EXPERT REVIEWS

HIV and malaria interactions: where do we stand?

Expert Rev. Anti Infect. Ther. 10(2), 153–165 (2012)

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Reversing the spread of HIV infection and the incidence of malaria constitute two of the Millenium Development Goals. However, despite recent achievements, both diseases still entail global heath problems. Furthermore, their overlapping geographical distribution raises concerns and challenges for potential immunological, clinical and therapeutic interactions. It has been reported that HIV infection increases malaria susceptibility and reduces the efficacy of antimalarial drugs. On the other hand, the effect of malaria on HIV-infected individuals has also been explored, with the parasitic infection increasing the risk of HIV disease progression and mother-to-child transmission of HIV. The spread of malaria and parasite resistance to antimalarials could also be accelerated by HIV-associated immunosuppresion. Current knowledge of the epidemiological, clinical, immunological and therapeutic interactions of the two diseases is reviewed in this article. We focus on the latest available data, pointing out key future research areas and challenges of the field.

Keywords: antimalarial • antiretrovirals • drug • epidemiology • HIV • immunity • impact • interaction • malaria

Malaria and HIV infection are currently considered two of the main global health problems, together causing over 2.5 million deaths in 2009 [1,2]. The WHO estimates that half of the world's population is at risk of malaria. Sub-Saharan Africa is the region where the infection exacts a major toll, accounting for almost 80% of the malaria cases in the world [2]. Children younger than 5 years of age and pregnant women are the most vulnerable populations to malaria. Women are also more vulnerable to the HIV infection/AIDS epidemic, [3–5] and in sub-Saharan Africa approximately 60% of people living with HIV are women [1]. The age group most frequently infected by HIV includes adults between 15 and 49 years of age. The HIV/AIDS epidemic has inflicted devastating demographic effects such as increased mortality and drops in life expectancy [3], mainly in sub-Saharan Africa, where almost 70% of the 32.8 million HIV-infected people live [1].

Both diseases, which are considered a cause and consequence of poverty, share determinants of vulnerability [6]. The potential consequences and public health impact of their overlapping geographical distribution have been described and studied in recent years [7–13]. Interactions of the two diseases have been found at the level of the host's vulnerability to infection. HIV infection is a risk factor for clinical and severe malaria, and *Plasmodium falciparum* infection is a risk factor for increased HIV viral load [14–21]. Moreover, dual infection has been shown to feed the spread of both diseases in sub-Saharan Africa [7] and treatment of coinfected patients raises concerns on the potential for drug interactions [22].

The substantial geographic and social overlap in populations afflicted with both HIV and malaria leads to opportunities for complex interactions at individual and population scales. Importantly, any association between both infections could have significant public health consequences as a result of their respective prevalences. However, understanding of the epidemiological, biological and clinical interactions between HIV and malaria has lagged, compared with the understanding of the interactions between HIV and pathogens that are common in the industrialized world. In the present article, we review the current knowledge and gaps on the HIV-1 and *P. falciparum* malaria interactions at the clinical, immunological and therapeutic level, and discuss the public health challenges.

HIV impact on malaria: epidemiological evidence

HIV infection may increase the burden of malaria by increasing susceptibility to infection or by reducing the preventive and therapeutic

 10.1586/ERI.11.167 ISSN 1478-7210

efficacy of antimalarial drugs, since both are dependent on the immune response of the host. However, the first reports in the 1990s failed to demonstrate significant interactions between malaria and HIV in coinfected children and adults who had acquired semi-immunity to malaria [8], possibly due to limitations of the study designs and lack of information on the degree of immunosuppression. In the early 2000s, the clinical impact of HIV infection on malaria infection and disease was revealed [12,23], and appeared to be dependent on the dynamics of malaria transmission and the degree of HIV-associated immunosuppression [24]. HIV-infected individuals who have not acquired immunity against malaria show a marked increase in malaria severity, in contrast to those with naturally acquired immunity to malaria, in whom HIV infection is associated with only a moderate increase in clinical malaria [25]. More recently, malaria has been reported as a risk factor of concurrent HIV infection at the population level [10]. Findings of HIV and malaria interactions are described below by type of populations at risk: nonpregnant adults, children and pregnant women.

Nonpregnant adults

Several reports have shown that HIV infection among nonpregnant adults living in areas of high malaria transmission is associated with a modest increase in the frequency of clinical episodes of malaria and parasitemia [26]. Some of these studies showed that rates of clinical malaria were inversely related to CD4 T-cell counts [15,21,27]. It has also been reported that in areas of low malaria transmission, HIV-infected adults have a greater risk of severe malaria with more frequent hospitalization compared with their uninfected counterparts [28]. Although it was initially suggested that HIV infection does not increase the incidence of severe malaria in adults with naturally acquired immunity against malaria [29], a recent report has shown that HIV infection is also an important risk factor for severe malaria in adults from an area of high malaria transmission, primarily in those with low CD4 T-cell counts [14]. Moreover, HIV-infected patients with CD4 T-cell counts <350/µl were found to be at higher risk of severe imported malaria compared with HIV-uninfected individuals [30,31]. Overall, these studies suggest that HIV-infected adults with suppressed immunity represent, next to children and pregnant women, an additional vulnerable group for malaria.

