] These findings have been supported by evidence from studies conducted in areas with high malaria transmission before the introduction of the test-and-treat policy (table 1), in which antiretroviral therapy is prescribed following diagnosis of HIV infection irrespective of CD4 cell count, which was recommended by WHO in 2016.[12,26] A cohort study performed in Mozambique

between 2005 and 2010[12] reported that children with both malaria and HIV presented with a higher total parasite burden (measured as plasma concentrations of *P falciparum* histidine-rich protein-2 [PfHRP2]) than children with malaria only.[12] Plasma PfHRP2 concentrations were positively correlated with the severity of immunosuppression.[12] The clinical presentation of malaria in children with both malaria and HIV from areas with high malaria transmission seems to be age-related.[11,12] Severe forms of co-infection tend to be found in older children, as HIV can stunt age-related acquisition of natural immunity to malaria.[11,12] A meta-analysis including 22 studies in sub-Saharan Africa from 1991 to 2018 reported that the odds of having severe malaria were significantly higher in children with both malaria and HIV (odds ratio [OR] 9·69) than in adults with both malaria and HIV (OR 2·68).[13]

In pregnant individuals living in areas with high malaria transmission, malaria and HIV co-infection increases the risk of placental, peripheral, and cord blood infections; high density parasitaemia; severe anaemia; febrile malaria illness; and maternal death.[10,11] Malaria and HIV co-infection also increases the risk of fetal anaemia, low birthweight, prematurity, intrauterine growth restriction, and neonatal mortality.[10,11,14] Furthermore, pregnant women with HIV have been reported to not develop malaria-specific immunity, which might explain their increased risk of severe malaria in subsequent pregnancies (table 1).[27] HIV seems to impair the ability of pregnant individuals to acquire antibodies to variant surface antigens expressed on the surface of parasitised erythrocytes and opsonising antibodies to placental parasites, weakening their resistance to placental malaria.[27]

Adults with both malaria and HIV might be another vulnerable group. Although some studies have reported no differences in the severity of malaria between people with HIV and people without HIV,[28] a meta-analysis (which also included pregnant women and children) found that people with HIV and malaria had a greater risk of severe malaria.[13] Additionally, a higher risk of in-hospital mortality and anaemia among adults with both malaria and HIV than among those who live with malaria or HIV only has been reported in studies in several sub-Saharan Africa countries.[15,16] For instance, a South African cohort study carried out in 2004 among adults presenting with fever and peripheral parasitaemia in an area of unstable malaria transmission found that 47% of enrolled people living with HIV had severe malaria versus only 30% of those without HIV (p=0·003).[29] More recently, a study conducted in 2014 among children and adults living with HIV in Cameroon found that the risk of presenting with malaria was decreased in participants who were on antiretroviral therapy (23·5% *vs* 6·8%, p=0·03), suggesting an improvement in immunity leading to better protection against malaria.[16]

Hematological and immunological effects of HIV and malaria co-infection

A 2021 meta-analysis[13] reported that people with HIV and severe malaria had higher leukocyte counts than people with *Plasmodium* spp mono-infection (mean difference of 1570 cells/µL, p<0·001; table 1).[13] Leucocyte counts were also higher in people with high parasitaemia than in those with low and moderate parasitaemia.[13] Moreover, no difference in mean neutrophil counts were reported between individuals with both malaria and HIV and individuals with malaria only (mean difference of 980 cells/µL, p=0·5).[13]

A study performed among children and adults in Cameroon in 2019 reported that CD4 counts were lower in people with both malaria and HIV than people with malaria or HIV only: 54·4% of people with both malaria and HIV had CD4 counts of 500 cells/µL or less, whereas most people with HIV only had CD4 counts of 500 cells/µL or more (64·07%, p≤0·025; table 1).[17] Innate immune responses are the first line of defense in malaria infection.[30] A balanced inflammatory response, characterised by an early pro-inflammatory and a secondary immunoregulatory response, is required to adequately control parasitaemia while limiting host pathology.[30] Natural killer and T cells are implicated in the innate response to malaria.[30] In turn, HIV infection leads to the dysregulation of inflammatory responses, and both enhanced and reduced inflammatory responses have been reported in the context of malaria and HIV co-infection.[18,19,31] In terms of enhanced inflammatory response, a study conducted in Mozambique in 2010 found that people with both malaria and HIV showed the highest percentages of HLA-DR and CD38 activation-associated membrane molecules (markers of CD8+ T-cell activation).[18] Similarly, an additional study has reported higher concentrations of interleukin-8, interleukin-12, and interferon-gamma in people with both malaria and HIV than in people with malaria only, suggesting that malaria and HIV co-infection dysregulates the immune response, contributing to the progression of both diseases.[19]

Evidence regarding the effects of HIV on antimalarial humoral response is contradictory (table 1). Although some studies have found no effect on malaria antibody production,[32] others have reported a decrease in response to *P falciparum* antigens.[20,32] In a prospective study among adults in Rwanda,[20] malaria and HIV co-infection was associated with an expansion of atypical memory B cells beyond those induced by malaria alone.[20] Co-infection has been associated separately with B cell dysfunction, specifically with hyperactivated but dysfunctional memory B cells (referred to as exhausted or atypical cells).[33] This dysfunction was further illustrated by a study among Kenyan adults, in which HIV was associated with a decrease in *P falciparum* antibodies' apical membrane antigen 1 (AMA1)-specific naive and resting memory B cells, but an increase in the

