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The effect of HIV on malaria in the context of the current standard of care for HIV-infected populations in Africa

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Abstract

HIV infection affects the clinical pattern of malaria. There is emerging evidence to suggest that previously documented interactions may be modified by recently scaled-up HIV and malaria interventions. Prophylaxis with trimethoprim–sulfamethoxazole (TS) in combination with use of insecticide-treated nets can markedly decrease the incidence of malaria in HIV-infected pregnant and nonpregnant adults and children even in the setting of antifolate resistance-conferring mutations that are currently common in Africa. Nonetheless, additional interventions are needed to protect HIV-infected people that reside in high-malaria-transmission areas. Artemether–lumefantrine and dihydroartemisinin–piperaquine are highly efficacious and safe for the treatment of uncomplicated malaria in HIV-infected persons. Coadministration of antiretroviral and antimalarial drugs creates the potential for pharmacokinetic drug interactions that may increase (causing enhancement of malaria treatment efficacy and post-treatment prophylaxis and/or unanticipated toxicity) or reduce (creating risk for treatment failure) antimalarial drug exposure. Further studies are needed to elucidate potentially important pharmacokinetic interactions between commonly used antimalarials, antiretrovirals and TS and their clinical implications. Data on the benefits of long-term TS prophylaxis among HIV patients on antiretroviral therapy who have achieved immune-reconstitution are limited. Studies to address these questions are ongoing or planned, and the results should provide the evidence base required to guide the prevention and treatment of malaria in HIV-infected patients.

Keywords

antimalarial treatment; antiretroviral therapy; HIV infection; malaria; malaria prevention

Introduction & rationale

Several studies conducted over the last two decades have advanced our understanding of the effects of HIV infection on the natural history of malaria. HIV immune suppression raises the risk of parasitemia and clinical malaria in nonpregnant adults [1–4], and this risk increases with increasing immunosuppression [1,2,4,5]. Numerous studies have

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demonstrated higher risks of parasitemia and placental malaria in HIV-infected pregnant women of all gravidities compared with HIV-uninfected women [6–8]. Dual infection with HIV and malaria is associated with poor pregnancy outcomes [9–11], and intermittent preventive therapy (IPTp) with two doses of sulfadoxine–pyrimethamine (SP; which is routinely given to pregnant women in Africa) may be less effective in preventing malaria in HIV-infected compared with HIV-uninfected women [12]. HIV infection has also been found to increase the risk of severe malaria and death in areas where malaria transmission is low or unstable [13–16]. Lastly, response to antimalarial therapy may be reduced in severely immunosuppressed patients receiving certain antimalarial drug regimens [17,18]. There is emerging evidence to suggest that previously documented interactions may be modified by recently scaled-up HIV and malaria interventions. In this review, we highlight the effect of HIV infection on malaria morbidity in the context of the current standard of care for HIV-infected populations, including wide availability of insecticide-treated nets (ITNs), trimethoprim–sulfamethoxazole (TS) prophylaxis, IPTp with SP or TS in pregnant women, and the wide availability of artemisinin-based combination therapies (ACTs) to treat malaria and antiretrovirals to treat HIV infection. We also review the impact of therapies for each infection upon the other. While malaria influences HIV infection, this article is not intended to address this interaction aspect.

ITNs for prevention of malaria in HIV-infected individuals

The use of ITNs is considered one of the most effective prevention measures for malaria. Randomized controlled trials demonstrated that the use of ITNs at the community level was associated with a 50% reduction in the incidence of malaria and a 16% reduction in all-cause mortality in children under 5 years of age, even in areas of high HIV prevalence [19–21]. In Ugandan HIV-infected and -uninfected children, ITN use alone was associated with a 43% reduction in the incidence of malaria [22]. Use of ITNs in malaria-endemic regions is one of the basic care and prevention interventions for individuals with HIV/AIDS, and HIV-infected patients are prioritized in bed net distribution campaigns. While their efficacy has not been compared between HIV-infected patients and HIV-uninfected individuals, the widespread use of ITNs is expected to reduce malaria risk in HIV-infected populations, although the magnitude of protection may be compromised by inconsistent use and the emergence of resistance to insecticides [23,24].