Children

Early studies suggested that, contrary to what happens in adults, HIV infection and malaria were not associated in young children from malaria-endemic areas because their naive immune system is not affected by HIV infection [13,32,33]. However, in the early 2000s it was found that the rates of parasitemia, parasite densities, the risk of severe anemia and hospitalization due to malaria were higher among HIV-infected children (reviewed in [34]). In Malawi, HIV infection was reported in 16% of children admitted to the hospital with severe malaria, a prevalence that appears to be higher than that expected among community children, although no formal comparison was made [35]. A study conducted in Uganda showed that HIV-infected children with severe malarial anemia suffered higher all-cause and malaria-related mortality than HIV-uninfected children [36]. Recent reports suggest that HIV is also associated with hospital admission for severe malaria, clinical cerebral malaria and high parasite densities in children [37,38]. However, no association has been found between clinical malaria and low CD4 T-cell counts [38], in accordance with a previous study showing that lower CD4 T-cell counts were associated with higher incidence of pneumonia, sepsis and TB, but not of malaria [29]. Moreover, these associations were only found in children but not in infants, suggesting that HIV might stunt the age-related acquisition of natural immunity to malaria, thus having little effect among the youngest children who have not yet acquired this immunity [13].

Pregnant women

The impaired ability of HIV-infected pregnant women to control *P. falciparum* infections was first suggested by two cross-sectional studies in Malawi that found a higher prevalence of parasitemia at the first antenatal visit among HIV-infected women compared with HIV-uninfected women [39]. Additional studies have illustrated that HIV infection in pregnant women increases the risk of placental, peripheral and cord blood infections, high parasitemia density, severe anemia, febrile malaria illness, delivery of low-birth-weight and preterm infants, intrauterine growth retardation, post-neonatal mortality and maternal death as a result of frequent and severe malaria infections [23,39–43]. As this trend was more pronounced in multigravidae women, HIV infection has been suggested to attenuate the relative protection against the adverse effects of malaria observed with increased parity [44] and to place more pregnancies at risk for complications associated with malaria. This observation was explained by an increased immunosuppression in multigravidae due to longer duration of the HIV infection than in primigravidae or, alternatively, by alterations of the immune memory mechanisms responsible for the parity-associated protection against malaria.

The increasing prevalence of HIV infection and access to programs preventing HIV mother-to-child transmission (MTCT) implies that in Africa, very large numbers of HIV-uninfected children are being born to HIV-infected mothers. These children present increased morbidity and mortality in their first years of life compared with children born to uninfected women, especially when the mothers have a more advanced HIV infection [45,46]. In Kenya, both HIV exposure and HIV infection were found to be associated with increased prevalence of severe malarial anemia during acute *P. falciparum* infection, independent of parasite density [47]. This finding suggested that children born to HIV-positive mothers may be predisposed to hematological complications when infected with malaria. The underlying mechanisms for the latter are presently unclear, and may range from impairment of hematological and/or immunological development due to *in utero* HIV exposure, reduced transfer of antimalarial antibodies from mothers to the fetus, lack of prenatal care by HIV-infected mothers, increased exposure to other infections apart from HIV, such as TB, and exposure to antiretroviral drugs [46,48]. Additional investigations are required to confirm all these speculations.

Impact of HIV on antimalarial immunity

The interactions between HIV and malaria may be explained in part by the effect each disease has on the host's immunity. Immunological interactions are bound to be complex and dependent on the timing of the infection [49]. Several studies have analyzed the effect of HIV-associated immunosuppression on the acquisition and persistence of immune malaria responses [50–57].

Nonpregnant adults

It has recently been shown that severe malaria is more frequent in HIV-infected nonpregnant adults than in uninfected individuals [14,15]. HIV is also associated with decreased levels of serum IgG to apical membrane antigen-1 (AMA-1), a protein expressed by *P. falciparum* merozoites [57]. However, no association was found between HIV and antibodies against *Plasmodium* antigens on the surface of infected erythrocytes [57], leaving the question of how the susceptibility to severe malaria caused by HIV might occur. HIV is known to induce the production of Th2-type cytokines such as IL-10 and TGF-β, which are also associated with poor delivery outcomes [49,58,59]. However, there is a lack of well-designed studies addressing the specific impact of these cytokines on the development of immunity to malaria infection. Recent studies have shown that B cells from adults residing in malaria-endemic regions with intense *P. falciparum* transmission exhibit an atypical memory phenotype, similar to the one found in HIV-infected individuals [60,61]. Evidence of B-cell exhaustion caused by both infections [62,63] suggest that the interaction between these two players may be synergistic in terms of impairing the humoral response to malarial antigens.