	Country or region	Study period	Study design	N	Study objectives	Interactions described
Hendriksen et al (2012)[12]	Mozambique	2005–10	Prospective cohort of children with severe anemia	655	Assess the effects of HIV and malaria co-infection on the diagnosis, clinical presentation, and outcome of individuals with severe malaria	Children with both malaria and HIV presented with more severe acidosis, anaemia, and respiratory distress, and higher peripheral blood parasitaemia and plasma *Plasmodium falciparum* histidine-rich protein-2 than children with only malaria; during hospitalisation, deterioration in coma score, convulsions, respiratory distress, and pneumonia were more common in children with both malaria and HIV than in children with only malaria; mortality was higher in children with both malaria and HIV than in children with only HIV
Mahittikorn et al (2021)[13]	Sub-Saharan Africa (22 out of 23 included studies)	1991–2018	Meta-analysis of studies among children, pregnant women, and non-pregnant adults	1126	Estimate the prevalence and characteristics of severe malaria caused by co-infection with HIV	The pooled prevalence of severe malaria in individuals with both malaria and HIV was 43·0% (23 studies); the odds of severe malaria were significantly higher in individuals with both malaria and HIV than in individuals with *P falciparum* alone and also significantly higher in children than in adults; individuals with both malaria and HIV with severe malaria had a higher mean parasite density than individuals with monoinfection and higher leukocyte counts; mean neutrophil and lymphocyte counts were similar between individuals with both malaria and HIV and individuals with *P falciparum* alone
Ivan et al (2013)[14]	Rwanda	2010–11	Prospective cohort of pregnant women with HIV	980	Assess the major risk factors for malaria infection in pregnant women with HIV	A CD4 count of 350 cells/μL or lower was associated with malaria (odds ratio 3·37, 95% CI 2·11–5·38; p=0·0005); anti-retroviral therapy had no effect on risk of malaria
Berg et al (2014)[15]	Mozambique	2011–12	Cross-sectional study among non-pregnant adults with fever or suspected malaria and healthy control individuals	268	Assess the impact of HIV on the clinical presentation and mortality of malaria	The in-hospitality mortality of individuals with both malaria and HIV was higher than in individuals without HIV (p=0·018); co-infection with HIV was an independent risk factor for death; individuals with both malaria and HIV had significantly more frequent respiratory distress, bleeding disturbances, hypoglycaemia, liver and renal failure, and high malaria parasitaemia compared with individuals with malaria alone
Sandie et al (2019)[16]	Cameroon	2014	Cross-sectional study among adults and children	411	Establish the prevalence of malaria parasites and haematological abnormalities in people with HIV	Among people with HIV, anaemic individuals had a higher prevalence of malaria parasites than non-anaemic individuals (p=0·01) and the risk of presenting with malaria was lower when participants were on ART (p=0·03); among the participants with HIV who had not started ART, the prevalence of malaria parasite was higher than in those who had started ART (23·5% *vs* 6·8%; p=0·03); participants with both malaria and HIV had lower mean haemoglobin concentrations, red blood cell counts, and haematocrit
Ejigu et al (2022)[17]	Ethiopia	2019	Cross-sectional study among adults and children	206	Compare red blood cell indices and anaemia in people with both malaria and HIV and those without malaria and correlate these indices with CD4 cell count	Red blood cell, haemoglobin, haematocrit, and mean cell volume indices were lower in participants with HIV and malaria; there was a positive correlation between CD4 counts with red blood cells and haemoglobin in individuals with both malaria and HIV; the prevalence of anaemia was higher in individuals with both malaria and HIV
Chavale et al (2012)[18]	Mozambique	2010	Cross-sectional study among adults	99	Evaluate the severity of anaemia, *P falciparum* parasite density, and impairment of the cellular immune response in adults with both malaria and HIV	Anaemia was most prevalent in the group with both malaria and HIV; a significant variation in parasite density was observed in this group; CD4 counts were significantly lower in adults with both malaria and HIV than in adults with HIV or malaria only; the highest CD38 expression was detected in the group with both malaria and HIV
Davenport et al (2012)[19]	Kenya	NA	Prospective cohort of children	477	Explore the inflammatory mediator profiles associated with worsening anaemia in children with both HIV and malaria	IL-12, monokine induced by interferon-γ (or CXC chemokine ligand 9), eotaxin (or C-C motif chemokine 11), and granulocyte-macrophage colony-stimulating factor differed significantly and progressively increased across the groups, from the HIV-negative group to the exposed group exposed to HIV, to the HIV-positive group; three components were significantly higher in the HIV-1-positive group and HIV-exposed group; there were significant positive correlations between Hb and IL-1Ra, IL-7, IL-17, IFN-α, IFN-γ, and monokine induced by interferon-γ (or CXC chemokine ligand 9) in the HIV-negative with malaria group, and between haemoglobin and IL-4, IL-5, IL-12, and eotaxin in the group with both malaria and HIV; IL-12 had the strongest association with anaemia in the group with both malaria and HIV

(Table 1 continues on next page)

proportion of AMA1-specific B cells with an activated or atypical phenotype.[21] Lower concentrations of immunoglobulin G against AMA1 were also found in a study among Malawian adults with both malaria and HIV than in their counterparts without HIV, along with lower concentrations of opsonising antibodies against the three parasite lines that were tested.[22] These findings suggest an incompetency in clearing parasites and

	Country or region	Study period	Study design	N	Study objectives	Interactions described
(Continued from previous page)						
Subramaniam et al (2015)[20]	Rwanda	2011	Prospective study among adults	86	Assess the effect of HIV infection on antibody responses to malaria	The mean range of *P falciparum* immunoglobulin G reactivity and the overall IgG reactivity across individuals with both malaria and HIV were lower than the mean range across the HIV-negative group; people with HIV and malaria had a higher percentage of atypical memory B cells than HIV-negative individuals
Frosch et al (2017)[21]	Kenya	2012	Cross-sectional study among adults	190	Assess whether changes in the phenotypes of circulating B cells that target a specific antigen correlate with a change in immunoglobulin concentration for that same antigen	HIV infection is associated with a decrease in *P falciparum* apical membrane antigen 1-specific resting memory B cells, but an increase in the proportion of apical membrane Ag1-specific B cells with an activated or atypical phenotype; these changes mirror those in the overall B cell population
Hasang et al (2014)[22]	Malawi	2000–01	Prospective study among adults	339	Establish the relationship between malaria antibodies, HIV infection, markers of immune compromise, and risk of incident parasitaemia	Adults with HIV had significantly lower mean concentrations of opsonising antibodies to all parasite lines and lower concentrations of antibodies to AMA-1 and MSP2 than adults without HIV; opsonising antibody titres against some isolates were positively correlated with CD4 count and negatively associated with HIV viral load; adults who developed parasitaemia during follow-up had lower opsonising antibody concentrations than adults who did not (independent of their HIV status)
Hochman et al (2015)[23]	Malawi	1996–2010	Cross-sectional study among children	96	Identify differences or similarities in the presentation and pathology of cerebral malaria between children with HIV and children without HIV	Monocyte and platelet accumulations were substantially (>two-fold) greater in children with HIV than in children without HIV with autopsy-confirmed cerebral malaria
Mbale et al (2016)[24]	Malawi	1996–2011	Retrospective study among children	135	Explore the effect of HIV on cerebral malaria to uncover the role of systemic inflammation in cerebral malaria pathogenesis	Children with HIV and cerebral malaria had lower median plasma concentrations of tumour necrosis factor, interleukin-10, and sICAM-1 than children with cerebral malaria but without HIV; HIV-status did not significantly affect parasite density or mortality; children with HIV were older and more likely to have comorbidities
Roberds et al (2022)[25]	Kenya	2018–20	Prospective cohort of adults	300	Define the effect of HIV–malaria co-infection, ART, cotrimoxazole, and artemether lumefantrine on *P falciparum* gametocyte transcript prevalence and parasite transmission to *Anopheles gambiae*	There was a significant relationship between log transformed 18S copy numbers and gametocyte transcript prevalence; for adults who were newly diagnosed with HIV, the initiation of ART and cotrimoxazole was associated with a significant effect on the reduction of gametocyte transcript prevalence in the subsequent month

AMA=apical membrane antigen. ART=antiretroviral therapy. IFN=interferon. IL=interleukin. MSP2= merozoite surface protein 2. NA=not available. sICAMs=soluble intracellular adhesion molecules.