TS prophylaxis against malaria in nonpregnant adults & children

Although TS was initially studied as a method of preventing common opportunistic infections in HIV-infected patients as described below, it is now clear that daily TS is also highly effective for the prevention of malaria. As a result, HIV-infected patients using this intervention are at a much lower risk of malaria compared with their HIV-uninfected counterparts not receiving chemoprophylaxis [22]. In a study from rural Uganda, malaria incidence was approximately fivefold lower in children and adults taking TS prophylaxis compared with controls [25]. Our group has reported similar protective efficacy against malaria of TS among HIV-infected children living in an urban area in Uganda [22], and continued TS prophylaxis among HIV-exposed but uninfected children until 4 years of age compared with 2 years of age was associated with a 53% reduction in malaria incidence in rural areas of high malaria transmission intensity [26]. Additional evidence of the protective efficacy of TS against malaria has been provided by trials in HIV-uninfected individuals. A randomized trial in Mali of children aged 5–15 years showed that daily TS prophylaxis had a 99.5% protective efficacy against episodes of clinical malaria and a 97% efficacy against infection [27]. Additional health benefits of TS in HIV-infected individuals have been demonstrated. TS was associated with a 33% reduction in mortality in HIV-infected Ugandan children [25,28]. Antiretroviral therapy (ART)-naive HIV-infected Zambian

children randomized to receive TS had slower decreases in weight-for-age and height-for-age, and greater increase in hemoglobin level compared with those not receiving TS [29]. These observations and other benefits of TS prophylaxis support its continued and expanded use in these populations. Moreover, African studies show that the treatment is very well tolerated [25,30,31] despite the potential for TS to cause side effects such as rash and blood disorders.

The impact of multiple interventions provided as part of HIV care on the incidence of malaria has been evaluated in a few studies. Considering multiple sequential interventions in HIV-infected adults in a high malaria transmission area in eastern Uganda, malaria incidence decreased from 50.8 episodes per 100 person-years at baseline to 9.0 with daily TS, 3.5 with TS and ART, and 2.1 with TS, ART and ITNs [32]. Overall, the provision of TS, ART and ITNs was associated with a 95% reduction in the frequency of malaria in this population [32]. In a study of HIV-infected Ugandan children, use of both TS and ITNs was associated with a 97% reduction in malaria incidence compared with a population of HIV-uninfected children from the same area [22]. In this urban area of relatively low malaria transmission, malaria accounted for only 4% of febrile episodes in the HIV-infected cohort, compared with 33% in the HIV-uninfected cohort that was not receiving TS or ITNs [22]. Overall, available findings strongly support the promotion of combination prevention interventions to achieve significant reductions in malaria incidence in at-risk populations. In addition, these findings highlight the need for confirmatory diagnosis of malaria in those receiving interventions that markedly decrease malaria incidence, with provision of malaria therapy only when the diagnosis is confirmed.

Many studies demonstrating the benefits of daily TS were performed in areas, such as Uganda, with high prevalence of parasite polymorphisms (five common mutations in the *Plasmodium falciparum dhfr* and *dhps* genes) that mediate an intermediate level of resistance to antifolate antimalarials, including TS [33]. These polymorphisms likely impact on the protective efficacy of TS, as supported by a much higher protective efficacy seen in Mali, an area with lower prevalence of antifolate resistance mutations seen elsewhere, compared with other areas [27]. In addition, there are concerns that the increasing prevalence of antifolate-resistant parasites, in part due to selection by frequent use of TS, may impact on the protective efficacy of TS. In this regard, a study in Uganda showed that TS prophylaxis was highly effective against malaria despite high prevalence of five antifolate resistance-mediating mutations, but that it was associated with the selection of an additional mutation (*dhfr* 164L) that leads to high-level resistance, and will likely prevent any benefits of TS [33]. In another Ugandan study with a different design, TS prophylaxis was not associated with increased prevalence of mutations associated with antifolate resistance [34]. In any event, it is likely that resistance to antifolates is limiting the efficacy of TS for the prevention of malaria, and new regimens with improved efficacy are greatly needed, especially for use in children and pregnant women. In summary, despite some concerns about increasing resistance selection, the efficacy of TS prophylaxis in reducing the incidence of malaria and preventing morbidity and mortality in HIV-infected patients is well established, even in the setting of antifolate resistance-conferring mutations that are currently common in Africa.