Children

Maternal antibodies against *Plasmodium* antigens transferred from the mother to the fetus are among the first antimalarial defenses available in the newborn. Interestingly, IgG levels to tetanus toxoid and to malarial antigens have been shown to be decreased in infants born to HIV-infected women [58,59] or women with placental malaria [58], showing the potential effect of each maternal infection on the transfer of antibodies to the newborn. These studies suggest that the mother's HIV status may have a greater impact on the infant's immunity than the HIV status of the infant.

There is a lack of studies comparing levels of antibodies between HIV-infected and -uninfected infants and children. One study showed that HIV-positive infants had similar levels of antibodies against *P. falciparum* antigens on the sporozoite and merozoite [59]. Another study showed that levels of IgG towards several malarial antigens in response to acute infection were similar in 37-month-old HIV-positive and -negative infants, except for antibodies to the merozoite protein AMA-1, which were found to be lower in the presence of HIV infection [56]. Unfortunately there is currently little data on how the levels of IgG to antigens in the surface of infected erythrocytes, which have been associated with severe disease, are being modulated by HIV either in maternal transfer or in infants. Also, HIV-negative children born to HIV-positive mothers may, as a baseline, have an altered immune status when compared with HIV-negative children born to HIV-negative mothers [64]. Antibody subtypes to specific antigens may be more important than the total levels of IgG to malarial antigens or the breadth of antigens that those antibodies recognize [65]. It should be emphasized that any study focusing on antimalarial immunity should control for both maternal malaria infection and maternal HIV status.

Adding to the complexity of the matter, levels of antimalarial antibodies do not always seem to correlate with protection, but instead may be a marker of exposure [59,66]. Several studies have shown that serology has the potential to provide estimates of malaria transmission intensity [67]. Serology is currently under evaluation as a tool to assess malaria endemicity and spatial variation in malaria exposure, the impact of control programs and to detect malaria foci following eradication activities. In particular, reverse catalytic models have been performed on age-specific antibody prevalences to estimate seroconversion rates [68], a measure related to the force of malaria infection that can inform of medium- and long-term trends in malaria transmission. Although serological markers are a promising tool, future studies will need to evaluate the impact that HIV infection may have on the rate of conversion to seropositive and the rate of reversion from seropositive to seronegative [69].

Pregnant women

HIV has an important impact on humoral immunity to *P. falciparum* antigens on the surface of infected erythrocytes that accumulate in the placenta through adhesion to chondroitin sulfate A [70]. It has been demonstrated that HIV-positive women possess less antibodies against placental-type parasites when compared with HIV-negative women [53,55], which may contribute to the increased number of parasites observed in the placentas of HIV-positive women and lead to a higher risk of poor pregnancy outcomes compared with HIV-negative women [23]. In women going through their first pregnancy (primigravid women), this impairment seems to occur during the antibody acquisition stage of the immune response to these new antigens [50] and may have a differential impact on the different antibody classes and subclasses, thus manipulating their resulting function [50,53,54]. HIV-positive primigravid women were also found to have antibodies that bound with less affinity to epitopes on placental-type antigens when compared with HIV-negative primigravid women [71]. As suggested by Rogerson *et al.* [72] and recently demonstrated [50,51], functional antibody assays may represent a better measure of these functional alterations. Despite this impairment of antibody responses to pregnancy-specific antigens, these are by no means the only malarial antigens that are affected in HIV-positive pregnant women. It has been shown that pregnant women have lower levels of antibodies to antigens present in merozoites [55] and on the surface of infected erythrocytes isolated from children [52], suggesting a broader impact of HIV on antibody-mediated immunity against malaria in pregnant women. Of importance, immunological studies conducted in the context of intermittent preventive treatment during pregnancy (IPTp) have shown that a reduction in exposure to malaria (through the protective effect

of IPTp) may have a greater effect on antimalarial antibody responses of HIV-positive women compared with HIV-negative women [73], possibly because maternal immunity is impaired by viral infection.

Malaria in pregnancy is associated with changes in levels of various cytokines. HIV infection reduces the production of IFN-γ by maternal immune cells stimulated *in vitro* with crude malarial antigens [74], thus potentially depriving the placenta of a cytokine associated with improved pregnancy outcomes [75]. IL-12 (an IFN-γ-regulating cytokine) is also reduced in HIV-positive pregnant women [76]. Moreover, the levels of these cytokines have been shown to be associated with the numbers of CD4 T-cell counts [74,76].

Monocyte/macrophage populations can change in HIV–malaria-coinfected pregnant women with an increase in percentage of $CD16^+$ macrophages carrying the virus [77]. HIV is also able to inhibit monocyte/macrophage functions [78,79], but it is not known how changes in these populations and their function may influence the outcome of placental malaria infection in HIV-positive pregnant women. It could be expected that HIV-positive women would have monocytes/macrophages with a diminished ability to clear parasites (both in the spleen and the placenta) as well as a reduced ability to present antigens and thus contribute to the slower acquisition of a humoral response against *P. falciparum*.