Table 1: **Studies published after (and including) 2012 assessing the effects of HIV and malaria co-infection**

a subsequent increased risk of parasitaemia among individuals with both malaria and HIV.[34]

Cerebral malaria

Cerebral malaria involves complex immunological and haematological mechanisms. It is characterised by the accumulation of infected red blood cells in the brain microvasculature, causing a blockage in blood circulation and oxygen supply with subsequent ischaemia to brain tissue.[35] This effect is often accompanied by intravascular and perivascular pathology, including inflammation, impaired vasoregulation, and blood–brain barrier dysregulation.[35] In turn, HIV infection is associated with the expansion of monocyte subsets and platelet activation, leading to monocyte activation and the formation of circulating monocyte–platelet complexes.[36] A study that performed autopsies on children with confirmed cerebral malaria living with HIV and without HIV, and control individuals without malaria, found that children with autopsy-confirmed cerebral malaria had a nine-times higher risk of presenting accumulations of intravascular monocytes and platelets (but not neutrophils) in their brain tissue than children with a non-malarial cause of coma (table 1).[23] These monocyte and platelet accumulations were significantly greater in children with HIV and cerebral malaria than in children without HIV with cerebral malaria.[23]

Additionally, cerebral malaria is associated with a reduction in lymphocyte subsets in peripheral blood (CD4 cells, B cells, and natural killer cells),[37] which is exacerbated by HIV.[37] Low CD4 counts are further reduced when children present with cerebral malaria, which suggests that cerebral malaria might compound the HIV-related loss of CD4 cells from peripheral blood.[38] Another study found that children with HIV and cerebral malaria had lower median plasma concentrations of interleukins (particularly, tumour necrosis factor and

interleukin-10) and soluble intracellular adhesion molecules than children with cerebral malaria without HIV.[24] This finding did not have an effect on parasite density and the clinical course of the cerebral malaria; thus, the authors hypothesised that systemic inflammation might not be the primary driver of pathogenesis in cerebral malaria, but rather the local effects associated with infected red blood cells.[24]

Treatment and prevention of malaria in people living with HIV

Effectively preventing and managing malaria in people living with HIV requires, as in populations without HIV, a comprehensive approach, which includes the use of long-lasting insecticide-treated nets, indoor residual spraying, chemoprevention, early diagnosis, and prompt and effective antimalarial treatment.[39] Few studies evaluating malaria prevention and treatment strategies have specifically targeted people living with HIV. In this population, considering patients' antiretroviral therapy (ART) regimens and the concurrent medications used to prevent opportunistic infections is essential.[39]

Regarding malaria prevention, WHO recommends the following strategies (among others) in areas with high malaria transmission: intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine and pyrimethamine, perennial malaria chemoprevention with sulfadoxine and pyrimethamine, or seasonal malaria chemoprevention with sulfadoxine, pyrimethamine, and amodiaquine in children.[1]

However, chemoprevention with sulfadoxine and pyrimethamine is contraindicated in individuals on cotrimoxazole prophylaxis, which is recommended for preventing opportunistic infections in pregnant individuals and children living with HIV or children who are exposed to HIV in settings with high prevalence of bacterial infections and malaria, because both are sulfa-based, antifolate drugs. Other drug candidates, such as mefloquine and dihydroartemisinin plus piperaquine, have been evaluated for IPTp among pregnant women and children living with HIV or who have been exposed to HIV, but to date, there is no specific strategy for malaria prevention among these populations.[40–44]

The recommended treatment for uncomplicated *P falciparum* malaria involves early diagnosis followed by a 3-day treatment course of artemisinin-based combination therapies.[39] People living with HIV and malaria should also receive prompt and effective antimalarial treatment. Additionally, since 2015, WHO recommends early initiation of ART for all people living with HIV, regardless of their WHO clinical stage and at any CD4 cell count level.[45] Current first-line ART regimen include dolutegravir in combination with a nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) backbone, which can consist of tenofovir disoproxil fumarate and lamivudine or emtricitabine for adults and adolescents, and abacavir and lamivudine for children. A raltegravir-based regimen is recommended as the preferred first-line regimen for neonates.[46] Alternative first-line ART regimens include tenofovir disoproxil fumarate, lamivudine, and efavirenz for adults and adolescents, abacavir, lamivudine, and ritonavir-boosted lopinavir or tenofovir alafenamide, lamivudine, and dolutegravir for children, and zidovudine, lamivudine and nevirapine for neonates.

Drug interactions

HIV integrase inhibitors

Current evidence indicates that co-administration of first-line artemisinin-based combination therapies regimens with dolutegravir is both safe and effective, suggesting that dolutegravir dose adjustments are not necessary.[47,48] However, this current evidence is mainly based on pharmacokinetic studies in healthy volunteers, and clinical evidence for efficacy and safety among people living with HIV on ART is scarce. Two pharmacokinetic studies in healthy volunteers in Uganda[48] assessed potential interactions between standard adult doses of artemether and lumefantrine or artesunate and amodiaquine, plus a daily 50 mg dose of dolutegravir. Dolutegravir did not significantly affect the maximum concentration in plasma, time to maximum concentration, and area under the concentration-time curve for either of the antimalarial treatments (table 2).[48] Combining dolutegravir with artemether and lumefantrine or artesunate and amodiaquine reduced dolutegravir trough concentrations by 37% and 42%, respectively.[48] However, these concentrations remained above the 300 ng/mL target, suggesting that dolutegravir dose adjustments are not necessary during the standard 3-day treatment of artemether and lumefantrine or artesunate and amodiaquine.[48] There is little evidence regarding drug interactions between raltegravir and artemisinin-based combination therapies, however, considering that raltegravir is not metabolised through CYP450 enzymes, it is unlikely to cause clinically significant interactions.[65]

NRTIs

Tenofovir disoproxil fumarate, lamivudine, emtricitabine, and abacavir are currently part of the first-line ART regimen for adults and children. Drug interactions between tenofovir disoproxil fumarate, emtricitabine, or abacavir and artemisinin-based combination therapies are not expected, as NRTIs are not metabolised via the CYP450 enzyme system, but increased exposure to lamivudine might occur when used alongside sulfadoxine and pyrimethamine (table 2).[65] Nevertheless, clinical evidence regarding NRTI interactions with antimalarial drugs is scarce, with most studies centered on zidovudine.

Treatment with artesunate and amodiaquine has been found to be efficacious for uncomplicated malaria in

	Amodiaquine	Artemether	Artesunate	Dihydroartemisinin	Lumefantrine	Mefloquine	Piperaquine
Dolutegravir	Decreased dolutegravir concentrations, but unlikely to be of clinical significance[48]	Decreased dolutegravir concentrations, but unlikely to be of clinical significance[48]	Decreased dolutegravir concentrations, but unlikely to be of clinical significance[48]	NA	Decreased dolutegravir concentrations, but unlikely to be of clinical significance[48]	NA	NA
Zidovudine	Increased risk for neutropenia[49]	NA	NA	NA	NA	NA	NA
Efavirenz	Increased plasma concentration of amodiaquine and increased risk for hepatotoxicity[50]	Decreased plasma concentration of artemether[51–54]	NA	Decreased plasma concentration of dihydroartemisinin[55]	Decreased plasma concentration of lumefantrine[51–54]	Decreased plasma concentration of mefloquine[56]	Reduced exposure to piperaquine and possible increased risk of QT interval prolongation[57–59]
Nevirapine	Possible decreased plasma concentration of amodiaquine, unlikely to be of clinical significance;[58,60] transient liver function abnormalities and neutropenia, not clinically significant[58]	Decreased plasma concentration of artemether[54]	Increased plasma concentration of artesunate[61]	NA	No substantial effect on lumefantrine's bioavailability[54]	Decreased plasma concentration of mefloquine[56]	Potential increase of piperaquine bioavailability with little clinical significance[58,59]
Ritonavir-boosted lopinavir	NA	Decreased plasma concentration of artemether[62]	NA	Decreased plasma concentration when artesunate or artemether is given with lopinavir or ritonavir[62]	Increased plasma concentration of lumefantrine[62,63]	Decreased plasma concentration of both mefloquine and lopinavir or ritonavir[64]	No changes in piperaquine bioavailability or the concentration of piperaquine[58]

NA=No drug interaction described in the literature.