TS & SP prophylaxis during pregnancy

Malaria in pregnancy can lead to serious maternal and fetal morbidity and mortality; hence, access to effective preventive strategies is essential. For over a decade, the standard practice for prevention of malaria in pregnancy in countries with stable malaria transmission has been IPTp with two doses of SP given after quickening [101]. This practice has been shown to reduce the risk of peripheral parasitemia and placental malaria, low birth weight and

maternal anemia [35–37]. The efficacy of IPTp with SP in the prevention of placental malaria is reduced in HIV-infected women, but improved by monthly administration [12]. The consensus based on these studies was that in areas with intense transmission of *falciparum* malaria and a high prevalence of HIV infection, monthly SP IPTp should be adopted. However, the relative benefits of two-dose or monthly SP during pregnancy remain unclear. An alternative intervention for this population is TS. Daily TS prophylaxis is now the standard of care for HIV-infected individuals living in several settings in Africa. The protective efficacy of daily TS against malaria among pregnant women has not been established, and randomized controlled trials to evaluate this are no longer possible, as this is now the standard of care for all HIV-infected individuals. However, SP and TS are similar antifolates with similar antimalarial potencies, suggesting that daily TS will provide similar, if not better protection than does intermittent SP. Supporting this contention, in a cross-sectional study in Malawi, after adjusting for age, CD4 count, bed net use, number of antenatal visits and number of pregnancies, HIV-infected women who received TS or both TS and IPTp with SP were significantly less likely to have malaria parasitemia than those who received only IPTp with SP [38]. Daily TS was also associated with decreased prevalence of anemia. However, data on the adverse effects of TS prophylaxis during pregnancy on infant outcomes are limited. In a cross-sectional study in Uganda, HIV-infected women on daily TS had a similar prevalence of placental malaria as HIV-uninfected women on IPTp-SP [39]. Drawing from these findings, daily TS appears to offer at least as potent antimalarial protection as IPTp with SP, and the concurrent administration of the two agents is not warranted [40]. Consistent with this conclusion, the current WHO recommendation is that HIV-infected pregnant women in malaria endemic areas who are already receiving TS prophylaxis should not also receive IPTp-SP.

Is TS needed for those with antiretroviral immune reconstitution?

Clinical trials and observational studies of HIV-infected adults and children across Africa have shown that TS prophylaxis reduces mortality, morbidity and hospital admissions [25,28,30,31,41,42], even in areas of high background bacterial resistance. WHO guidelines recommend that TS prophylaxis be given to all symptomatic HIV-infected adults in resource-limited settings with CD4 counts lower than 350 cells per μl (WHO Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults 2006) [102]. However, many countries recommend that individuals on ART discontinue TS when CD4 counts rise above 200 cells/mm^3 because the primary goal has been seen as prevention of *Pneumocystis jirovecii* pneumonia [43,44]. However, in sub-Saharan Africa, where the incidence of malaria is high, continuing TS prophylaxis when CD4 counts rise above 200 cells/mm^3 may be beneficial. In one study among adult patients on ART with CD4 counts >200 cells/μl randomized to continue or discontinue TS, those discontinuing TS had a 32.5-fold increased risk of malaria compared with those who continued TS over a 4-month follow-up period [45]. In a large retrospective cohort study in Malawi, investigators reported a 41% reduction in mortality during the first 6 months after ART initiation in clinics providing TS prophylaxis compared with clinics not providing TS [46]. In the Development of Antiretroviral Therapies (DART) trial [47], TS prophylaxis after ART initiation in adults reduced mortality and the incidence of malaria for at least the 18 months over which data was gathered, providing strong motivation for provision of TS prophylaxis for at least 18 months after adults are started on combination ART in Africa. Whether TS may be discontinued after prolonged ART is unclear.