Malaria impact on HIV

Although it is now well demonstrated that interactions between malaria and HIV are bidirectional, there are considerably less data on the effects of malaria on HIV pathogenesis, transmission and immunity than on the effects of HIV on malaria pathogenesis and immunity. Epidemiological data points to a clear impact of malaria on general morbidity in HIV-positive patients. Furthermore, evidence suggests an effect of *P. falciparum* infection on HIV MTCT, although current epidemiological data remain inconclusive. In addition, biochemical evidence suggests that malaria, particularly *P. falciparum*, leads to changes in the dynamics of HIV replication as well as to imbalances in cytokines and chemokines.

HIV disease progression

HIV RNA viral load and peripheral CD4 T-cell counts are hallmarks of diagnosis and monitoring of HIV-infected adults as well as key for determining risks of MTCT of HIV. Although no direct evidence has associated *P. falciparum* infection with HIV disease progression, both HIV RNA viral load and CD4 T-cell counts have been shown to be affected by *P. falciparum* infection in adults [16,18,80,81]. A prospective study in Malawi demonstrated that acute *P. falciparum* episodes increased HIV RNA viral load by 0.25 log which subsided within 8–9 weeks after malaria treatment [16,82]. This confirmed an earlier cross-sectional study showing a sevenfold increase in HIV RNA viral load during a parasitemic *P. falciparum* episode (reviewed in [83]). Furthermore, a study in HIV-infected pregnant women in Malawi showed that placental malaria was associated with a twofold increase in placental HIV RNA [18].

Recent reports have shown a positive association between parasitemia and viral load among HIV-infected pregnant women [84], although no association was found between parasitemia and progression to HIV disease or AIDS-related death. However, mortality was higher among women with lower levels of immunosuppression, suggesting that malaria may be especially detrimental in individuals with higher CD4 T-cell counts, as already suggested by Kublin *et al.* [16]. The authors proposed that this was a function of relatively more T cells available for HIV viral replication after cytokine stimulation by malaria parasites among individuals with higher CD4 T-cell counts.

P. falciparum infection has been hypothesized to lead to increased HIV infectivity. Indeed, *in vitro* stimulation of peripheral blood mononuclear cells from HIV-infected individuals with *P. falciparum* antigen leads to reactivation, replication and release of HIV virions [85]. *P. falciparum* antigens increase TNF-α production [86], potentially causing a boost in cell capacity to replicate HIV. *P. falciparum* antigens also upregulate CCR5, a coreceptor essential for HIV entry into target cells [87], which could increase permissivity of cells to infection. Hemozoin, a parasite by-product of digested hemoglobin, is responsible for much of the increase in TNF-α and CCR5 expression, and could thus potentially increase the transmission of HIV from monocyte-derived dendritic cells to CD4 T cells, although this remains to be confirmed *in vivo* [88]. HIV replication is increased in activated T cells and monocytes, and a recent study showed that fetal cord blood cells activated by malaria exposure are more susceptible to HIV replication [89]. Finally, HIV replicates both in CD4 T cells and macrophages but the proportion of replication attributable to macrophages is very low (<2%). It has been shown that *P. falciparum* activation of $CD14^+$ macrophages increases the percentage of macrophages producing HIV as well as increasing HIV replication in CD4 T cells [90].

Another point of interaction between malaria and HIV pathogenesis is that *P. falciparum* infection has been shown to decrease CD4 T-cell counts. CD4 T-cell counts below 200 cells/μl in an HIV-infected individual are an AIDS-defining criterion. In a Zambian study it was observed that the malaria-induced decrease in absolute CD4 T-cell counts is reversed by antimalarial treatment in both HIV-positive and HIV-negative adults with uncomplicated malaria [91]. The decrease in CD4 T-cell counts was observed both for clinical and asymptomatic *P. falciparum* infection [92]. However, in HIV-infected patients with low CD4 T-cell counts, malaria treatment led to a more modest recuperation in CD4 T-cell counts. A small study in Uganda also suggested that repeated *P. falciparum* episodes were associated with a more rapid decline of CD4 T-cell counts [93]. The authors found that the mean CD4 T-cell decline was greater with increasing number of malaria episodes across all baseline CD4 levels. This study suggested that repeated malaria episodes in HIV-infected individuals could decrease CD4 T-cell counts by an additional >40 counts/μl/year as compared with HIV-infected adults with no malaria episodes.

Anemia is the most frequent hematologic abnormality of HIV disease [94,95] and is thought to be strongly associated with mortality in HIV-infected adults and children, regardless of its

etiology [96]. Furthermore, anemia in HIV-positive individuals has been associated with increased risk of progression to AIDS and death independent of CD4 T-cell counts or WHO clinical stage of disease [97]. *P. falciparum* is also associated with anemia. Anemia caused by HIV and by *P. falciparum* infection is thought to have at least an additive effect if not act in synergy. Indeed, a clinical malaria episode in HIV-infected individuals leads to a lower mean hemoglobin level than in HIV-uninfected patients [57,98]. This is compounded by a slower hematological recovery in HIV-infected adults as compared with HIV-negative adults following a malaria episode and successful parasite clearance [99]. Thus, frequent malaria episodes, in addition to contributing to increases in HIV RNA viral loads and decreases in CD4 T-cell counts, may also progressively worsen anemia and thus accelerate immunosuppression.