Table 2: **Summary of the described drug interactions between antiretroviral and antimalarial drugs**

children living with HIV. However, children with HIV on treatment with zidovudine and cotrimoxazole showed a significantly higher risk of neutropenia and had more episodes of pneumonia after initiating treatment with artesunate and amodiaquine than children without ART or children not living with HIV.[49] This result can be explained by the concomitant use of different myelosuppressive agents, such as zidovudine, cotrimoxazole, and amodiaquine. Accordingly, WHO recommends avoiding the use of artesunate and amodiaquine for the treatment of uncomplicated *P falciparum* malaria in people living with HIV on treatment with zidovudine and cotrimoxazole.[39] Similarly, pyrimethamine might adversely affect folate metabolism in people taking myelosuppressive agents, such as zidovudine or cotrimoxazole.[56]

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz is currently part of the alternative first-line ART. Several studies conducted among diverse populations on treatment with efavirenz, including adults, children and pregnant women living with HIV and malaria,[47,51,52,56] revealed an increased incidence of recurrent malaria after malaria treatment with artemether and lumefantrine (table 2). Efavirenz is a potent inductor of CYP450 enzymes, which metabolise artemether and lumefantrine, substantially reducing artemether and lumefantrine exposure.[51–53] Some authors suggest extending the duration or increasing the dosing frequency of artemether and lumefantrine treatment for people living with HIV on efavirenz.[52] Nevertheless, there is currently no evidence for an extended 5-day artemether and lumefantrine treatment strategy for people living with HIV, even though this treatment has been shown to be safe and effective in children without HIV in areas with high malaria transmission.[66] Efavirenz also has clinically significant interactions with amodiaquine, inducing liver injury due to increased amodiaquine exposure, as revealed by a clinical trial, which was prematurely discontinued due to adverse hepatic events in healthy volunteers.[50] Consequently, the WHO malaria guidelines contraindicate use of the combination of efavirenz and amodiaquine.[39] Additionally, efavirenz might potentially enhance the effect of piperaquine in prolonging the QT interval.[57] However, a clinical trial among adults from Malawi and Mozambique with uncomplicated *P falciparum* malaria who were on efavirenz-based or nevirapine-based ART showed QT interval increases of 30% in the efavirenz group that was not clinically detectable and resolved spontaneously over time.[57] Finally, pregnant women on efavirenz and IPTp with dihydroartemisinin and piperaquine need dose adjustments due to the lower exposure to dihydroartemisinin and piperaquine.[55,58]

Nevirapine has limited use in current clinical practice but interacts with some artemisinin-based combination

therapies. It reduces exposure to artemether and has a minor effect on dihydroartemisin exposure, with no substantial effect on lumefantrine's bioavailability.[54,58] Although nevirapine decreases exposure to amodiaquine and potentially increases the bioavailability of piperaquine, its clinical effect on efficacy is uncertain.[59,60] Furthermore, there is evidence of nevirapine increasing artesunate exposure.[61] Both efavirenz and nevirapine also have the potential to decrease mefloquine exposure through the induction of the CYP3A4 enzyme.[56] Similarly, nevirapine levels have been found to be reduced in pregnant women receiving mefloquine as IPTp, indicating possible drug interactions between the two drugs.[67] This finding might explain the two-fold increased risk of vertical transmission of HIV in mefloquine recipients, which was reported in a randomised placebo-controlled trial evaluating mefloquine for IPTp in women living with HIV on cotrimoxazole prophylaxis.[41]

Protease inhibitors

Ritonavir-boosted lopinavir is an alternative to first-line HIV treatment regimens for children. Current evidence shows that combining ritonavir-boosted lopinavir with artemether and lumefantrine is safe and effective. Studies in healthy volunteers and people living with HIV (both adults and children) have reported that combining ritonavir-boosted lopinavir with artemether and lumefantrine increases lumefantrine exposure while decreasing exposure to artemether and dihydroartemisinin (table 2).[62,63] However, this heightened lumefantrine exposure does not extend QT intervals during single dosing or with a standard six-dose regimen.[51,63] The combination of ritonavir-boosted lopinavir with dihydroartemisinin and piperaquine has also been found to be safe and effective among children living with HIV on ART.[68]

Regarding interactions between artesunate and mefloquine and ritonavir-boosted lopinavir, a pharmacokinetic study in healthy Thai adults[64] showed a 50% reduction in the area under the concentration-time curve of dihydroartemisinin and a significant decrease in day 7 mefloquine exposure. A decrease in the systemic exposure of both lopinavir and ritonavir was also observed.[64] On the other hand, coadministration of pyronaridine and artesunate with ritonavir in healthy adults has been shown to significantly increase ritonavir exposure, minimally affecting pyronaridine concentrations.[69] Despite increased artesunate concentrations and decreased dihydroartemisinin exposure, ritonavir's effect on pyronaridine and artesunate does not appear to have clinical relevance, given that pyronaridine's 90% CI closely aligned with the acceptable range, and artesunate's pharmacokinetics showed considerable individual variability. This coadministration temporarily raised transaminase concentrations, which normalised within 2 months.[69]

Risk of co-infection and effect on transmission

Risk of malaria among people living with HIV and the effect of co-infection on malaria transmission

People living with HIV can experience weakened immune systems, hindering parasite clearance, and damage to the spleen—a key organ in controlling malaria infection. Due to this impaired immunological response in HIV infection, people living with HIV also face an increased acquisition risk of malaria.[70] In sub-Saharan Africa, HIV was estimated to increase malaria prevalence by 1·3% and malaria-related mortality by 4·9%, resulting in an additional 3 million clinical malaria cases and 65 000 malaria-related deaths annually in sub-Saharan Africa.[70] Some authors suggest that intensified malaria incidence due to HIV is particularly pronounced in areas with low malaria transmission, and attribute this trend to the absence of acquired natural immunity.[71] This evidence is mostly related to *P falciparum*. However, a recent study in Brazil published in 2022[72] reported that HIV is also a risk factor for *P vivax* malaria infection, with an adjusted relative risk of 2·77 (95% CI 1·46–5·28).

On the other hand, there is extensive evidence for increased malaria parasite density associated with HIV-mediated immunity in people living with HIV, making this population more infectious to mosquitoes.[73] However, the possible effect of this increased parasitaemia on malaria transmission is frequently suggestive or speculative. A study conducted in Kenya[73] found no significant association between HIV and malaria transmission in people living with HIV receiving ART and cotrimoxazole prophylaxis. By contrast, a cross-sectional study, also conducted in Kenya,[74] reported an increased risk of gametocytemia in people newly diagnosed with HIV not on ART compared with people living without HIV. This study is the first of its kind designed to evaluate the epidemiological effect of HIV-1 co-infection on the prevalence of asymptomatic gametocytaemia and its findings suggest that people living with HIV might have an increased risk of transmitting malaria parasites.