In summary, TS offers clear benefits for HIV-infected individuals, but data on the benefits of long-term TS prophylaxis among HIV patients on ART who have achieved immune-reconstitution are limited. Ongoing trials in Kenya and Uganda to determine whether TS

confers benefits in HIV-infected adults on ART who have evidence of immune recovery should offer guidance in this area.

ACTs in HIV-infected individuals

Malaria treatment outcomes are a concern in HIV-infected individuals, as impaired cell-mediated immunity caused by HIV may impact on the response to standard antimalarial treatment. ACTs are now widely recommended as first-line drugs for the treatment of uncomplicated malaria in nearly all African countries. However, data on the safety and efficacy of ACTs in HIV-infected populations are still limited. In a randomized controlled trial in Zambia of artemether–lumefantrine (AL) versus SP for the treatment of uncomplicated malaria in HIV-infected adults, the frequency of malaria treatment failure with either therapy increased significantly with advancing immunosuppression (Table 1) [17]. However, a study in Uganda using molecular genotyping showed that the increased risk of clinical treatment failure in HIV-infected individuals was a result of increased new infections rather than recrudescences, implying that the impact of HIV infection after treatment for malaria was an increased risk of recurrent infection rather than decreased drug efficacy [48]. In this study, the risk of clinical treatment failure due to new infection was over threefold higher for HIV-1-infected adults than for HIV-uninfected patients (Table 1). In a recent study in Uganda, both HIV-infected and -uninfected children responded well to treatment for uncomplicated malaria with artesunate/amodiaquine (AS/AQ), without an increased risk of recurrent malaria in the HIV-infected cohort (Table 1) [49]. In cohorts of HIV-infected Ugandan children given ITNs, TS prophylaxis and ART when indicated, three ACTs (AS/AQ, AL or dihydroartemisinin–piperaquine [DP] were all 100% efficacious after adjustment by genotyping (Table 1) [Gasasira AF, Unpublished Data]. However, AS/AQ was associated with a remarkably high risk of neutropenia in HIV-infected (45%), but not uninfected (6%) children, and was also poorly tolerated, with frequent malaise and anorexia compared with AL. DP was not directly compared with AS/AQ, but this regimen lowered the risk of recurrent parasitemia over 28 days compared with AL. In summary, AL and DP were highly efficacious and safe for the treatment of uncomplicated malaria in HIV-infected children. AS/AQ, though also highly efficacious, was poorly tolerated, with significant toxicity [49]. Thus, based on limited available data, malaria treatment policy in HIV-infected populations can follow standard recommendations, except that AQ regimens should be avoided in HIV-infected individuals if possible.

Interactions between antimalarial & antiretroviral drugs

The WHO recommends use of ACTs for treatment of uncomplicated malaria and intravenous AS in preference to quinine for severe malaria [101]. In regions with high prevalence of HIV and malaria, coinfected individuals will frequently receive concurrent therapy for malaria and HIV. Co-administration of ART and antimalarial drugs creates the potential for pharmacokinetic drug interactions due to induction or inhibition of cytochrome (CYP) enzymes or drug transporters [50]. These interactions may enhance antimalarial drug exposure, causing unanticipated toxicity, or reduce exposure, creating risk for treatment failure and selection of resistant parasites. Antimalarial therapy may also impact on ART pharmacokinetics; however, this is of less concern since antimalarial therapy is short in duration. Significant interactions are particularly likely to occur when antimalarial drugs are co-administered with non-nucleoside reverse transcriptase inhibitors or protease inhibitors (PIs), because these drugs are substrates, inducers and/or inhibitors of CYP enzymes involved in the metabolism of components of ACTs as well as quinine. Specifically, the non-nucleoside reverse transcriptase inhibitors (nevirapine and efavirenz) induce while PIs inhibit CYP enzymes. Of the PIs, ritonavir is the most potent CYP inhibitor [51].