Since repeated episodes of malaria are very common in many malaria-endemic areas of the world, frequent infections by *P. falciparum* could lead to repeated increases in viral load and decreases in CD4 T-cell counts which would allow for few intervals of recovery. This, coupled with the overall higher burden of opportunistic infections in sub-Saharan African countries, could be associated with slightly shorter untreated median survival times in HIV-positive adults from Africa, although this still remains to be confirmed [100]. Additional studies assessing *P. falciparum* and HIV disease progression through malaria prevention clinical trials in HIV-infected individuals would be necessary to confirm the full interaction between these two diseases.

P. falciparum & MTCT of HIV

Vertical transmission of HIV occurs at an approximate rate of 25–40% in nonantiretroviral-treated breastfeeding populations [101]. Maternal RNA viral load and low CD4 T-cell count (reviewed in [102]) as well as malnutrition [103] and anemia [104] have been described as independent risk factors for MTCT. In addition to these risk factors, common infections in sub-Saharan Africa such as syphilis [105] or helminth infections [106] have also been suggested to increase MTCT. The impact of *P. falciparum* on HIV MTCT is unclear, particularly because interactions between HIV and malaria operate in both directions (reviewed in [23]). Since maternal HIV RNA viral load is a recognized risk factor for MTCT, a malaria-induced increase in HIV replication may increase the risk of MTCT [107]. Fetal cells exposed to malaria may also be in a heightened state of activation and thus be more permissive to HIV replication [89]. Independent of HIV viral load, imbalances in inflammatory cytokines triggered by malaria infection of the placenta have also been suggested to impact MTCT. Placental malaria in immunosuppressed HIV-infected women leads to decreased production of IFN-γ, a cytokine important in the antimalarial response, increased TNF-α expression and increased CCR5 expression. On the other hand, placental malaria in immunocompetent HIV-infected women show an accompanying increased production of chemokines important for inhibition of HIV entry (MIP1α, RANTES; reviewed in [108]).

Nevertheless, epidemiological studies assessing the impact of placental malaria on MTCT have been inconsistent. Several studies have suggested that placental malaria leads to an increase MTCT of HIV. An initial study in Uganda reported an association of placental malaria with increased peripartum HIV transmission. A study in Kenya suggested that higher parasitemia levels (>10,000 parasites/ml) were associated with higher MTCT whereas lower-density parasitemia was associated with decreased risk of MTCT [109–112]. By contrast, other studies have suggested that there is no association between placental malaria and MTCT [112,113]. A nested case–control study of placental malaria conducted in rural Rwanda in the early 1990s and recently published shows an association between placental malaria and early infant HIV infection, before antiretroviral therapy or prophylaxis [114]. The impact of placental malaria on MTCT may depend on a balance of cytokines favoring HIV replication and entry (TNF-α, CCR5) and those inhibiting HIV entry (MIP-1α, RANTES).

Impact of *P. falciparum* on heterosexual HIV transmission

As much as HIV RNA level is associated with increased HIV MTCT, there is an association between increasing plasma HIV RNA levels and heterosexual transmission of HIV [115–117]. Studies in discordant couples have indeed shown that each log increase in HIV viral load is associated with a rate ratio of 2.45 for heterosexual HIV transmission [116]. Furthermore, studies in both Uganda and Quebec (Canada) have suggested that 50% of onward transmission of HIV occurs during acute HIV infection and during the first 6 months of infection, where HIV RNA levels are up to 2 logs higher than during the chronic phase [115,117,118]. As discussed previously, an individual episode of *P. falciparum* infection has been shown to increase HIV RNA levels both *in vivo* and *in vitro*. Furthermore, adults living in high-malaria-endemic areas are exposed to repeated episodes of malaria and may also harbor malaria parasites asymptomatically. As a consequence, these individuals may sustain higher HIV RNA loads than those individuals living in low-malaria-transmission areas. A study using mathematical modeling sought to characterize the interaction of multiple *P. falciparum* episodes, transient increases in HIV RNA and HIV transmission. This modeling was performed in an approximate population of 200,000 individuals in Kisumu (Kenya) living in a malaria-endemic region. The results showed that repeated malaria infection could account for an excess of 8500 HIV infections between 1980 and 2005 [7]. The mathematical model paved the way for a recent study showing an epidemiological association between *P. falciparum* infection and heterosexual HIV transmission in countries with a high prevalence of HIV infection. These investigators combined demographic and health surveys using geographical information systems in regions of Kenya, Malawi and Tanzania. They found that those individuals living in an area with high intensities of *P. falciparum* transmission had a twofold higher probability of being infected with HIV as compared with individuals living in an area with low malaria transmission [10]. After controlling

for multiple socioeconomic factors, they observed that malaria could account for up to 27% of new HIV infections in an area with high HIV prevalence and malaria transmission intensity. However, the association between *P. falciparum* and heterosexual HIV transmission was not found in western Africa, where HIV prevalence is approximately 1.5% [119]. Thus, the contribution of *P. falciparum* infection to HIV transmission may vary according to HIV prevalence and stage of the HIV epidemic.

