Unveiling HIV and malaria interactions: latest evidence and knowledge gaps

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Summary (Up to 150 words)

The geographical distribution of malaria and human immunodeficiency virus (HIV) infections widely overlap in sub-Saharan Africa, constituting a complex global health challenge. The interaction of both infections raises concerns for potential immunological, clinical and therapeutic interactions. It has been reported that both diseases exacerbate the transmission of the other, including a possible vertical transmission of HIV in pregnant women coinfected with malaria. Coinfection also increases the risk of suffering 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 on the epidemiological, clinical, immunological and therapeutic interactions of both infections. We focus on the latest available data, and we identify key knowledge gaps that should be addressed in order to guide policy makers to provide optimal HIV and malaria prevention, care and treatment in the most disadvantaged populations.

Introduction

Malaria and human immunodeficiency virus (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 (SSA) (1). Consequently, malaria and HIV coinfection is common in this region, leading to opportunities for complex disease interactions at both individual and population levels (2).

The available evidence suggests that malaria and HIV have a synergistic effect, with coinfection exponentially exacerbating the adverse effects of one infection on the other, thus adversely impacting prognosis and complicating the prevention and treatment of both diseases (figure 1) (2, 3). Moreover, malaria and HIV coinfection has been demonstrated to fuel the spread of both diseases in SSA, and treatment of coinfected individuals has raised concerns about the potential drug interactions (4, 5).

Therefore, gaining a comprehensive understanding of their interaction is imperative for effective control, particularly in SSA, where the burden of the two diseases concentrates. This comprehensive review summarizes the latest evidence on the burden of malaria and HIV coinfection, the impact on the transmission of one infection on the other, as well as its implications on biological, clinical, and immunological outcomes. It also discusses the therapeutic strategies for managing both malaria and HIV in coinfected patients, concluding with some knowledge gaps and policy implications.

The overlapping HIV and malaria burden

It is estimated that in 2022 there were 249 million cases of malaria worldwide, resulting in 0.61 million related deaths (1). SSA 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 under the age of five and pregnant women were the most affected groups (6). With regard to HIV, there were an estimated 39 million people living with HIV (PLHIV) in 2022,with approximately 1.3 million new diagnoses and 0.63 million deaths (7). More than half PLHIV were women and girls (53%), and children under 15 accounted for around 10% of all new HIV infections (7). Similar to malaria, the global HIV epidemic has the greatest impact on SSA, with an estimated 67% of PLHIV 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 SSA (Figure 2) (6-8). The most severely affected areas 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, there is also a social overlap. Both diseases disproportionately affect the poorest segments of the population, who lack access to quality education, information, and state services, all of which are especially relevant in SSA (2).

The prevalence of malaria and HIV coinfection has been estimated to be overall 19% in SSA, with values of 26% in non-pregnant adults, 12% in pregnant women, and 9% in children (9). Furthermore, a 2018 review reported varying prevalences of malaria and HIV coinfection across different populations and regions in SSA, 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 (2).

Physiopathology and clinical implications of HIV and malaria co-infection

Clinical implications of HIV and malaria co-infection

Previous studies have reported that children with malaria and HIV coinfection suffer an increased prevalence of severe clinical malaria, which presents with severe acidosis, anemia, respiratory distress, convulsions and increased peripheral blood parasitemia, and mortality (10, 11). These findings have been supported by the evidence from studies conducted in high malaria transmission areas before the "test and treat" policy (table 1), whereby antiretroviral therapy should be prescribed following HIV diagnosis irrespectively of CD4 cell count, recommended by the WHO in 2016 (12, 13). A cohort study performed in Mozambique between 2005 and 2010 reported that co-infected children presented with higher total parasite burden than malaria mono-infected children, measured as plasma *Plasmodium falciparum* histidine-rich protein-2 (PfHRP2) (12). Plasma PfHRP2 concentrations positively correlated with the severity of immunosuppression (12). The clinical presentation of malaria in malaria and HIV coinfected children from high malaria transmission areas seems to be age-related (11, 12). In this sense, severe forms of coinfection tend to be found in older children given that HIV might stunt the age-related acquisition of natural immunity to malaria (11, 12). A meta-analysis including 22 studies performed in SSA from 1991 to 2018 reported that the odds of severe malaria were significantly higher in co-infected children (odds ratio, OR 9.69) than in coinfected adults (OR 2.68) (14).

In pregnant women living high malaria transmission areas, malaria and HIV coinfection increases the risk of placental, peripheral and cord blood infections, high density parasitemia, severe anemia, febrile malaria illness and maternal death (10, 11). Malaria and HIV coinfection also increases the risk of fetal anemia, low-birth-weight, prematurity, intrauterine growth restriction and neonatal mortality (10, 11, 15). Furthermore, it has been reported that HIV-infected women do not seem to develop the malaria specific immunity, which may explain the increased risk of malaria severity in subsequent pregnancies (table 1) (16). HIV seems to impair the ability of pregnant women to acquire antibodies to variant surface antigens expressed on the surface of parasitized erythrocytes and opsonizing antibodies to placental parasites, weakening the resistance to placental malaria (16).

Adults with malaria and HIV coinfection may be considered an additional vulnerable group. Although some studies have reported no differences in severe malaria between PLHIV and individuals without HIV (17), a meta-analysis (including also pregnant women and children) found that coinfected individuals had a greater risk of suffering from severe malaria (14). Additionally, a higher risk of in-hospital mortality and anemia among malaria and HIV coinfected adults in comparison to those mono-infected has been reported in studies performed in several SSA countries (18, 19). For instance, a South African cohort study carried out in 2004 in an area of unstable malaria transmission among adults presenting with fever and peripheral parasitemia found that 47% of enrolled PLHIV had severe malaria *versus* only 30% of those without HIV (p=0.003) (20). Interestingly, more recently, a study conducted in 2014 among children and adults living with HIV in Cameroon found that the risk of presenting malaria was decreased in those participants that were on antiretroviral therapy (23.5% *versus* 6.8%, p=0.03), suggesting an improvement of the immune system leading to a better protection against malaria (19).

Hematological and immunological effects of HIV and malaria co-infection

A recent meta-analysis has reported that PLHIV with severe malaria had higher leukocyte counts than patients with *Plasmodium* spp. mono-infection (mean difference, 1570 cells/µL, $p < 0.001$) (table 1) (14). The leucocyte counts were also higher in patients with high parasitemia compared with those with low and moderate parasitemia (14). Moreover, no difference in mean neutrophil counts between malaria and HIV coinfected and mono-infected individuals were noted (mean difference, 980 cells/µ, p=0.5) (14).