There are limited clinical data on antimalarial–antiretroviral interactions and their effects. Co-administration of efavirenz and AS/AQ to healthy volunteers increased AQ exposure and decreased exposure to its metabolite desethylamodiaquine, with subsequent asymptomatic increase in transaminase levels several weeks after treatment discontinuation (Figure 1) [52]. During treatment of uncomplicated malaria in Uganda, AS/AQ was associated with a remarkably higher risk of neutropenia than in HIV-uninfected children, as noted above, and this effect was most marked in children receiving ART (Figure 1) [49]. Recent data have demonstrated significant interactions between AL and either nevirapine or lopinavir/ritonavir (LPV/r). In South African HIV-infected individuals, co-administration of AL with nevirapine resulted in reduced artemether and dihydroartemisinin exposure, with enhanced lumefantrine exposure (Figure 1) [53]. In healthy volunteers, co-administration of LPV/r with AL resulted in significantly increased lumefantrine exposure, decreased dihydroartemisinin exposure, and a trend towards decreased artemether exposure (Figure 1) [54]. Data from HIV-infected adults in Uganda showed a similar trend when a single dose of AL was co-administered with LPV/r. In this study, co-administration resulted in significant reduction in artemether exposure, with significant increase in lumefantrine exposure [55]. Similar findings of increased lumefantrine exposure due to the interaction between AL have been reported in HIV infected children in Uganda [56]. In addition to these pharmacokinetic interactions, protease inhibitors such as lopinavir remain of particular interest in malaria endemic areas as they have been shown to have direct antiparasitic activity against *P. falciparum* [57] as well as synergistic antimalarial effects when used concurrently with lumefantrine [58]. Interactions involving quinine and ART have been reported. In Nigeria, concurrent administration of nevirapine and quinine led to significant reduction in the plasma levels of quinine, with elevated plasma levels of the major metabolite 3-hydroxyquinine [59], while concurrent administration of quinine and ritonavir led to marked elevation in plasma levels of quinine with a decrease in levels of 3-hydroxyquinine (Figure 1) [60].

As mentioned above, antimalarial–antiretroviral drug interactions may have serious implications regarding treatment of HIV-malaria coinfected individuals and need urgent attention. Subtherapeutic drug concentrations pose a risk for treatment failure and development of resistance. This is of particular concern in HIV-infected individuals, because they have been shown to present with higher parasitemia [61], an independent risk for treatment failure [62]. Evidence for poor treatment outcome possibly resulting from the effects of drug interactions was presented in a case study in Nigeria, which demonstrated increasing parasitemia despite treatment with quinine in the presence of nevirapine, possibly due to decreased quinine exposure [63]. Adjustment of the antimalarial dose coupled with close monitoring for toxicity may be necessary when interactions resulting in reduced exposure are expected. On the other hand, interactions resulting in enhanced pharmacokinetic drug exposure may enhance malaria treatment efficacy and post-treatment prophylaxis (as was the case with LPV/r and AL), but may exacerbate unanticipated drug toxicity. There is, therefore, an urgent need to further evaluate interactions between ART and antimalarial drugs.

Conclusion

HIV infection affects the clinical pattern of malaria. However, the effect of HIV infection on malaria has been changing over the past few years. The wider implementation of ITNs, TS prophylaxis and ART might substantially reduce the morbidity of malaria in HIV-infected patients. Therefore, from a public health standpoint, HIV infection may no longer be considered a risk factor for malaria among those accessing care for HIV infection, and as such, individuals are now, paradoxically, protected from malaria due to their unique use of TS prophylaxis. The available data are strong, and support continued implementation of

these low-cost interventions to prevent malaria, including use of ITNs and TS prophylaxis for all HIV-infected individuals at significant risk of malaria in Africa. Available data also suggest that ACTs are generally effective in treating malaria in HIV-infected patients. Thus, malaria treatment policy in HIV-infected individuals can follow standard recommendations, except that AQ-containing regimens should be avoided in patients with HIV infection, especially those receiving ART, if possible. In addition, interactions between ARTs and antimalarials deserve attention. Interactions may enhance antimalarial activity, but also exacerbate toxicity. Adjustment of antimalarial dosing may be necessary to avoid toxicity, but adequate data to guide dosing adjustments are not yet available.