Treatment & prevention: potential drug interactions

The concomitant treatment or prevention of malaria and HIV infection may be challenging owing to the potential for drug interactions [22]. In addition, the increased and improved access to antiretroviral (ARV) therapy in most sub-Saharan countries, together with the scale-up of new combination of antimalarials in the same region, raises further concerns since limited data exist on pharmacokinetic interactions between the two drug groups [34,120].

Malaria prevention programs for persons infected with HIV have not been well defined in areas both endemic for *P. falciparum* and harboring high HIV incidence. In some areas of southern Africa, the proportion of the population with HIV seropositivity reaches up to 30–40% [121] [Gonzalez R *et al.*, Unpublished Data], and an additional 3% may be in early acute phases of infection when HIV-specific antibodies are undetectable [122].

Antiretrovirals

The main three classes of ARV drugs are HIV nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). In malaria-endemic countries, the first-line ARV treatment includes two NRTIs such as zidovudine (AZT) and lamivudine (3TC), and one NNRTI, namely nevirapine (NVP) or efavirenz (EFV), rather than protease inhibitors drugs [123]. The NNRTIs and the PIs are metabolized by the same cytochrome P450 isoenzyme family as many antimalarial drugs [6,22,124].

The PIs also inhibit *P. falciparum* growth [125,126] and impair the CD36-mediated cytoadherence of infected erythrocytes as well as prevent their clearance by nonopsonic phagocytosis [127]. Hobbs *et al.* have also recently proved that lopinavir and saquinavir inhibit the pre-erythrocytic stage of parasite development in the rodent model [128]. In addition, *in vitro* data show a synergistic effect of the PI with some antimalarials such as chloroquine and mefloquine (MQ), and controversial information exist on their potential interaction with artemisinin derivatives [129–132]. The clinical relevance of the antimalarial effect of the PI still needs to be established [34], whereas NNRTIs have been shown to decrease the prevalence of clinical malaria when combined to cotrimoxazole (CTX; trimethoprim–sulfamethoxazole) in a study conducted in Uganda [81].

Antimalarials

The current recommended drugs for treatment of *P. falciparum* uncomplicated malaria include artemisinin-based combination therapies (ACTs) [133]. Artemether–lumefantrine, artesunate (AS) plus amodiaquine, AS plus MQ, AS plus sulfadoxine-pyrimethamine (SP) and dihydroartemisin plus piperaquine are the recommended ACTs used in malaria-endemic countries. Artemisinin monotherapy is not recommended and the choice of the ACT in a country is based on the level of resistance of the partner medicine in the combination. Severe *P. falcipaum* malaria constitutes a medical emergency and parenteral AS is the recommended treatment by the WHO.

Some antimalarials have proven antiretroviral activity, such as chloroquine, MQ and primaquine (reviewed in [134]) but no sound population-based studies have been conducted so far to evaluate how this translates into clinical outcomes and/or to better immunity status (both cellular and humoral) in HIV-infected individuals.

German *et al.* reported two cases of hepatotoxicity due to a drug interaction between EFV and AQ plus AS [135]. The risk of neutropenia was also higher in HIV-infected children treated with AS-AQ, especially in the context of concurrent antiretroviral use [136]. AQ was thus contraindicated in patients receiving EFV (reviewed in [34]).

MQ, lumefantrine and artemisinin derivatives are CYP3A4 substrates; therefore, serum concentrations are expected to increase with coadministration of some PIs, although nonconclusive data exist [124]. Halofantrine is contraindicated in patients receiving PI [34].

Past publications have analyzed in detail the potential drug interactions of the different ARVs and currently used antimalarial drugs [22,134]. However, further pharmacokinetic and clinical data are needed to guide dosing recommendations when antimalarial drugs are coadministered with ARVs.

Other drugs

CTX daily prophylaxis is recommended in HIV-infected patients to prevent opportunistic infections when CD4 T-cell count drop below 200 cells/µl [137] and in pregnant women with any level of CD4 T-cell counts. CTX also has proven antimalarial effects [34] reducing the incidence of parasitemia and clinical malaria [81,138], but the immunological mechanisms (if any) behind this are still obscure. Besides its beneficial clinical effect, the widespread use of CTX could accelerate the development of resistance to antifolate drugs such as SP [6]. However, a study conducted in Kenya showed that daily CTX prevented malaria and reduced incidence of antifolate-resistant *P. falciparum* while increasing pneumococcus and commensal *Escherichia coli* resistance [139]. A recent systematic review on this subject concluded that evidence exists that CTX prophylaxis protects against resistance to other antibiotics but that more carefully designed studies are needed to answer the question conclusively [140].