A study performed among children and adults in Cameroon in 2019 reported that CD4+ T cell count were lower in co-infected patients than in patients infected with malaria or HIV only: 54.4% of coinfected patients had CD4 count ≤500, while most of the HIV mono-infected presented CD4 count ≥500 cells/µl (64.07%), p≤0.025) (table 1) (21). Innate immune responses are the first line of defense in malaria infection (22). A balanced inflammatory response characterized by an early pro-inflammatory and a secondary immunoregulatory response is required to adequately control parasitemia while limiting host pathology (22). Natural killer and T cells are implicated in the innate response to malaria (22). In turn, HIV infection leads to a dysregulation of inflammatory responses, and both enhanced and reduced inflammatory responses have been reported in the context of malaria and HIV coinfection (23-25). In terms of enhanced inflammatory response, a study conducted in Mozambique in 2010found that coinfected patients exhibited the highest percentages of HLA-DR and CD38 (marker of CD8+ T cell activation) (24). Similarly, an additional study has reported higher levels of IL-8, IL-12 and IFNγ in coinfected patients than in malaria mono-infected patients only, suggesting that malaria and HIV coinfection dysregulates immune response, contributing to the progression of both diseases (25).

The evidence regarding the effects of HIV on antimalarial humoral response is contradictory (table 1). While some studies found no effect on malaria antibody production, others have reported a decrease in the response to *Plasmodium falciparum* antigens (26, 27). In a prospective study performed among adults in Rwanda, malaria and HIV coinfection was associated with an expansion of atypical memory B cells beyond those induced by malaria alone (26). In this sense, coinfection has been associated separately with B cell dysfunction, specifically hyperactivated but dysfunctional memory B cells referred to as exhausted or atypical (28). This is further illustrated by a study performed among Kenyan adults, where HIV infection was associated with a decrease in *Plasmodium falciparum* antibodies apical membrane antigen 1 (AMA1)-specific naïve and resting memory B cells, but an increase in the proportion of AMA1-specific B cells with an activated or atypical phenotype (29). Lower levels of IgG against AMA1 were also found in a study conducted among malaria and HIV coinfected Malawian adults in comparison to their counterparts without HIV, as well as lower levels of opsonizing antibodies against the three parasite lines that were tested (30). These findings suggest incompetency in clearing parasites and subsequent increased risk of parasitemia in coinfected individuals (31).

Cerebral malaria

Cerebral malaria involves complex immunologic and hematologic mechanisms. It is characterized by the accumulation of infected red blood cells (iRBC) in the brain microvasculature, causing a blockage in blood circulation and oxygen with subsequent ischemia to brain tissue (32). This is often accompanied by intra and peri-vascular pathology, including inflammation, impaired vasoregulation and blood-brain barrier dysregulation (32). In turn, chronic HIV infection is associated with expansion of monocyte subsets and platelet activation, leading to monocyte activation and formation of circulating monocyte-platelet complexes (33). A study that performed autopsies on children living with HIV and without HIV with confirmed cerebral malaria, and controls without malaria, found that children with autopsy-confirmed cerebral malaria had a nine-times higher risk of presenting accumulations of intravascular monocytes and platelets in brain tissue, but not neutrophils, than did children with non-malarial cause of coma (table 1) (34). These monocyte and platelet accumulations were significantly greater in children living with HIV than in those children without HIV with cerebral malaria (34).

Additionally, cerebral malaria is associated with a reduction in lymphocyte subsets in peripheral blood (CD4+ T cells, B cells, and NK cells) (35), which is exacerbated by HIV infection (35). Low CD4+ T cell count is further reduced when the child presents with cerebral malaria, which suggests that cerebral malaria may compound the HIV-related loss of CD4+T cells from

peripheral blood (36). A study performed among children living with HIV and without HIV with cerebral malaria found that the former had lower median plasma levels of interleukins (particularly, TNF and interleukin-10), and soluble intracellular adhesion molecules (37). In this study, this did not have an effect on parasite density and the clinical course of cerebral malaria; thus, the authors hypothesized that a systemic inflammation may not the primary driver of pathogenesis in cerebral malaria, but rather local iRBC-associated effects (37).

Treatment and prevention of malaria in PLHIV

Effectively preventing and managing malaria in PLHIV requires, as in uninfected populations, 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 (38). Few studies evaluating malaria prevention and treatment strategies have specifically targeted PLHIV. In this population, it is essential to consider the patient's antiretroviral therapy (ART) regimen and the concurrent medications used to prevent opportunistic infections (38).

Regarding malaria prevention, currently the World Health Organization (WHO) recommends among others, the following strategies in high malaria transmission areas: intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) in pregnancy (IPTp) and perennial malaria chemoprevention (PMC) with SP or seasonal malaria chemoprevention with SP-amodiaquine in children (1).

However, chemoprevention with SP is contra-indicated in individuals on cotrimoxazole prophylaxis, which is recommended to prevent opportunistic infections in women and children living with HIV or children who are HIV exposed 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-piperaquine have been evaluated for IPTp among women and children living with HIV and HIV exposed, but to date, there is no specific strategy for malaria prevention among these populations (39-43).

The recommended treatment of uncomplicated *Plasmodium falciparum* malaria involves early diagnosis followed by a three-day treatment course of artemisinin-based combination therapies (ACTs) (38). PLHIV with malaria should also receive prompt and effective antimalarial treatment. Additionally, since 2015, WHO recommends early initiation of ART for all PLHIV regardless of WHO clinical stage and at any CD4 cell count level (44). Current first-line ART regimen includes dolutegravir (DTG) in combination with a nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) backbone which can consist of tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC) for adults and adolescents, and abacavir (ABC) and 3TC for children. A raltegravir (RAL)-based regimen is recommended as the preferred first-line regimen for neonates (45). Alternative first-line ART regimens include TDF+3TC+efavirenz (EFV) for adults and adolescents, ABC+3TC+lopinavir/ritonavir (LPV/r) or tenofovir alafenamide (TAF)+3TC+DTG for children, as well as zidovudine (AZT)+3TC+nevirapine (NVP) for neonates.