Implications for future research & future perspective

Recent studies have demonstrated that prophylactic TS in combination with ITNs can markedly decrease the incidence of malaria in HIV-infected pregnant and nonpregnant adults and children. However, in high-transmission regions, malaria remains common even with these two interventions. In our ongoing studies in Tororo in eastern Uganda, children <5 years of age get more than two episodes of malaria per person year of follow up [56], suggesting that additional measures for the prevention of malaria in HIV-infected children residing in high-malaria-transmission areas are needed. Other efficacious chemoprophylactic regimens such as monthly DP need further evaluation [64]. In addition, preliminary clinical studies have shown that HIV PIs protect against malaria. Should their efficacy be confirmed, this may change the balance towards using more PI-based regimens in resource-poor settings, especially in areas with high malaria transmission intensity. Thus, HIV PIs may offer a new opportunity to prevent malaria, and the choice of PI-based ART to treat HIV-infected people in high malaria incidence regions could be a strategic intervention in malaria control. However, the high cost of HIV PIs is a barrier to their widespread use in resource-limited settings.

Available data show that optimal modern antimalarial regimens are efficacious for the treatment of malaria in HIV-infected and uninfected populations. However, less efficacious antimalarial treatments are associated with increased treatment failure among HIV-infected individuals with low CD4 cell counts. It will be important to further assess whether HIV-related immunosuppression adversely impacts upon the efficacy of potent antimalarial drugs such as ACTs. Also, antimalarial drug combinations may lead to toxicity due to HIV-specific factors or drug interactions. Thus, research on the safety of malaria therapies in HIV-infected Africans and further studies to elucidate potentially important pharmacokinetic interactions between commonly used antimalarials, antiretrovirals and TS and their clinical implications are urgent priorities.

More research is needed to determine whether continuing TS prophylaxis may be beneficial even among HIV-infected individuals who have experienced immune recovery in response to ART, and whether there is any risk of increased rates of malaria if TS is discontinued after an extended period of use. The risk of selection of antifolate resistance with TS prophylaxis also needs further research. While it appears that the benefits of TS prophylaxis to malaria control outweigh any risks at this time, the finding of rare mutations, such as *dhps* 164L known to mediate high-level antifolate resistance, indicates the need for ongoing surveillance for these mutations and others that may emerge with continued TS use. Most importantly, more studies are needed to identify the clinical implications of the spread of these mutations on the efficacy of TS and SP, the antimalarials used for IPTp in pregnant HIV-infected (TS) and HIV-uninfected (SP) women.

Studies to address these questions are ongoing or planned and the results should provide an evidence base to guide the prevention and treatment of malaria in HIV-infected patients.

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Executive summary

Effect of HIV on malaria

- HIV disease increases the risk of parasitemia and clinical malaria in pregnant and nonpregnant adults and in children.
- There is emerging evidence to suggest that previously documented interactions may be modified by recently scaled-up HIV and malaria interventions.

Malaria prevention in HIV-infected populations

- HIV-infected patients are prioritized in bed net distribution campaigns, and the widespread use of insecticide-treated nets (ITNs) is expected to reduce malaria risk in these populations. However, the emergence of resistance to insecticides threatens the effectiveness of this intervention.
- Daily trimethoprim–sulfamethoxazole (TS) has led to significant reduction in malaria incidence in HIV-infected populations even in the setting of high population levels of antifolate resistance-conferring mutations.
- The use of ITNs and TS reduces malaria-associated morbidity, but among high-risk groups living in high malaria-transmission areas, the protection afforded by these interventions is far from complete.
- Daily TS may provide better protection against malaria among pregnant women than intermittent sulfadoxine–pyrimethamine does.
- A synergistic effect is seen with a combination of interventions; TS, ITNs and antiretroviral therapy (ART).
- Widespread TS use may lead to further selection and spread of antifolate-resistant malaria parasites, and higher-level antifolate resistance may subsequently diminish the protective efficacy of TS.
- TS prophylaxis after ART initiation in adults reduces mortality and the incidence of malaria for at least 18 months, but data on the benefits of long-term TS prophylaxis among HIV patients on ART who have achieved immune-reconstitution are limited.
- Lopinavir/ritonavir increases and extends lumefantrine exposure and thereby reduces rates of recurrent malaria after treatment with artemether–lumefantrine.