Antimalarial treatment failure

Few studies have examined the effect of HIV infection on the response to antimalarial treatment (reviewed in [72]). In Uganda, the risk of clinical treatment failure after antimalarial treatment was higher for HIV-infected adults than for HIV-uninfected adults [141]. However, molecular genotyping revealed

that clinical treatment failures were due to new infections rather than recrudescences. The increased risk of re-infection after successful treatment may be a result of HIV-mediated weakening of immune responses to liver-stage parasites or an increased risk of being bitten by *Anopheles* mosquitoes in those with HIV-related febrile illnesses [24]. Consistent with the study conducted in Uganda [141], decreased CD4 T-cell counts in the Malawian population were not associated with impaired response to antimalarial therapy or diminished ability to clear SP-resistant parasites [142], suggesting that the capacity to resolve malaria infection with SP-resistant parasites after treatment with SP was not impaired by advanced HIV-associated immunosuppression. However, other studies have shown that the risk of genotypically confirmed recrudescent parasitemia 45 days after SP or artemether–lumefantrine was higher in Zambian HIV-infected patients with a CD4 T-cell count <300 cells/µl compared with those with a CD4 T-cell count ≥300 cells/µl [91]. Similarly, the risk of treatment failure after treatment with SP was higher in Kenyan HIV-infected adults with CD4 T-cell counts <200 cells/µl compared with HIV-uninfected adults, but only in the presence of anemia [98].

There are currently no data on how HIV may affect response to treatment of clinical malaria in pregnancy. Previous studies showed that HIV-infected women had higher rates of persistent and breakthrough parasitemia, as well as peripheral and placental parasitema at delivery, indicating a poorer response to prophylaxis [13]. A randomized trial from Malawi showed the superiority of more frequent doses of IPTp to reduce the risk of placental malaria in women with HIV infection [143]. Moreover, prevalence of parasites with molecular markers of SP resistance after IPTp with SP were higher among HIV-positive women than in HIV-negative women [144], suggesting that HIV-infected women with impaired antimalarial immunity clear resistant parasites less effectively.

It has been suggested that the HIV epidemic may increase the emergence and spread of antimalarial drug resistance. By increasing the malaria parasite biomass, HIV may also increase the *de novo* generation of mutations involved in antimalarial drug resistance [145]. Inadequate parasite clearance in immune-compromised HIV-infected patients may result in a delayed response to treatment, increased recrudescence with shortening of the average period between clinical attacks and further spread of resistant strains. Moreover, HIV infection may accelerate progression of malaria infections to symptomatic illness, increasing the probability of treatment and contact between the parasite and the drug. In addition, immune-suppressed HIV-infected adults suffer frequently from non-malaria-attributable acute fevers that may be misdiagnosed as malaria and treated as such [146], increasing antimalarial drug pressure. If these speculations are confirmed, a higher prevalence of resistant parasites could be expected in areas where HIV infection is highly prevalent.

Malaria prevention in HIV-infected pregnant women

Prevention of malaria in HIV-infected pregnant women is a priority given their increased susceptibility [147]. Control of malaria in pregnancy in areas of stable transmission currently rely on: the use of insecticide-treated nets; IPTp with at least two treatment doses of SP; and effective and prompt case management of malaria illness [148]. It has been shown that more doses of antimalarial IPT are required for effective prevention in HIV-infected women [143]. However, SP is not recommended in women receiving daily CTX because of the potential for drug interactions. Consequently, malaria prevention strategies specifically designed for HIV-infected pregnant women still need to be evaluated and improved since it is unclear whether CTX prophylaxis would be effective enough in preventing the harmful effects of malaria in pregnant women.

Expert commentary

Despite the extended literature and reviews of the last decades about HIV–malaria interactions, there is still an urgent need for more basic and clinical research in this area. Current research is highly skewed to the effect of HIV on malaria infection, whereas the effect of *Plasmodium* infection on HIV seems to have received much less attention. Moreover, most of the evidence comes from studies conducted in sub-Saharan Africa where the two diseases have the highest burden. Further research should be conducted in different malaria transmission settings to assess the HIV interaction with other *Plasmodium* species.

Although there is a growing body of clinical research in some groups at particular risk, especially in pregnant women, further studies in other populations, such as adults with naturally acquired immunity against malaria, are needed. Also, the consequences of HIV infection during pregnancy on maternal mortality need to be addressed. Importantly, the effect of HIV on *Plasmodium* submicroscopic infections needs to be determined [149]. Additional studies should focus on unravelling the effect of HIV on treatment response to develop evidence-based recommendations for HIV-infected individuals from malaria-endemic areas, especially in children receiving ACTs. Also, antimalarial efficacy when combined with ARV treatment needs to be assessed, as well as the consequences of HIV infection on the emergence and spread of antimalarial resistance and IPTp efficacy.