Drug interactions

HIV integrase inhibitors

Current evidence indicates that co-administration of first-line ACT regimens with DTG, is both safe and effective, suggesting that DTG dose adjustments are not necessary (46, 47). However, current evidence is mainly based in pharmacokinetic studies in healthy volunteers, and clinical evidence for efficacy and safety among PLHIV on ART is limited. Two pharmacokinetic studies in

healthy volunteers in Uganda assessed potential interactions between standard adult doses of artemether-lumefantrine or artesunate-amodiaquine and a daily 50 mg dose of DTG. DTG did not significantly impact the maximum concentration in plasma, time to maximum concentration, and the area under the concentration-time curve (AUC) for either of the antimalarial treatments (table 2) (47). Combining DTG with artemether-lumefantrine or artesunate-amodiaquine reduced DTG trough concentrations by 37% and 42%, respectively (47). However, these levels remained above the 300 ng/ml target, suggesting that DTG dose adjustments are not necessary during the standard three-day treatment of artemether + lumefantrine or artesunate + amodiaquine (47). There is limited evidence regarding drug interactions between RAL and ACTs , however considering that RAL is not metabolized through CYP450, so it is unlikely to cause clinically significant interactions (48).

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
TDF, 3TC, FTC, and ABC are currently part of the first-line ART regimen for adults and children. Drug interactions between TDF, FTC, and ABC with ACTs are not expected as NRTIs are not metabolized via the CYP450 enzyme system, but increased exposure to 3TC may occur when used alongside SP (table 2) (48). Nevertheless, clinical evidence regarding NRTI interactions with antimalarial drugs is limited, with most studies centered on AZT.

In this regard, treatment with artesunate plus amodiaquine has been found to be efficacious for uncomplicated malaria in children living with HIV. However, children with HIV on AZT and cotrimoxazole showed a significantly higher risk of neutropenia and presented more episodes of pneumonia after initiating treatment with artesunate plus amodiaquine compared to children without ART or those not living with HIV (49). This can be explained by the concomitant use of different myelosuppressive agents, such as AZT, cotrimoxazole and amodiaquine. Accordingly, WHO recommends avoiding the use of artesunate-amodiaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in PLHIV under treatment with AZT as well as cotrimoxazole (38). Similarly, pyrimethamine may adversely affect folate metabolism in patients taking myelosuppressive agents, such as AZT or cotrimoxazole (50).

Non-nucleoside reverse transcriptase inhibitors (NNRTI)
EFV is currently part of the alternative first-line ART. Several studies conducted among diverse populations, including malaria-infected adults and children, and pregnant women living with HIV, revealed an increased incidence of recurrent malaria after malaria treatment with artemether and lumefantrine (table 2) (46, 50-52). EFV is a potent inductor of CYP450 enzymes, which metabolize artemether and lumefantrine, significantly reducing artemether-lumefantrine exposure. (51-53). Some authors suggest extending the duration or increasing the dosing frequency of artemether-lumefantrine treatment for PLHIV on EFV (52). Nevertheless, there is currently no evidence of extended duration 5-day artemether-lumefantrine treatment for PLHIV, even though it has been proven to be safe and effective in children without HIV in areas with high malaria transmission (54). EFV also showed significant interactions with amodiaquine inducing liver injury due to increased amodiaquine exposure, as revealed by a clinical trial prematurely discontinued toe to adverse hepatic events in healthy volunteers (55). Consequently, the WHO malaria guidelines contraindicate the combination of EFV with amodiaquine (38). Additionally, EFV may potentially enhance the effect of piperaquine in prolonging the QT interval (56). However, a clinical trial among adult patients from Malawi and Mozambique with uncomplicated *P. falciparum* malaria who were on efavirenz-based or nevirapine-based ART showed 30% QT prolongation in the EFV group that were no clinically detectable and resolved spontaneously over time (56). Finally, pregnant women on EFV and for IPTp with dihydroartemisinin-piperaquine need dose adjustments among due to the lower exposure to dihydroartemisinin and piperaquine (57, 58).

NVP has limited use in current clinical practice but interacts with some ACTs. It reduces exposure to artemether and has a minor impact on dihydroartemisin exposure, with no substantial effect on lumefantrine's bioavailability (58, 59). While NVP decreases exposure to amodiaquine and potentially increases the bioavailability of piperaquine, its clinical impact on efficacy is uncertain (60, 61). Furthermore, there is evidence of NVP increasing artesunate exposure. (62) Finally, both EFV and NVP have the potential to decrease mefloquine exposure through the induction of CYP3A4 (50). Similarly, NVP levels have been found to be reduced in pregnant women receiving mefloquine as IPTp indicating possible drug interactions between the two drugs (63). This finding might explain the two-fold increased risk of mother to child transmission (MTCT) of HIV in mefloquine recipients reported in a randomized placebo-controlled trial evaluating mefloquine for IPTp in women living with HIV on cotrimoxazole prophylaxis (40).

Protease inhibitors:
LPV/r is included in as alternative to first-line HIV treatment regimen for children. Current evidence revealed that that combining LPV/r with artemether-lumefantrine is safe and effective. In particular, studies in healthy volunteers and PLHIV, both adults and children, reported that combining LPV/r with artemether-lumefantrine increases lumefantrine exposure while decreasing exposure to artemether and dihydroartemisinin (table 2) (64, 65). However, this heightened lumefantrine exposure does not extend QT intervals during single dosing or with a standard six-dose regimen (51, 65). The combination of LPV/R with dihydroartemisinin and piperaquine was also found to be safe and effective among children living with HIV on ART (66).

Regarding interactions between artesunate-mefloquine and LPV/r, a pharmacokinetic study in healthy Thai adults showed a 50% reduction in the AUC of dihydroartemisinin and a significant decrease in day 7 mefloquine exposure. Additionally, a decrease in the systemic exposure of both lopinavir and ritonavir was observed (67). On the other hand, co-administration of pyronaridine/artesunate with ritonavir in healthy adults significantly increased ritonavir exposure, minimally affecting pyronaridine. Despite increased artesunate levels and decreased dihydroartemisinin exposure, ritonavir's impact on pyronaridine/artesunate appears to lack clinical relevance, given that pyronaridine's 90% confidence interval closely aligns with the acceptable range, and artesunate's pharmacokinetics exhibit considerable individual variability. This co-administration temporarily raised transaminase levels, which normalized within two months (68).

Risk of co-infection and impact on transmission

Risk of malaria among PLHIV and impact of malaria transmission
PLHIV may experience weakened immune systems, hindering parasite clearance, and spleen damage —a key organ in controlling malaria infection. Due to this impaired immunological response in HIV infection, PLHIV also face an increased risk of malaria infection (69). In SSA, HIV was estimated to increase malaria prevalence by 1.3% and malaria-related mortality by 4.9%, resulting in an additional three million clinical malaria cases and 65,000 malaria-related deaths annually in Africa (69). Some authors suggest that the intensified malaria incidence due to HIV is particularly pronounced in areas of low malarial transmission, attributed to the lack of acquired natural immunity (70). Of note, this evidence is mostly related to *P. falciparum*. However, a recent study in Brazil reported that HIV is also a risk factor for *Plasmodium vivax* malaria infection, with an adjusted relative risk of 2.77 (95% confidence interval: 1.46-5.28).