Artemisinin-based combination therapy & antimalarial–antiretroviral interactions in HIV-infected populations

- Presumptive therapy for malaria should be avoided in HIV-infected individuals on TS prophylaxis; rather, the malaria diagnosis should be confirmed before febrile patients are treated for malaria.
- Artemether–lumefantrine and dihydroartemisinin–piperaquine are generally effective and safe to treat malaria in HIV-infected individuals.
- Amodiaquine-containing combinations should be avoided in HIV-infected patients taking ART because of the high risk of neutropenia.
- Co-administration of antiretroviral and antimalarial drugs creates the potential for pharmacokinetic drug interactions that may increase antimalarial

drug exposure (causing enhancement of malaria treatment efficacy and post-treatment prophylaxis and/or unanticipated toxicity), or reduce exposure (leading to risk of treatment failure).

Conclusion & future perspective

- From a public health standpoint, HIV infection may no longer be considered a risk factor for malaria among those accessing care for HIV infection, as such, individuals are now, paradoxically, protected from malaria due to their unique use of TS prophylaxis.
- Urgent identification of additional measures for the prevention of malaria in HIV-infected children residing in high-malaria-transmission areas is needed.
- HIV protease inhibitors may offer a new opportunity to prevent malaria in HIV infection.
- Treatment for malaria in the HIV-infected population should follow current guidelines for the non-HIV-infected population, but amodiaquine-containing combinations should be avoided in HIV-infected patients.
- There is a need for further studies to monitor resistance of malaria parasites to both TS and sulfadoxine–pyrimethamine, and to assess the effect of resistance on protective efficacy.
- Ongoing surveillance and clinical studies are needed to evaluate the potential interactions and adverse events that may result from co-administration of therapies for malaria and HIV infection.
- Ongoing trials in Kenya and Uganda to determine whether TS confers benefits in HIV-infected adults on ART who have evidence of immune recovery should offer guidance in this area.