Studies need to be conducted to clarify the impact of *Plasmodium* infection on HIV disease progression in both pregnant and nonpregnant individuals and children, in areas of different malaria endemicity, maturity of the HIV epidemic and HIV subtype. Studies are necessary to assess the impact of repeated *Plasmodium* infections on HIV immune escape which could accelerate disease progression. More and better designed studies looking at the impact of *Plasmodium* infections on HIV viral load, in the presence and absence of ARV treatment, are also needed. Of some concern is the issue of how much *Plasmodium* might impact heterosexual HIV transmission. A recent study suggests that HIV transmission in areas with low HIV prevalence such as western sub-Saharan Africa may not be affected by *Plasmodium* infections [119]. The models suggest an increase but this may depend on transmission intensity of *Plasmodium*, HIV prevalence, stage of the HIV epidemic and its distribution in the population.

Detailed understanding of the immune mechanisms during HIV and malaria coinfection is highly relevant for the development of new preventive and therapeutic interventions. Identification of correlates of protection is one of the priority areas, as well as the description of the antimalarial immune responses that are affected by HIV infection (Ig class and function, as well as the target antigens) and that are important for prevention of disease. As a consequence of reductions in antimalarial immunity, HIV-positive individuals may constitute an especially vulnerable group to parasite variants that have a selective advantage in naive hosts and are associated with severe disease [150]. It is crucial to understand how immunological memory to malaria is developed and how HIV can interfere with memory responses in naturally exposed populations. Importantly, the ability to maintain antibody responses against *P. falciparum* may also be suppressed by HIV infection, compromising the utility of serological marker tools as indicators of exposure to malaria in those populations where HIV infection reaches high prevalence [69]. Finally, the impact of ARV treatment on the acquisition and maintenance of immunity against malaria needs to be evaluated. Studies measuring the activity of monocytes/macrophages towards opsonized and unopsonized *Plasmodium* parasites in HIV patients under different ARV regimens also need to be conducted, thus linking a predicted function index with a real functional assessment.

From the latest data released by the WHO [2], as well as from the UNAIDS [1], it seems evident that both the number of malaria-related deaths and malaria cases, as well as the incidence of HIV infection, are decreasing in sub-Saharan Africa. It is uncertain how the decline of these two infections (together with the results of the RTS,S/AS01 vaccine trials [151]) is going to be received by the public health and political authorities. A decline in the levels of awareness and funding is a risk and may result in strong resurgences of both infections in the long haul. It is important to continue to educate populations, the relevant authorities as well as funding bodies regarding the dangers of these two infections so that a continued and sustained decrease is maintained.

Five-year view

There are some clinical trials currently ongoing specifically designed to explore some of the aforementioned gaps in knowledge such as monitoring of resistance to sulfa-drugs when CTX is used [201], evaluation of the efficacy of CTX to prevent malaria in HIV-positive women [202–204], pharmacokinetics of ARVs and antimalarials when coadmininistered [205,206], and evaluation of antimalarials for IPTp in HIV-infected pregnant women [207]. The field will probably also start looking with more emphasis into the interactions with *Plasmodium vivax*, especially in the context of future activities leading to malaria elimination and eradication [152]. Studies will continue to elucidate the impact of *P. falciparum* both on HIV MTCT and on heterosexual transmission. We also need robust data about the effect of HIV infection in pregnancy on maternal and infant mortality, an issue poorly examined that will become more relevant with increasing access to and duration of ARVs for prevention of HIV transmission from mother to children. Research focusing on the impact of *P. falciparum* on HIV disease progression and death will require longitudinal studies to develop guidelines for malaria prevention in HIV-infected individuals, but will be difficult to conduct owing to current reductions in malaria transmission observed in many African countries [2]. Of special relevance in the context of current declines in malaria transmission, it will be critical to understand the impact of HIV on immunological memory against malaria, as HIV infection may accelerate the waning of immunity and predispose HIV-positive individuals to severe malaria in situations of resurgences of malaria transmission.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- HIV infection increases prevalence of malaria in children, adults and pregnant women.
- Specific guidelines for the treatment of malaria in HIV-infected people on antiretrovirals need to be developed.
- *Plasmodium falciparum* infection leads to decrease in CD4 T-cell counts and an increase in HIV viral load but the consequences on HIV disease progression are unknown.
- *P. falciparum* may increase HIV transmission in communities with endemic HIV (high HIV prevalence) and have no effect in areas with a concentrated HIV epidemic (low HIV prevalence).
- Future studies are needed to identify specific correlates of protection against malaria and how HIV infection can affect specific antimalarial immune responses.
- Declines in malaria transmission may change the paradigm in the conception of studies addressing key issues of the coinfection of malaria and HIV.
- Further studies are needed to evaluate whether the HIV epidemic can pose challenges to the success of malaria elimination campaigns in different malaria transmission and HIV prevalence settings.

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