On the other hand, there is extensive evidence on the increased malaria parasite density associated with HIV-mediated immunity in PLHIV, making this population more infectious to mosquitoes (71). However, the possible impact of this increased parasitemia on malaria transmission is frequently suggestive or speculative. A study conducted in Kenya found no

significant association between HIV and malaria transmission in PLHIV receiving ART and cotrimoxazole prophylaxis (71). By contrast, a cross-sectional study, also conducted in Kenya, reported an increased risk of gametocytemia in newly diagnosed PLHIV, not on ART, compared to people living without HIV (72). This study is the first of its kind designed to evaluate the epidemiological impact of HIV-1 co-infection on the prevalence of asymptomatic gametocytemia in the field and its findings suggest that PLHIV may have an increased risk of transmitting malaria parasites.

HIV infection risk in malaria patients and impact of malaria on HIV transmission

Among PLHIV, both *in vitro* and *in vivo* studies have revealed that malaria co-infection causes a transient increase in HIV viral load (VL) for several weeks post-antimalarial treatment, threatening ART effectiveness and heightening the HIV infectiousness of co-infected individuals (2, 73). Thus, malaria and HIV coinfection may have an impact on HIV disease progression and transmission, potentially contributing to the high HIV prevalence in SSA. A study in Malawi demonstrated a ten-fold increase in HIV VL in co-infected individuals with febrile malaria, translating to a roughly 2.5-fold increase in HIV transmission probability (74-76). This resulted in more than 8,500 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). It is important to note that the potentially significant impact of malaria on HIV epidemiology is mostly based on early estimates of the effect on VL in PLHIV not receiving ART.

Geographical variations in the impact of malaria on HIV transmission have also been noted. In areas with high malaria and HIV prevalence, particularly in Eastern SSA, individuals faced approximately double the risk of HIV infection compared to regions with lower malaria rates (77). Conversely, in populations with low HIV prevalence, as observed in Western SSA, no evidence of association between HIV and malaria was found, suggesting that malaria may not significantly impact the spread of HIV in populations with low HIV prevalence (77). The same authors 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 behavioral and environmental distinctions (78).

Malaria and mother to child transmission of HIV

With regard to the impact of malaria on the risk of MTCT of HIV, there are conflicting results and most of them are from research conducted before ART was recommended to all PLHIV (table 3). An association between high-density placental malaria and increased MTCT was reported in studies conducted in Kenya and Uganda (79-81). In Rwanda, the association was particularly relevant in primigravidae (82). However, other studies have not observed this effect of malaria on MTCT and results remain inconsistent (83-85).

An association of presumptive clinical malaria with increased risk of MTCT of HIV has also been reported in a cohort study conducted in Tanzania (86). Furthermore, clinical malaria during pregnancy was found to be an independent risk factor associated with an increased risk of MTCT in a multicenter placebo-controlled trial evaluating mefloquine for IPTp (40).

On the other hand, maternal HIV VL at the time of delivery is the most important and recognized risk factor for MTCT (87). Importantly, peripheral and placental HIV VL have been found to be increased in co-infected pregnant women from Malawi (88). Additionally, *in vitro* analysis of cord blood cells of Kenyan infants exposed to malaria have been reported to be more likely to

become infected with HIV than those of North American infants (89). Finally, HIV-associated impairment of antibody responses in pregnant women may also contribute to higher transmission of *Plasmodium falciparum* to their infants (90).

Conclusions and knowledge gaps

The high burden of malaria and HIV infection in SSA presents a double blow to the region, which is presently worst hit by the presence of other infectious diseases, such as tuberculosis and Ebola outbreaks. The last WHO technical consultation analyzing malaria and HIV interactions dates from 2004 (3). While some of the research gaps identified at that time have been, at least partially, addressed, others remain unanswered twenty years later.

Recent studies have evaluated the effect of malaria on HIV transmission and its findings support previous evidence suggesting that malaria is a risk factor for HIV acquisition (73, 75, 91). However, discrepancies persist in how malaria influences HIV transmission across SSA. Eastern areas of the region with high malaria and HIV prevalence exhibit a doubling of HIV infection risk, while in Western areas, with lower HIV rates, there is a lack of evidence of a significant association between HIV and malaria (77). 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 coinfection, and reviewed in this article, were performed before 2016, when the WHO recommended the "test and treat" policy, whereby every person diagnosed with HIV should start ART regardless CD4 cell count (13). Thus, there is scarcity of information regarding the presentation of malaria and HIV coinfection in the context of widespread ART and subsequent control of HIV infection. In turn, the conflicting evidence regarding the impact of malaria on MTCT of HIV will be currently difficult to assess given the well-established PMTCT and ART programs in pregnancy which result in very low vertical transmission rates in SSA countries. Regarding prevention of malaria in pregnant women and children living with HIV or HIV-exposed, alternative drugs to SP for prevention of malaria have been evaluated in individuals on cotrimoxazole prophylaxis. Nevertheless, to date no suitable and tailored treatments have been found and recommended for prevention of malaria in these populations (39, 40). Of note, results of two recently completed randomized placebo-controlled clinical trials evaluating dihydroartemisin-piperaquine for IPTp in pregnant women living with HIV on cotrimoxazole prophylaxis have reported a reduced risk of malaria infection in the intervention group (42, 43). These findings make the drug a promising candidate to be considered for IPTp in pregnant women living with HIV. Similarly, the evaluation of alternative drugs for PMC in HIV-exposed infants on cotrimoxazole prophylaxis is urgently needed. On the other hand, in last years, drug interactions between antimalarial and ARV drugs have been assessed, which may help optimize malaria treatment in PLHIV. This includes the interactions between DTG (currently first-line ART) and first-line antimalarial drugs such as artemether and lumefantrine, which provided reassuring results (47). However, further research is needed on the interactions between ART and second line therapy antimalarial drugs, as well as antimalarials used for chemoprevention and those under research for prevention among pregnant women living with HIV.