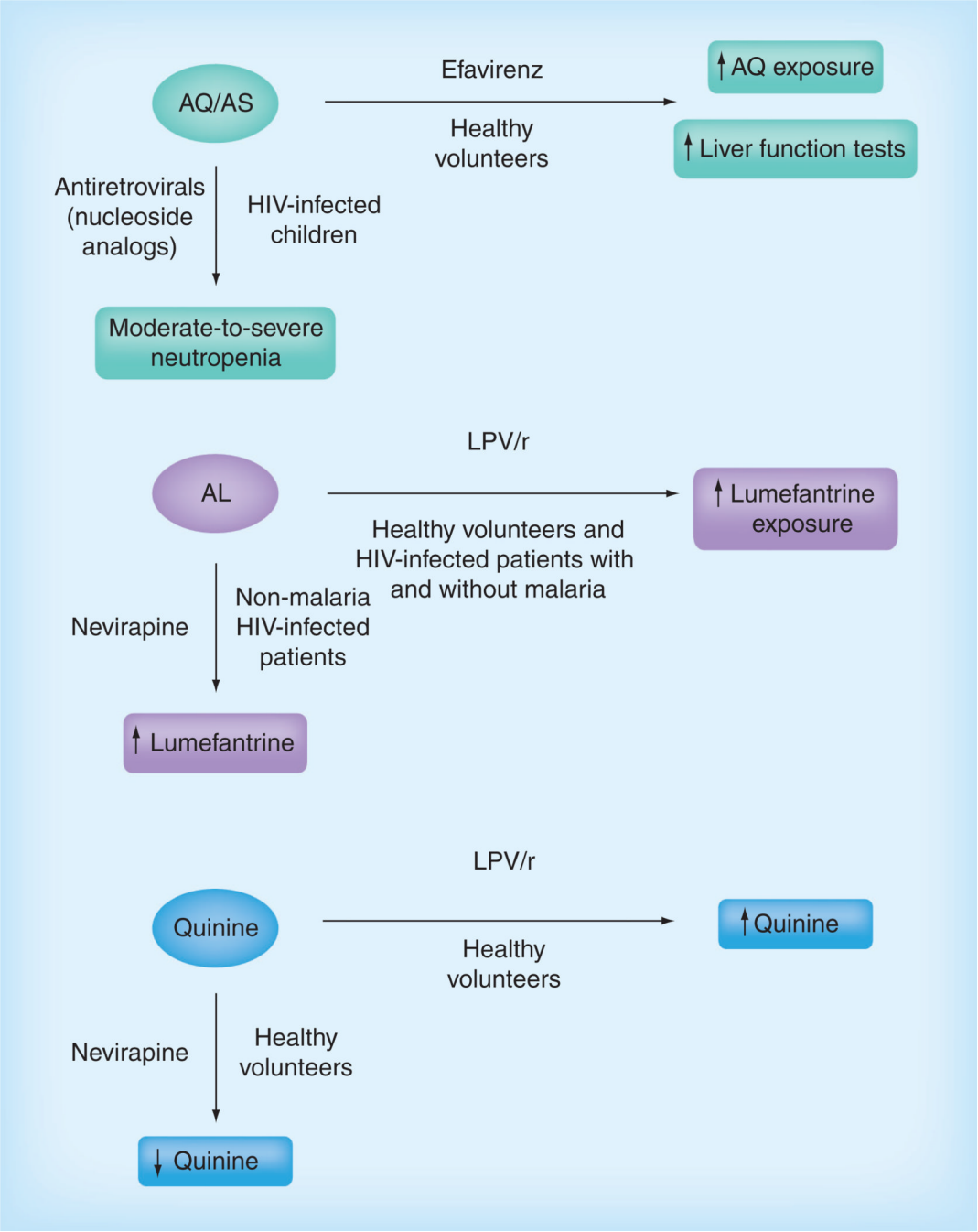

Figure 1. Summary of potential interactions between commonly used antimalarials and antiretroviral drugs

AL: Artemether–lumefantrine; AQ: Amodiaquine; AS: Artesunate; LPV/r: Lopinavir/ritonavir.

Table 1

Summary of studies reporting response to artemisinin-based combination therapy in HIV-infected individuals with uncomplicated malaria.

Study site (years)	Study population	Sample size	Drug regimens	Duration of follow-up (days)	Treatment outcome	Comments	Ref.
Uganda (2002–2004)	Adults and children	n = 1965 HIV^+ 95 HIV^- 1870	AQ + AS	28	Higher risk of treatment failure in HIV^+ adults (HR: 3.28; 95% CI: 1.25–8.59; p = 0.02)	No increased risk of treatment failure in HIV^+ children	[48]
Uganda (2005–2006)	Children	n = 160 HIV^+ 26 (on TS) HIV^- 134	AQ/AS	28	Proportion with adequate response HIV^+ 94% HIV^- 84%	AQ/AS equally efficacious in both cohorts	[49]
Zambia (2003–2005)	Adults	n = 971 HIV^+ 320 HIV^-651	SP + AL	45	Treatment failure HIV^+ 13.9% HIV^- 11.5%	Higher risk of recrudescence in HIV^+ patients with a CD4 cell count <300 cells/μl	[17]
Uganda (2007–2009)	Children	n = 55 205 episodes of malaria	AL versus DP	28	Both treatments were 100% efficacious in preventing recrudescent parasites	Higher risk of recurrent parasitemia due to new infection in AL (34%) compared with DP (7.1%)	[Gasasira AF, Unpublished Data]

AL: Artemether–lumefantrine; AQ: Amodiaquine; AS: Artesunate; DP: Dihydroartemisinin–piperaquine; HR: Hazard ratio; SP: Sulfadoxine–pyrimethamine; TS: Trimethoprim–sulfamethoxazole.