HIV infection risk in people with malaria and the effect of malaria on HIV transmission

Among people living with HIV, both in vitro and in vivo studies have revealed that malaria co-infection causes a transient increase in HIV viral load for several weeks post antimalarial treatment, threatening ART effectiveness and heightening the risk of HIV transmission of individuals with both malaria and HIV.[2,75] Thus, malaria and HIV co-infection might have an effect on HIV disease progression and transmission, potentially contributing to the high prevalence of HIV in sub-Saharan Africa. A study in Malawi[76] showed a ten-fold increase in HIV viral load in individuals with HIV and febrile malaria, translating to a roughly 2·5-fold increase in HIV transmission probability.[76–78] This increase resulted in more than 8500 HIV infections

attributed to the malaria–HIV interaction in western Kenya over a decade, making the population-attributable fraction of HIV cases linked to malaria approximately 20%.[5] The effect of malaria on HIV epidemiology is mostly based on early estimates of its effect on viral load in people living with HIV who are not receiving ART.

Geographical variations in the effect of malaria on HIV transmission have also been noted. In areas with high prevalences of malaria and HIV, particularly in eastern sub-Saharan Africa, individuals face approximately double the risk of acquiring HIV compared with people in regions with lower malaria rates.[79] Conversely, in populations with low prevalences of HIV, as observed in western sub-Saharan Africa, no evidence of an association between HIV and malaria has been found, suggesting that malaria might not substantially affect the spread of HIV in populations with low prevalences of HIV.[79] Authors have suggested various contributors to this disparity, including differences in the replicative capacity and infectiousness of dominant HIV subtypes in these regions, variations in circumcision rates, and other behavioural and environmental distinctions.[80]

Malaria and vertical transmission of HIV

Regarding the effect of malaria on the risk of vertical transmission of HIV, there are conflicting results. Most of these results are from research conducted before ART was recommended to all people living with HIV (table 3). An association between high-density placental malaria and increased vertical transmission was reported in studies conducted in Kenya and Uganda.[81–83] In Rwanda, the association was particularly relevant in people pregnant for the first time.[84] However, studies in other sub-Saharan African countries have not observed this effect of malaria on vertical transmission and results remain inconsistent.[85–87]

An association of presumptive clinical malaria with increased risk of vertical transmission of HIV has also been reported in a cohort study conducted in Tanzania.[88] Furthermore, clinical malaria during pregnancy was found to be an independent risk factor associated with an increased risk of vertical transmission in a multicentre placebo-controlled trial evaluating mefloquine for IPTp.[41]

On the other hand, maternal HIV viral load at the time of delivery is the most important and recognised risk factor for vertical transmission.[89] Importantly, peripheral and placental HIV viral load have been found to be increased in pregnant women with both malaria and HIV in Malawi.[90] Additionally, in vitro analysis of cord blood cells of Kenyan infants exposed to malaria has reported that they are more likely to acquire HIV than those of North American infants.[91] Finally, HIV-associated impairment of antibody responses in pregnant women might also contribute to greater transmission of *P falciparum* to their infants.[92]

Conclusions and knowledge gaps

The high burden of malaria and HIV infection in sub-Saharan Africa presents a double blow to the region, which is presently worst affected by the presence of other infectious diseases, such as tuberculosis and Ebola virus disease. The last WHO technical consultation analysing malaria and HIV interactions dates from 2004.[3] Although some of the research gaps identified at that time have been, at least partly, addressed, others remain unanswered 20 years later.

Studies performed since the last WHO technical consultation on malaria and HIV interactions have evaluated the effect of malaria on HIV transmission and their findings support previous evidence suggesting that malaria is a risk factor for HIV acquisition.[75,76,93] However, discrepancies persist in terms of how malaria influences HIV transmission across sub-Saharan Africa. Eastern areas of the region with high prevalences of malaria and HIV show a doubling of HIV infection risk, whereas in western areas, with lower HIV rates, there is little evidence of a significant association between HIV and malaria.[79] Insufficiently investigated factors drive this regional disparity, necessitating further exploration.

In addition, most of the studies performed to assess the clinical aspects of HIV and malaria co-infection, and reviewed in this Review, were performed before 2016, when WHO first recommended the test-and-treat policy, whereby every person diagnosed with HIV should start ART regardless of their CD4 cell count.[26] Thus, there is a scarcity of information regarding the presentation of malaria and HIV co-infection in the context of widespread ART and subsequent control of HIV infection. In turn, the conflicting evidence regarding the effect of malaria on vertical transmission of HIV is difficult to assess given the well established prevention of vertical transmission and ART programmes available in pregnancy, which result in very low vertical transmission rates in sub-Saharan African countries. Regarding the prevention of malaria in pregnant individuals and children who are living with HIV or are exposed to HIV, alternative drugs to sulfadoxine and pyrimethamine for the prevention of malaria have been evaluated in people on cotrimoxazole prophylaxis. Nevertheless, to date no suitable and tailored treatments have been found and recommended for the prevention of malaria in these populations.[40,41] Results from two recently completed randomised placebo-controlled clinical trials[43,44] evaluating the use of dihydroartemisin and piperaquine for IPTp in individuals living with HIV receiving cotrimoxazole prophylaxis have reported a reduced risk of malaria infection in the intervention group. These findings make the drug a promising candidate for IPTp in people living with HIV. Similarly, the evaluation of alternative drugs for perennial malaria chemoprevention in infants exposed to HIV receiving cotrimoxazole prophylaxis is urgently needed. On the other hand, in the past few years, drug interactions between antimalarial and antiretroviral drugs have been

	Country	Study period	Study design	N	Findings
González et al (2014)[41]	Kenya, Tanzania, and Mozambique	2010–13	Secondary analysis of randomised controlled trial among pregnant women	1071	Clinical malaria was associated with vertical transmission in adjusted multivariate analysis (RR 4·76, 95% CI 2·01–11·24)
Ayisi et al (2004)[81]	Kenya	1996–2000	Prospective cohort of mother–infant pairs	512	Low-density placental malaria (<10 000 parasites/μL) was associated with reduced vertical transmission (ARR 0·4); in women with both malaria and HIV, high-density placental malaria (>10 000 parasites/μL) was associated with increased risk of vertical transmission (ARR 2·0) compared with low-density malaria
Brahmbhatt et al (2008)[82]	Uganda	1994–2000	Prospective cohort of mother–infant pairs	109	Placental malaria was associated with vertical transmission adjusted for maternal HIV viral load (RR 7·9, 95% CI 1·4–58·5)
Brahmbhatt et al (2003)[83]	Uganda	1994–99	Secondary analysis of a community-randomised trial of sexually transmitted disease control for HIV prevention among pregnant women	668	Placental malaria was associated with vertical transmission (RR 2·85, 95% CI 1·53–5·32)
Bulterys et al (2011)[84]	Rwanda	1989–94	Nested case-control study in a prospective cohort study of mother–infant pairs	60	Placental malaria was associated with vertical transmission (aOR 6·3, 95% CI 1·4–29·1), especially among primigravidae
Msamanga et al (2009)[85]	Malawi, Zambia, and Tanzania	2001–03	Secondary analysis of randomised controlled trial among pregnant women	2126	Placental malaria was not associated with the infant's HIV-1 status at birth (p=0·67)
Inion et al (2003)[86]	Kenya	1996–99	Cross sectional study among pregnant women	649 (n=372 HIV-positive; n=277 HIV-negative)	Increased prevalence of placental malaria in women with HIV; no association was found between placental malaria and either maternal virus load
Naniche et al (2008)[87]	Mozambique	2003–06	Secondary analysis of randomised controlled trial among pregnant women	207	Placental malaria was associated with a decrease in vertical transmission (aOR 0·23, 95% CI 0·06–0·89; p=0·034)
Ezeama et al (2014)[88]	Tanzania	2004–08	Prospective cohort of mother–infant pairs with HIV	2368	HIV vertical transmission risk increased by 29% (95% CI 4–58) per malaria episode in pregnancy

aOR=attributable odds ratio. ARR=absolute risk reduction. RR=risk ratio.