In conclusion, the latest evidence indicates that while HIV infection alters the immunological response to and the clinical characteristics of malaria, malaria increases the HIV VL potentially enhancing HIV transmission. Additionally, drug interactions between ART and antimalarial drugs both for treatment and prevention may hamper its efficacy, potentially hindering the control of both infections. Importantly, no specific malaria control strategies tailored for PLHIV, who are at increased risk of infection, have been developed to date. Finally, it is essential to consider HIV and malaria interactions in the development of control guidelines and both disease elimination plans.

Search strategy and selection criteria

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

Contributors

RG and AFR conceived and designed the review. AFR, ASL, SFL and RG wrote the drafts of the review. RG critically revised all the draft.

Conflicts of interest

We declare that we have no conflicts of interest.

Figures

Figure 1. Diagram of HIV and malaria most relevant interactions. LBW: low birthweight, FGR: fetal growth restriction, MTCT: mother-to-child transmission

Figure 2. People living with HIV (millions, 2022) in areas where malaria is transmitted (incidence of malaria per 1,000 people at risk, 2020). Sources: Our world in data, (8) UNAIDS. (7)

References

1. WHO. World Malaria Report 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. 2004.
4. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. AIDS. 2005;19(10):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(5805):1603-6.
6. Skinner-Adams TS, McCarthy JS, Gardiner DL, Andrews KT. HIV and malaria co-infection: interactions and consequences of chemotherapy. Trends Parasitol. 2008;24(6):264-71.
7. UNAIDS. Available from : https://www.unaids.org/en/resources/documents/2023/2022_unaids_data. 2023. Date accessed: November 17, 2023.
8. World Health Organization (via World Bank) – processed by Our World in Data Incidence of malaria 2023. Available from: https://ourworldindata.org/grapher/incidence-of-malaria. Date accessed: November 17, 2023.
9. Naing C, Sandhu NK, Wai VN. The Effect of Malaria and HIV Co-Infection on Anemia: A Meta-Analysis. Medicine (Baltimore). 2016;95(14):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(7):541-56.
11. Gonzalez R, Ataide R, Naniche D, Menendez C, Mayor A. HIV and malaria interactions: where do we stand? Expert Rev Anti Infect Ther. 2012;10(2):153-65.
12. Hendriksen IC, Ferro J, Montoya P, Chhaganlal KD, Seni A, Gomes E, 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(8):1144-53.
13. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016.
14. 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(1):16655.
15. 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(8):e2380.
16. Ataide R, Hasang W, Wilson DW, Beeson JG, Mwapasa V, Molyneux ME, et al. Using an improved phagocytosis assay to evaluate the effect of HIV on specific antibodies to pregnancy-associated malaria. PLoS One. 2010;5(5):e10807.
17. 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;13:63-8.
18. Berg A, Patel S, Aukrust P, David C, Gonca M, Berg ES, 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(2):e88257.
19. 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(1):988.
20. 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(3):547-54.

21. 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(3):e0263865.
22. Stevenson MM, Riley EM. Innate immunity to malaria. Nat Rev Immunol. 2004;4(3):169-80.
23. Chaisavaneeyakorn S, Moore JM, Otieno J, Chaiyaroj SC, Perkins DJ, Shi YP, 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(1):127-31.
24. 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(8):985-92.
25. 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(7):652-8.
26. Subramaniam KS, Skinner J, Ivan E, Mutimura E, Kim RS, Feintuch CM, 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(4):e0124412.
27. Nnedu ON, O'Leary MP, Mutua D, Mutai B, Kalantari-Dehaghi M, Jasinskas A, et al. Humoral immune responses to Plasmodium falciparum among HIV-1-infected Kenyan adults. Proteomics Clin Appl. 2011;5(11-12):613-23.
28. Moir S, Fauci AS. B cells in HIV infection and disease. Nat Rev Immunol. 2009;9(4):235-45.
29. Frosch AE, Odumade OA, Taylor JJ, Ireland K, Ayodo G, Ondigo B, 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(12):4629-38.
30. 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(9):1407-14.
31. Patnaik P, Jere CS, Miller WC, Hoffman IF, Wirima J, Pendame R, 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(6):984-91.
32. Taylor TE, Fu WJ, Carr RA, Whitten RO, Mueller JS, Fosiko NG, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. Nat Med. 2004;10(2):143-5.
33. 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(2):170-6.
34. Hochman SE, Madaline TF, Wassmer SC, Mbale E, Choi N, Seydel KB, et al. Fatal Pediatric Cerebral Malaria Is Associated with Intravascular Monocytes and Platelets That Are Increased with HIV Coinfection. mBio. 2015;6(5):e01390-15.
35. Mandala WL, Msefula CL, Gondwe EN, Gilchrist JJ, Graham SM, Pensulo P, et al. Lymphocyte Perturbations in Malawian Children with Severe and Uncomplicated Malaria. Clin Vaccine Immunol. 2015;23(2):95-103.
36. Lyke KE, Burges R, Cissoko Y, Sangare L, Dao M, Diarra I, 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(10):5630-7.
37. Mbale EW, Moxon CA, Mukaka M, Chagomerana M, Glover S, Chisala N, et al. HIV coinfection influences the inflammatory response but not the outcome of cerebral malaria in Malawian children. J Infect. 2016;73(3):189-99.
38. WHO. Guidelines for malaria. 2023.

39. Natureeba P, Kakuru A, Muhindo M, Ochieng T, Ategeka J, Koss CA, et al. Intermittent Preventive Treatment With Dihydroartemisinin-Piperaquine for the Prevention of Malaria Among HIV-Infected Pregnant Women. J Infect Dis. 2017;216(1):29-35.
40. Gonzalez R, Desai M, Macete E, Ouma P, Kakolwa MA, Abdulla S, 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(9):e1001735.
41. Kamya MR, Kapisi J, Bigira V, Clark TD, Kinara S, Mwangwa F, 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(18):2701-9.
42. Gonzalez R, Nhampossa T, Mombo-Ngoma G, Mischlinger J, Esen M, Tchouatieu AM, 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.
43. Barsosio HC, Madanitsa M, Ondieki ED, Dodd J, Onyango ED, Otieno K, 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.
44. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015.
45. WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 2021.
46. Francis J, Barnes KI, Workman L, Kredo T, Vestergaard LS, Hoglund RM, 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(5).
47. Walimbwa SI, Lamorde M, Waitt C, Kaboggoza J, Else L, Byakika-Kibwika P, et al. Drug Interactions between Dolutegravir and Artemether-Lumefantrine or Artesunate-Amodiaquine. Antimicrob Agents Chemother. 2019;63(2).
48. EACS. Drug-drug Interactions between Anti-malarial Drugs & ARVs. 2023.
49. Gasasira AF, Kamya MR, Achan J, Mebrahtu T, Kalyango JN, Ruel T, 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(7):985-91.
50. Seden K, Gibbons S, Marzolini C, Schapiro JM, Burger DM, Back DJ, 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(3):e0173509.
51. Byakika-Kibwika P, Lamorde M, Mayito J, Nabukeera L, Namakula R, Mayanja-Kizza H, et al. Significant pharmacokinetic interactions between artemether/lumefantrine and efavirenz or nevirapine in HIV-infected Ugandan adults. J Antimicrob Chemother. 2012;67(9):2213-21.
52. Parikh S, Kajubi R, Huang L, Ssebuliba J, Kiconco S, Gao Q, et al. Antiretroviral Choice for HIV Impacts Antimalarial Exposure and Treatment Outcomes in Ugandan Children. Clin Infect Dis. 2016;63(3):414-22.
53. Hughes E, Mwebaza N, Huang L, Kajubi R, Nguyen V, Nyunt MM, 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(2):140-7.
54. Whalen ME, Kajubi R, Goodwin J, Orukan F, Colt M, Huang L, 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(3):443-52.

55. German P, Greenhouse B, Coates C, Dorsey G, Rosenthal PJ, Charlebois E, et al. Hepatotoxicity due to a drug interaction between amodiaquine plus artesunate and efavirenz. Clin Infect Dis. 2007;44(6):889-91.
56. Manning J, Vanachayangkul P, Lon C, Spring M, So M, Sea D, 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(10):6056-67.
57. Kajubi R, Huang L, Jagannathan P, Chamankhah N, Were M, Ruel T, et al. Antiretroviral Therapy With Efavirenz Accentuates Pregnancy-Associated Reduction of Dihydroartemisinin-Piperaquine Exposure During Malaria Chemoprevention. Clin Pharmacol Ther. 2017;102(3):520-8.
58. Banda CG, Dzinjalamala F, Mukaka M, Mallewa J, Maiden V, Terlouw DJ, 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(8).
59. 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.
60. Scarsi KK, Fehintola FA, Ma Q, Aweeka FT, Darin KM, Morse GD, et al. Disposition of amodiaquine and desethylamodiaquine in HIV-infected Nigerian subjects on nevirapine-containing antiretroviral therapy. J Antimicrob Chemother. 2014;69(5):1370-6.
61. Sevene E, Banda CG, Mukaka M, Maculuve S, Macuacua S, Vala A, 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(1):277.
62. Fehintola FA, Scarsi KK, Ma Q, Parikh S, Morse GD, Taiwo B, et al. Nevirapine-Based Antiretroviral Therapy Impacts Artesunate and Dihydroartemisinin Disposition in HIV-Infected Nigerian Adults. AIDS Res Treat. 2012;2012:703604.
63. Haaland RE, Otieno K, Martin A, Katana A, Dinh C, Slutsker L, 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(11):912-5.
64. German P, Parikh S, Lawrence J, Dorsey G, Rosenthal PJ, Havlir D, et al. Lopinavir/ritonavir affects pharmacokinetic exposure of artemether/lumefantrine in HIV-uninfected healthy volunteers. J Acquir Immune Defic Syndr. 2009;51(4):424-9.
65. Kredo T, Mauff K, Workman L, Van der Walt JS, Wiesner L, Smith PJ, et al. The interaction between artemether-lumefantrine and lopinavir/ritonavir-based antiretroviral therapy in HIV-1 infected patients. BMC Infect Dis. 2016;16:30.
66. Kakuru A, Achan J, Muhindo MK, Ikilezi G, Arinaitwe E, Mwangwa F, 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(3):446-53.
67. 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.
68. Morris CA, Lopez-Lazaro L, Jung D, Methaneethorn J, Duparc S, Borghini-Fuhrer I, et al. Drug-drug interaction analysis of pyronaridine/artesunate and ritonavir in healthy volunteers. Am J Trop Med Hyg. 2012;86(3):489-95.
69. Korenromp EL, Williams BG, de Vlas SJ, Gouws E, Gilks CF, Ghys PD, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. Emerg Infect Dis. 2005;11(9):1410-9.

70. 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(11):1343-56.
71. 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.
72. 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. 2020;10:600106.
73. 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.
74. Nyabadza F, Bekele BT, Rua 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.
75. Kublin JG, Patnaik P, Jere CS, Miller WC, Hoffman IF, Chimbiya N, 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(9455):233-40.
76. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. 2000;342(13):921-9.
77. 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(4):931-9.
78. Cuadros DF, Garcia-Ramos G. Variable effect of co-infection on the HIV infectivity: within-host dynamics and epidemiological significance. Theor Biol Med Model. 2012;9:9.
79. Ayisi JG, van Eijk AM, Newman RD, ter Kuile FO, Shi YP, Yang C, et al. Maternal malaria and perinatal HIV transmission, western Kenya. Emerg Infect Dis. 2004;10(4):643-52.
80. Brahmbhatt H, Sullivan D, Kigozi G, Askin F, Wabwire-Mangenm F, Serwadda D, et al. Association of HIV and malaria with mother-to-child transmission, birth outcomes, and child mortality. J Acquir Immune Defic Syndr. 2008;47(4):472-6.
81. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Sewankambo N, Lutalo T, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. AIDS. 2003;17(17):2539-41.
82. Bulterys PL, Chao A, Dalai SC, Zink MC, Dushimimana A, Katzenstein D, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1 in rural Rwanda. Am J Trop Med Hyg. 2011;85(2):202-6.
83. Msamanga GI, Taha TE, Young AM, Brown ER, Hoffman IF, Read JS, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. Am J Trop Med Hyg. 2009;80(4):508-15.
84. Inion I, Mwanyumba F, Gaillard P, Chohan V, Verhofstede C, Claeys P, et al. Placental malaria and perinatal transmission of human immunodeficiency virus type 1. J Infect Dis. 2003;188(11):1675-8.
85. Naniche D, Lahuerta M, Bardaji A, Sigauque B, Romagosa C, Berenguera A, et al. Mother-to-child transmission of HIV-1: association with malaria prevention, anaemia and placental malaria. HIV Med. 2008;9(9):757-64.
86. Ezeamama AE, Duggan C, Manji KP, Spiegelman D, Hertzmark E, Bosch RJ, 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(5):276-85.
87. Coutsoudis A, Kwaan L, Thomson M. Prevention of vertical transmission of HIV-1 in resource-limited settings. Expert Rev Anti Infect Ther. 2010;8(10):1163-75.