Table 3: **Summary of evidence regarding the effect of malaria on vertical transmission of HIV**

Search strategy and selection criteria

A comprehensive literature search of medical databases (Medline, the Cochrane library, and WHO) and non-medical search engines was undertaken between April and November, 2023. The search terms used were "malaria", "HIV", and "interactions". Special consideration was given to articles published since the last literature review on this topic by the research team (ie, articles published from January, 2012, to November, 2023). The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

assessed, which might help optimise malaria treatment for people living with HIV. This research includes assessments of the interactions between dolutegravir (currently a first-line ART drug) and first-line antimalarial drugs, such as artemether and lumefantrine, which have provided reassuring results.[48] However, further research is needed on the interactions between ART drugs and second line therapy antimalarial drugs, antimalarials used for chemoprevention, and those under research for prevention among pregnant individuals living with HIV.

In conclusion, the latest evidence indicates that HIV alters the immunological response to and clinical characteristics of malaria and malaria increases the HIV viral load, potentially enhancing HIV transmission. Additionally, drug interactions between ART and antimalarial drugs both for treatment and prevention might hamper their efficacy, potentially hindering the control of both infections. No specific malaria control strategies tailored for people living with HIV, who are at increased risk of malaria acquisition, have been developed. Considering HIV and malaria interactions in the development of control guidelines and both disease elimination plans is essential.

Contributors

RG and AF-R conceived and designed this Review. AF-R, AS-L, SF-L, and RG wrote the drafts of this Review. RG critically revised the drafts.

Declaration of interests

AF-R, SF-L, and RG were partly supported by the European and Developing Countries Clinical Trials Partnership 2 programme (grant numbers RIA2016MC-1613-MAMAH [AF-R and RG], RIA2020S-3272 -MULTIPLY [AF-R], and RIA2019PD-2882-UNIVERSAL [SF-L]), which is supported by the European Union. AS-L was supported by the Severo Ochoa predoctoral fellowship from ISGlobal and the predoctoral fellowship from the Secretariat of Universities and Research (Ministry of Enterprise and Knowledge of the Government of Catalonia), cofunded by the European Social Fund. ISGlobal acknowledges support from grant CEX2018-000806-S funded by Ministerio de Ciencia e Innovación/Agencia Estatal de Investigación/10.13039/501100011033, and support from the Generalitat de Catalunya through the Centres de Recerca de Catalunya Program.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations

References

1 WHO. World malaria report 2023. Geneva: World Health Organization, 2023.

2 Kwenti TE. Malaria and HIV coinfection in sub-Saharan Africa: prevalence, impact, and treatment strategies. *Res Rep Trop Med* 2018; **9:** 123–36.

3 WHO. Malaria and HIV interactions and their implications for public health policy. Geneva: World Health Organization, 2004.

4 Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. *AIDS* 2005; **19:** 995–1005.

5 Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science* 2006; **314:** 1603–06.

6 Skinner-Adams TS, McCarthy JS, Gardiner DL, Andrews KT. HIV and malaria co-infection: interactions and consequences of chemotherapy. *Trends Parasitol* 2008; **24:** 264–71.

7 UNAIDS. UNAIDS data 2022. UNAIDS, 2023. https://www.unaids.org/en/resources/documents/2023/2022_unaids_data (accessed Nov 17, 2023).

8 WHO, World Bank. Incidence of malaria, 2020. Our World in Data, 2023. https://ourworldindata.org/grapher/incidence-of-malaria (accessed Nov 17, 2023).

9 Naing C, Sandhu NK, Wai VN. The effect of malaria and HIV co-infection on anemia: a meta-analysis. *Medicine* 2016; **95:** e3205.

10 Flateau C, Le Loup G, Pialoux G. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. *Lancet Infect Dis* 2011; **11:** 541–56.

11 González R, Ataíde R, Naniche D, Menéndez C, Mayor A. HIV and malaria interactions: where do we stand? *Expert Rev Anti Infect Ther* 2012; **10:** 153–65.

12 Hendriksen IC, Ferro J, Montoya P, et al. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-coinfected children and adults in Mozambique. *Clin Infect Dis* 2012; **55:** 1144–53.

13 Mahittikorn A, Kotepui KU, De Jesus Milanez G, Masangkay FR, Kotepui M. A meta-analysis on the prevalence and characteristics of severe malaria in patients with *Plasmodium* spp and HIV co-infection. *Sci Rep* 2021; **11:** 16655.

14 Ivan E, Crowther NJ, Mutimura E, Osuwat LO, Janssen S, Grobusch MP. Helminthic infections rates and malaria in HIV-infected pregnant women on anti-retroviral therapy in Rwanda. *PLoS Negl Trop Dis* 2013; **7:** e2380.

15 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.

16 Sandie SM, Sumbele IUN, Tasah MM, Kimbi HK. Malaria parasite prevalence and Haematological parameters in HIV seropositive patients attending the regional hospital Limbe, Cameroon: a hospital-based cross-sectional study. *BMC Infect Dis* 2019; **19:** 988.

17 Ejigu S, Haile D, Solomon Y. Effect of malaria and HIV/AIDS co-infection on red blood cell indices and its relation with the CD4 level of patients on HAART in Bench Sheko Zone, Southwest Ethiopia. *PLoS One* 2022; **17:** e0263865.

18 Chavale H, Santos-Oliveira JR, Da-Cruz AM, Enosse S. Enhanced T cell activation in *Plasmodium falciparum* malaria-infected human immunodeficiency virus-1 patients from Mozambique. *Mem Inst Oswaldo Cruz* 2012; **107:** 985–92.

19 Davenport GC, Hittner JB, Were T, Ong'echa JM, Perkins DJ. Relationship between inflammatory mediator patterns and anemia in HIV-1 positive and exposed children with *Plasmodium falciparum* malaria. *Am J Hematol* 2012; **87:** 652–58.

20 Subramaniam KS, Skinner J, Ivan E, et al. HIV malaria co-infection is associated with atypical memory B cell expansion and a reduced antibody response to a broad array of *Plasmodium falciparum* antigens in Rwandan adults. *PLoS One* 2015; **10:** e0124412.

21 Frosch AE, Odumade OA, Taylor JJ, et al. Decrease in numbers of naive and resting B cells in HIV-infected Kenyan adults leads to a proportional increase in total and *Plasmodium falciparum*-specific atypical memory B cells. *J Immunol* 2017; **198:** 4629–38.

22 Hasang W, Dembo EG, Wijesinghe R, Molyneux ME, Kublin JG, Rogerson S. HIV-1 infection and antibodies to *Plasmodium falciparum* in adults. *J Infect Dis* 2014; **210:** 1407–14.

23 Hochman SE, Madaline TF, Wassmer SC, et al. Fatal pediatric cerebral malaria is associated with intravascular monocytes and platelets that are increased with HIV coinfection. *MBio* 2015; **6:** e01390–15.