88. Mwapasa V, Rogerson SJ, Molyneux ME, Abrams ET, Kamwendo DD, Lema VM, et al. The effect of Plasmodium falciparum malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. AIDS. 2004;18(7):1051-9.
89. Steiner K, Myrie L, Malhotra I, Mungai P, Muchiri E, Dent A, 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(6):899-907.
90. Naniche D, Serra-Casas E, Bardaji A, Quinto L, Dobano C, Sigauque B, 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(4):568-77.
91. Andreani G, Lodge R, Richard D, Tremblay MJ. Mechanisms of interaction between protozoan parasites and HIV. Curr Opin HIV AIDS. 2012;7(3):276-82.

Tables

Table 1. Studies assessing the effects of HIV and malaria co-infection published after 2012 (included)

Author and year	Study population and country	Study year(s)	Study design and sample size	Study objective(s)	Interactions described
Hendriksen IC et al, 2012 (12)	Children, Mozambique	2005-2010	Prospective cohort study of children with severe anemia (n=655)	Assess the effects of HIV and malaria coinfection on diagnosis, clinical presentation and outcome of patients with severe malaria	-Children with HIV coinfection presented with more severe acidosis, anemia, and respiratory distress, higher peripheral blood parasitemia and plasma *Plasmodium falciparum* histidine-rich protein-2 (PfHRP2). -During hospitalization, deterioration in coma score, convulsions, respiratory distress, and pneumonia were more common in HIV-coinfected children -Mortality was higher in coinfected children
Mahittikorn A et al, 2021 (14)	Children, pregnant women, non-pregnant adults SSA (22 out of 23 included studies)	1991-2018	Meta-analysis n=1126	Estimate the prevalence and characteristics of severe malaria caused by co-infection with HIV	-The pooled prevalence of severe malaria in malaria and HIV coinfected patients was 43.0% (23 studies). -The odds of severe malaria were significantly higher than in Plasmodium mono-infected patients and also significantly higher in children than in adults. -Co-infected patients with severe malaria had a higher mean parasite density than patients with monoinfection and higher leukocyte counts. -The mean neutrophil and lymphocyte counts were similar between co-infected patients and patients mono-infected with *Plasmodium falciparum*
Ivan E et al, 2013 (15)	Pregnant women, Rwanda	2010-2011	Prospective cohort study of pregnant women living with HIV (n=980)	Assess the major risk factors for malaria infection in pregnant women living with HIV	-A CD4 count =<350 cells/mm3 was associated with malaria (OR 3.37 [2.11–5.38]; p,0.0005). -Anti-retroviral therapy had no effect on the risk of malaria.
Berg A et al, 2014 (18)	Non-pregnant adults, Mozambique	2011-2012	Cross-sectional study of patients with fever and/or suspected malaria and healthy controls (n=268)	Assess the impact of HIV on the clinical presentation and mortality of malaria	-The in-hospitality mortality of the HIV and malaria co-infected patients was higher than in the patients without HIV (p=0.018). -Co-infection with HIV was an independent risk factor for death -Co-infected patients had significantly more frequent respiratory distress, bleeding disturbances, hypoglycaemia, liver and renal failure and high malaria parasitemia compared with the patients with malaria alone.
Sandie SM et al, 2019 (19)	Adults and children, Cameroon	2014	Cross-sectional study (n=411)	Determine the prevalence of malaria parasites and hematological abnormalities in patients living with HIV	-Among patients living with HIV, anemic patients had a higher prevalence of malaria parasite than non-anemic patients (p=0.01). -Among patients living with HIV, the risk of presenting malaria was lower when participants were on antiretroviral therapy (p=0.03). -Among the participants living with HIV who had not started the ART, prevalence of malaria parasite was higher (23.5%) compared with those that had started (6.8%) (p=0.03). -Co-infected participants had lower mean levels of hemoglobin concentration, red blood cell count and hematocrit.

Ejigu S et al, 2022 (21)	Children and adults, Ethiopia	2019	Cross-sectional study n=206	Compare RBC indices and anemia in HIV patients with malaria and HIV and those without malaria, and correlate these with CD4 level	-RBC, Hgb, HCT and MCV indices were lower in patients living with HIV with malaria -There was positive correlation between CD4 counts with RBC and Hgb in malaria-HIV co-infected -The prevalence of anemia was higher in co-infected individuals
Chavale H et al, 2012 (24)	Adults, Mozambique	2010	Cross-sectional study (n=99)	Evaluate the severity of anemia, *Plasmodium falciparum* parasite density and impairment of the cellular immune response in malaria and HIV coinfected adults	-Anemia was most prevalence in the coinfected group -A significant variation in parasite density was observed in the co-infected group -The CD4+ T cell counts were significantly lower in the coinfected group than in the HIV/AIDS only or malaria only patients -The highest CD38 expression was detected in the co-infected patients
Davenport GC et al, 2012 (25)	Children, Kenya	NA	Prospective cohort study of children with *Plasmodium falciparum* parasitemia (n=477)	Explore the inflammatory mediator profiles associated with worsening anemia in co-infected children.	-IL-12, MIG/CXCL9, eotaxin/CCL11, and GM-CSF differed significantly and progressively increased across the groups, from HIV negative to HIV-exposed, to HIV positive. -Three components were significantly higher in the HIV-1 positive and exposed groups -There was a significant positive correlations between Hb and IL-1Ra, IL-7, IL-17, IFN-α, IFN-γ, MIG/CXCL9) in the HIV negative with malaria group, and IL-4, IL-5, IL-12, Eotaxin/CCL11 in malaria and HIV coinfected group -IL-12 had the strongest association with anemia in the malaria and HIV coinfected group
Subramaniam KS et al, 2015 (26)	Adults, Rwanda	2011	Prospective study (n=86)	Assess the effect of HIV infection on antibody responses to malaria	-The mean breadth of *Plasmodium falciparum* IgG reactivity and the overall IgG reactivity across individuals living with HIV with malaria were lower than the mean breadth across HIV negative. -Subjects living with HIV with malaria had a higher percentage of atypical memory B cells in comparison to those HIV negative.
Frosch AE et al, 2017 (29)	Adults, Kenya	2012	Cross-sectional study (n=190)	Assess whether changes in the phenotypes of circulating B cells that target a specific antigen correlate with a change in Ig level for that same antigen	HIV infection is associated with a decrease in *Plasmodium falciparum* apical membrane Ag1-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 W et al, 2014 (30)	Adults, Malawi	2000-2001	Prospective study (n=339)	Determine the relationship between malaria antibodies, HIV infection, markers of immune compromise and risk of incident parasitemia	-HIV infected adults had significantly lower mean levels of opsonizing antibodies to all parasite lines and lower levels of antibodies to AMA-1 and MSP2. -Opsonizing antibody titers against some isolates were positively correlated with CD4 count and negatively associated with HIV viral load. -Those who developed parasitemia during follow up had lower opsonizing antibody levels independently of HIV status
Hochman SE et al, 2015 (34)	Children, Malawi	1996-2010	Cross-sectional study (n=96)	Identify differences or similarities in presentation and pathology of cerebral malaria between children living with HIV and without HIV	The monocyte and platelet accumulations were significantly (>2-fold) greater in children living with HIV than in children without HIV with autopsy-confirmed cerebral malaria
Mbale EW et al, 2016 (37)	Children, Malawi	1996-2011	Retrospective study (n=135)	Explore the effect of HIV on cerebral malaria to unravel the role of systemic inflammation in cerebral malaria pathogenesis	HIV-infected cerebral malaria cases had lower median plasma levels of TNF, interleukin-10 and sICAM-1 than cases without HIV. HIV-status did not significantly affect parasite density or mortality -Children living with HIV were older and more likely to have comorbidities