24 Mbale EW, Moxon CA, Mukaka M, et al. HIV coinfection influences the inflammatory response but not the outcome of cerebral malaria in Malawian children. *J Infect* 2016; **73:** 189–99.

25 Roberds A, Kifude C, Oyieko J, et al. Longitudinal impact of asymptomatic malaria/HIV-1 co-infection on *Plasmodium falciparum* gametocyte transcript expression and transmission to *Anopheles* mosquitoes. *Front Cell Infect Microbiol* 2022; **12:** 934641.

26 WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization, 2016.

27 Ataíde R, Hasang W, Wilson DW, et al. Using an improved phagocytosis assay to evaluate the effect of HIV on specific antibodies to pregnancy-associated malaria. *PLoS One* 2010; **5:** e10807.

28 Munyenyembe AU, Gausi K, Hiestand J, Mallewa J, Mandala W. The effect of frequent exposure to *P falciparum*, HIV-infection and other co-morbidities on development of severe malaria in Malawian adults. *Infect Drug Resist* 2020; **13:** 63–68.

29 Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. 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:** 547–54.

30 Stevenson MM, Riley EM. Innate immunity to malaria. *Nat Rev Immunol* 2004; **4:** 169–80.

31 Chaisavaneeyakorn S, Moore JM, Otieno J, et al. Immunity to placental malaria. III. Impairment of interleukin(IL)-12, not IL-18, and interferon-inducible protein-10 responses in the placental intervillous blood of human immunodeficiency virus/malaria-coinfected women. *J Infect Dis* 2002; **185:** 127–31.

32 Nnedu ON, O'Leary MP, Mutua D, et al. Humoral immune responses to *Plasmodium falciparum* among HIV-1-infected Kenyan adults. *Proteomics Clin Appl* 2011; **5:** 613–23.

33 Moir S, Fauci AS. B cells in HIV infection and disease. *Nat Rev Immunol* 2009; **9:** 235–45.

34 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:** 984–91.

35 Taylor TE, Fu WJ, Carr RA, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat Med* 2004; **10:** 143–45.

36 Singh MV, Davidson DC, Kiebala M, Maggirwar SB. Detection of circulating platelet-monocyte complexes in persons infected with human immunodeficiency virus type-1. *J Virol Methods* 2012; **181:** 170–76.

37 Mandala WL, Msefula CL, Gondwe EN, et al. Lymphocyte perturbations in Malawian children with severe and uncomplicated malaria. *Clin Vaccine Immunol* 2015; **23:** 95–103.

38 Lyke KE, Burges R, Cissoko Y, et al. Serum levels of the proinflammatory cytokines interleukin-1 beta (IL-1beta), IL-6, IL-8, IL-10, tumor necrosis factor alpha, and IL-12(p70) in Malian children with severe *Plasmodium falciparum* malaria and matched uncomplicated malaria or healthy controls. *Infect Immun* 2004; **72:** 5630–37.

39 WHO. Guidelines for malaria. Geneva: World Health Organization, 2023.

40 Natureeba P, Kakuru A, Muhindo M, et al. Intermittent preventive treatment with dihydroartemisinin-piperaquine for the prevention of malaria among HIV-infected pregnant women. *J Infect Dis* 2017; **216:** 29–35.

41 González R, Desai M, Macete E, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. *PLoS Med* 2014; **11:** e1001735.

42 Kamya MR, Kapisi J, Bigira V, et al. Efficacy and safety of three regimens for the prevention of malaria in young HIV-exposed Ugandan children: a randomized controlled trial. *AIDS* 2014; **28:** 2701–09.

43 González R, Nhampossa T, Mombo-Ngoma G, et al. Safety and efficacy of dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women with HIV from Gabon and Mozambique: a randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 2024; published online Jan 12. https://doi.org/10.1016/S1473-3099(23)00738-7.

44 Barsosio HC, Madanitsa M, Ondieki ED, et al. Chemoprevention for malaria with monthly intermittent preventive treatment with dihydroartemisinin–piperaquine in pregnant women living with HIV on daily co-trimoxazole in Kenya and Malawi: a randomised, double-blind, placebo-controlled trial. *Lancet* 2024; **403:** 365–78.

45 WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization, 2015.

46 WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization, 2021.

47 Francis J, Barnes KI, Workman L, et al. An individual participant data population pharmacokinetic meta-analysis of drug-drug interactions between lumefantrine and commonly used antiretroviral treatment. *Antimicrob Agents Chemother* 2020; **64:** e02394-19.

48 Walimbwa SI, Lamorde M, Waitt C, et al. Drug interactions between dolutegravir and artemether-lumefantrine or artesunate–amodiaquine. *Antimicrob Agents Chemother* 2019; **63:** e01310–18.

49 Gasasira AF, Kamya MR, Achan J, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis* 2008; **46:** 985–91.

50 German P, Greenhouse B, Coates C, et al. Hepatotoxicity due to a drug interaction between amodiaquine plus artesunate and efavirenz. *Clin Infect Dis* 2007; **44:** 889–91.

51 Byakika-Kibwika P, Lamorde M, Mayito J, et al. Significant pharmacokinetic interactions between artemether/lumefantrine and efavirenz or nevirapine in HIV-infected Ugandan adults. *J Antimicrob Chemother* 2012; **67:** 2213–21.

52 Parikh S, Kajubi R, Huang L, et al. Antiretroviral choice for HIV impacts antimalarial exposure and treatment outcomes in Ugandan children. *Clin Infect Dis* 2016; **63:** 414–22.

53 Hughes E, Mwebaza N, Huang L, et al. Efavirenz-based antiretroviral therapy reduces artemether–lumefantrine exposure for malaria treatment in HIV-infected pregnant women. *J Acquir Immune Defic Syndr* 2020; **83:** 140–47.

54 Maganda BA, Ngaimisi E, Kamuhabwa AA, Aklillu E, Minzi OM. The influence of nevirapine and efavirenz-based anti-retroviral therapy on the pharmacokinetics of lumefantrine and anti-malarial dose recommendation in HIV-malaria co-treatment. *Malar J* 2015; **14:** 179.

55 Kajubi R, Huang L, Jagannathan P, et al. Antiretroviral therapy with efavirenz accentuates pregnancy-associated reduction of dihydroartemisinin–piperaquine exposure during malaria chemoprevention. *Clin Pharmacol Ther* 2017; **102:** 520–28.

56 Seden K, Gibbons S, Marzolini C, et al. Development of an evidence evaluation and synthesis system for drug-drug interactions, and its application to a systematic review of HIV and malaria co-infection. *PLoS One* 2017; **12:** e0173509.

57 Manning J, Vanachayangkul P, Lon C, et al. Randomized, double-blind, placebo-controlled clinical trial of a two-day regimen of dihydroartemisinin–piperaquine for malaria prevention halted for concern over prolonged corrected QT interval. *Antimicrob Agents Chemother* 2014; **58:** 6056–67.

58 Banda CG, Dzinjalamala F, Mukaka M, et al. Pharmacokinetics of piperaquine and safety profile of dihydroartemisinin–piperaquine coadministered with antiretroviral therapy in malaria-uninfected HIV-positive malawian adults. *Antimicrob Agents Chemother* 2018; **62:** e00634-18.

59 Sevene E, Banda CG, Mukaka M, et al. Efficacy and safety of dihydroartemisinin–piperaquine for treatment of *Plasmodium falciparum* uncomplicated malaria in adult patients on antiretroviral therapy in Malawi and Mozambique: an open label non-randomized interventional trial. *Malar J* 2019; **18:** 277.

60 Scarsi KK, Fehintola FA, Ma Q, et al. Disposition of amodiaquine and desethylamodiaquine in HIV-infected Nigerian subjects on nevirapine-containing antiretroviral therapy. *J Antimicrob Chemother* 2014; **69:** 1370–76.

61 Fehintola FA, Scarsi KK, Ma Q, et al. Nevirapine-based antiretroviral therapy impacts artesunate and dihydroartemisinin disposition in HIV-infected Nigerian adults. *Aids Res Treat* 2012; **2012:** 703604.

62 German P, Parikh S, Lawrence J, et al. Lopinavir/ritonavir affects pharmacokinetic exposure of artemether/lumefantrine in HIV-uninfected healthy volunteers. *J Acquir Immune Defic Syndr* 2009; **51:** 424–29.

63 Kredo T, Mauff K, Workman L, et al. The interaction between artemether-lumefantrine and lopinavir/ritonavir-based antiretroviral therapy in HIV-1 infected patients. *BMC Infect Dis* 2016; **16:** 30.

64 Rattanapunya S, Cressey TR, Rueangweerayut R, Tawon Y, Kongjam P, Na-Bangchang K. Pharmacokinetic interactions between artesunate–mefloquine and ritonavir-boosted lopinavir in healthy Thai adults. *Malar J* 2015; **14:** 400.

65 European AIDS Clinical Society. Anti-malarial drugs & ARVs. European AIDS Clinical Society, 2023. https://www.eacsociety.org/media/guidelines-12.0.pdf (accessed Oct 4, 2023).

66 Whalen ME, Kajubi R, Goodwin J, et al. The impact of extended treatment with artemether–lumefantrine on antimalarial exposure and reinfection risks in Ugandan children with uncomplicated malaria: a randomized controlled trial. *Clin Infect Dis* 2023; **76:** 443–52.

67 Haaland RE, Otieno K, Martin A, et al. Short communication: reduced nevirapine concentrations among HIV-positive women receiving mefloquine for intermittent preventive treatment for malaria control during pregnancy. *AIDS Res Hum Retroviruses* 2018; **34:** 912–15.

68 Kakuru A, Achan J, Muhindo MK, et al. Artemisinin-based combination therapies are efficacious and safe for treatment of uncomplicated malaria in HIV-infected Ugandan children. *Clin Infect Dis* 2014; **59:** 446–53.

69 Morris CA, Lopez-Lazaro L, Jung D, et al. Drug–drug interaction analysis of pyronaridine/artesunate and ritonavir in healthy volunteers. *Am J Trop Med Hyg* 2012; **86:** 489–95.

70 Korenromp EL, Williams BG, de Vlas SJ, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. *Emerg Infect Dis* 2005; **11:** 1410–19.

71 Frosch AE, John CC. Immunomodulation in *Plasmodium falciparum* malaria: experiments in nature and their conflicting implications for potential therapeutic agents. *Expert Rev Anti Infect Ther* 2012; **10:** 1343–56.

72 Guerra CVC, da Silva BM, Muller P, et al. HIV infection increases the risk of acquiring Plasmodium vivax malaria: a 4-year cohort study in the Brazilian Amazon HIV and risk of vivax malaria. *Sci Rep* 2022; **12:** 9076.

73 Roberds A, Ferraro E, Luckhart S, Stewart VA. HIV-1 impact on malaria transmission: a complex and relevant global health concern. *Front Cell Infect Microbiol* 2021; **11:** 656938.

74 Stiffler DM, Oyieko J, Kifude CM, Rockabrand DM, Luckhart S, Stewart VA. HIV-1 infection is associated with increased prevalence and abundance of *Plasmodium falciparum* gametocyte-specific transcripts in asymptomatic adults in western Kenya. *Front Cell Infect Microbiol* 2021; **10:** 600106.

75 Yegorov S, Joag V, Galiwango RM, Good SV, Okech B, Kaul R. Impact of endemic infections on HIV susceptibility in sub-Saharan Africa. *Trop Dis Travel Med Vaccines* 2019; **5:** 22.

76 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:** 233–40.

77 Nyabadza F, Bekele BT, Rúa MA, Malonza DM, Chiduku N, Kgosimore M. The implications of HIV treatment on the HIV–malaria coinfection dynamics: a modeling perspective. *BioMed Res Int* 2015; **2015:** 659651.

78 Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000; **342:** 921–29.

79 Cuadros DF, Branscum AJ, Crowley PH. HIV–malaria co-infection: effects of malaria on the prevalence of HIV in east sub-Saharan Africa. *Int J Epidemiol* 2011; **40:** 931–39.

80 Cuadros DF, García-Ramos G. Variable effect of co-infection on the HIV infectivity: within-host dynamics and epidemiological significance. *Theor Biol Med Model* 2012; **9:** 9.

81 Ayisi JG, van Eijk AM, Newman RD, et al. Maternal malaria and perinatal HIV transmission, western Kenya. *Emerg Infect Dis* 2004; **10:** 643–52.

82 Brahmbhatt H, Sullivan D, Kigozi G, et al. Association of HIV and malaria with mother-to-child transmission, birth outcomes, and child mortality. *J Acquir Immune Defic Syndr* 2008; **47:** 472–76.

83 Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. *AIDS* 2003; **17:** 2539–41.

84 Bulterys PL, Chao A, Dalai SC, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1 in rural Rwanda. *Am J Trop Med Hyg* 2011; **85:** 202–06.

85 Msamanga GI, Taha TE, Young AM, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. *Am J Trop Med Hyg* 2009; **80:** 508–15.

86 Inion I, Mwanyumba F, Gaillard P, et al. Placental malaria and perinatal transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; **188:** 1675–78.

87 Naniche D, Lahuerta M, Bardaji A, et al. Mother-to-child transmission of HIV-1: association with malaria prevention, anaemia and placental malaria. *HIV Med* 2008; **9:** 757–64.

88 Ezeamama AE, Duggan C, Manji KP, et al. Clinical malaria diagnosis in pregnancy in relation to early perinatal mother-to-child transmission of HIV: a prospective cohort study. *HIV Med* 2014; **15:** 276–85.

89 Coutsoudis A, Kwaan L, Thomson M. Prevention of vertical transmission of HIV-1 in resource-limited settings. *Expert Rev Anti Infect Ther* 2010; **8:** 1163–75.

90 Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of *Plasmodium falciparum* malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. *AIDS* 2004; **18:** 1051–59.

91 Steiner K, Myrie L, Malhotra I, et al. Fetal immune activation to malaria antigens enhances susceptibility to in vitro HIV infection in cord blood mononuclear cells. *J Infect Dis* 2010; **202:** 899–907.

92 Naniche D, Serra-Casas E, Bardají A, et al. Reduction of antimalarial antibodies by HIV infection is associated with increased risk of *Plasmodium falciparum* cord blood infection. *J Infect Dis* 2012; **205:** 568–77.

93 Andreani G, Lodge R, Richard D, Tremblay MJ. Mechanisms of interaction between protozoan parasites and HIV. *Curr Opin HIV AIDS* 2012; **7:** 276–82.