Roberds A et al, 2022 (71)	Adults, Kenya	2018-2020	Prospective cohort study n=300	Define the impact of HIV-malaria coinfection, ART, CTX and A on *Plasmodium falciparum* gametocyte transcript prevalence and parasite transmission to the Anopheles gambiae	-There was a significant relationship between the log transformed 18S copy numbers and gametocyte transcript prevalence -For HIV newly diagnoses, the initiation of ART and CTX was associated with a significant impact on the reduction of gametocyte transcript prevalence in the subsequent month

ART: Antiretroviral therapy, NA: Not available, sICAM: soluble intracellular adhesion molecules

Table 2. Summary of described drug interactions between ARVs and antimalarial drugs

Concomitant medication	Amodiaquine (AQ)	Artemether	Artesunate (AS)	Dihydro-artemisinin (DHA)	Lumefantrine	Mefloquine	Piperaquine (PPQ)
Dolutegravir (DTG)	Decreased DTG concentrations, but unlikely to be of clinical significance (47)	Decreased DTG concentrations, but unlikely to be of clinical significance (47)	Decreased DTG concentrations, but unlikely to be of clinical significance (47)		Decreased DTG concentrations, but unlikely to be of clinical significance (47)		
Zidovudine (AZT)	Increased risk for neutropenia (49)						
Efavirenz (EFV)	Increased plasma concentration of AQ and increase the risk for hepatotoxicity (55)	Decreased plasma concentration of artemether (51-53, 59)		Decreased plasma concentration of DHA (57)	Decreased plasma concentration of Lumefantrine (51-53, 59)	Decreased plasma concentration of mefloquine (50)	Reduced exposure to piperaquine and possible increased risk of QT interval prolongation. (56, 58, 61)
Nevirapine (NVP)	Possible decreased plasma concentration of AQ unlikely to be of clinical significance (58, 60) Transient liver function abnormalities and neutropenia not clinically significant (58)	Decreased plasma concentration of artemether (59)	Increased plasma concentration of AS (62)		No substantial effect on lumefantrine's bioavailability (59)	Decreased plasma concentration of mefloquine (50)	Potential increase of PPQ bioavailability with limited clinical significance (58, 61)
Lopinavir/ritonavir (LPV/r)		Decreased plasma concentration of artemether (64)		Decreased plasma concentration when AS or artemether is given with LPV/r (64)	Increased plasma concentration of Lumefantrine (64, 65)	Decreased plasma concentration of both mefloquine and LPV/r (67)	No significant changes in PPQ bioavailability concentration of PPQ (58)

Table 3. Summary of evidence regarding the impact of Malaria on MTCT of HIV

Reference	Country	Study design	Findings
Gonzalez et al, 2014 (40)	Kenya, Tanzania, Mozambique, 2010-2013	Secondary analysis of randomized controlled trial among pregnant women (N=1071)	Clinical malaria associated with MTCT in adjusted multivariate analysis (RR=4.76; 95% CI :2.01–11.24)
Ayisi et al, 2004 (79)	Kenya 1996-2000	Prospective cohort of mother-infant pairs (N=512)	Low-density placental malaria (<10,000 parasites/µL) was associated with reduced MTCT (ARR 0.4). In women dually infected with malaria and HIV, high-density placental malaria (>10,000 parasites/µL) was associated with increased risk of MTCT (ARR 2.0), compared to low-density malaria.
Brahmbhatt et al, 2008 (80)	Uganda 1994- 2000	Prospective cohort of mother-infant pairs (N=109)	Placental malaria associated with MTCT adjusted for maternal HIV viral load (RR 7.9; 95% CI: 1.4 to 58.5)
Brahmbhatt et al, 2003 (81)	Uganda 1994-1999	Secondary analysis of a community-randomized trial of sexually transmitted disease control for HIV prevention (N=668 pregnant women)	Placental malaria associated with MTCT (RR 2.85, 95% CI 1.53–5.32)
Bulterys et al, 2011 (82)	Rwanda, 1989- 1994	Nested case-control study in a prospective cohort study of mother-infant pairs (N=60)	Placental malaria associated with MTCT (adjusted odds ratio [aOR] = 6.3; 95% CI: 1.4–29.1), especially among primigravidae.
Msamanga et al, 2009 (83)	Malawi, Zambia, Tanzania, 2001-2003	Secondary analysis of randomized controlled trial among pregnant women (N=2126)	Placental malaria was not associated with the infant HIV-1 infection status at birth (p= 0.67).
Inion et al, 2003 (84)	Kenya 1996- 1999	Cross sectional study among delivering women (N=649; n=372 HIV-infected and n=277 uninfected)	Increased prevalence of placental malaria in HIV–infected women No association was found between placental malaria and either maternal virus load.
Naniche et al, 2008 (85)	Mozambique 2003-2006	Secondary analysis of randomized controlled trial among pregnant women (N=207)	Placental malaria was associated with a decrease in MTCT (AOR 0.23; 95% CI 0.06–0.89; p=0.034).
Ezeama et al, 2014 (86)	Tanzania 2004-2008	Prospective cohort of HIV-infected mother-infant pairs (N=2368)	HIV MTCT risk increased by 29% (95% CI 4–58%) per malaria in pregnancy episode.

aOR: Attributable Odds Ratio; RR: Risk ratio, MTCT: Mother-to-child transmission; 95%CI: 95% Confidence Interval