

Prophylaxis and treatment of malaria in HIV-infected populations

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Malaria and HIV infection are among the most important infectious diseases worldwide. Management of each infection may affect the other. Insecticide-impregnated bed nets and prophylaxis with trimethoprim-sulfamethoxazole have greatly reduced the incidence of malaria in HIV-infected individuals. Artemisinin-based combination therapies are highly effective malaria treatments, although recrudescence and new infections after therapy occur more commonly in HIV-infected than uninfected patients. These immune dysregulatory effects of HIV on malaria treatment outcomes may, however, be less important in children. Interactions of malaria and HIV therapies may lead to unanticipated risks of adverse events. Antiretroviral protease inhibitors demonstrate *in vitro* antimalarial activity. Further study is needed on the impacts of different therapies on the prevention of malaria, selection of resistance and toxicity.

Malaria and HIV infection are two of the most important infectious diseases worldwide, accounting for a combined 4 million deaths annually [1]. Several interactions between malaria and HIV infection have been established. In this review, we highlight the influence of HIV infection on malaria, and the implications for prevention and treatment of malaria in HIV-infected children and nonpregnant adults. First, having HIV infection could disrupt the acquired immune response to malaria and thereby may increase the incidence and severity of malaria [2]. A recent study using modeling methods calculated that in the Kisumu District, western Kenya, HIV infection may be responsible for 980,000 excess malaria episodes over the last 28 years [3]. Second, acute malaria elevates HIV viral load and so may increase the risk of HIV transmission [4]. Thus, malaria co-infection in HIV-infected individuals may be an important factor in promoting the spread of HIV in Africa. Third, HIV infection may be associated with reduced efficacy of antimalarial treatment, as detailed later in this review. Fourth, therapies for each infection may impact upon the other, leading to unanticipated effects on drug efficacy or toxicity [5]. Fifth, routine interventions for HIV may impact upon the incidence of malaria. As antiretroviral therapy (ART), trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis and new antimalarial treatments are being scaled-up in sub-Saharan Africa, it is useful to examine the tools we have to prevent malaria in HIV-infected populations and potential challenges for treatment of malaria-HIV co-infection.

Malaria prophylaxis in HIV-infected individuals

Proven effective malaria control interventions are currently available, including insecticide-treated bed nets (ITNs) for children and pregnant women, intermittent preventive therapy (IPT) in pregnancy, effective case management and indoor residual spraying in low transmission settings. Recent studies have demonstrated dramatic protection against malaria from daily TMP-SMX, an intervention developed for prevention of other infections in HIV-infected individuals.

Trimethoprim-sulfamethoxazole prophylaxis & effect on malaria risk

TMP-SMX is now widely recommended for HIV-infected adults and children in Africa. As a result of its efficacy, access to TMP-SMX prophylaxis is rapidly increasing in sub-Saharan Africa as part of a basic care package for HIV-infected patients. TMP-SMX prophylaxis is primarily aimed at prevention of opportunistic and other bacterial infections common in HIV, and several studies have shown significant protection against *Pneumocystis pneumonia*, toxoplasmosis and bacterial infections [6-8]. However, TMP-SMX also has well-recognized antimalarial properties [9], and this added advantage has led to increased interest in evaluating its impact on malaria among HIV-infected individuals in sub-Saharan Africa. Recent studies in HIV-infected adults have reported substantial reduction in the malaria burden among those receiving TMP-SMX. The definition of malaria used in these studies was presentation with fever or

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history of fever in the presence of malaria parasitemia. One study from the Ivory Coast reported a hazard ratio of 0.16 (0.04–0.86) [6] associated with TMP–SMX prophylaxis, and other studies from Uganda have reported similar findings, with reduction in malaria incidence ranging from 69% (incidence rate ratio [IRR]: 0.31; 95% confidence interval [CI]: 0.13–0.72) [10] to 76% (IRR: 0.24; 95% CI: 0.13–0.38) (Table 1) [11]. In one of the studies from rural Uganda, provision of TMP–SMX together with ART and ITNs was associated with a 95% reduction in the frequency of malaria (IRR: 0.05; 95% CI: 0.03–0.08) [11]. In the same location, those living in the same household as HIV-infected individuals receiving TMP–SMX were also reported to have a lower malaria incidence (IRR: 0.64; 95% CI: 0.50–0.83) compared with those living with HIV-infected persons not receiving TMP–SMX [12].

There are fewer data on the effect of TMP–SMX on malaria frequency in children. In urban Uganda, use of both TMP–SMX and ITNs in HIV-infected children led to a 97% reduction in malaria incidence (IRR: 0.03; 95% CI: 0.01–0.10). In this mesoendemic area, malaria was rarely the cause of fever among HIV-infected children receiving TMP–SMX (malaria accounted for only 4% of febrile episodes in the HIV-infected cohort compared with 33% in the HIV-uninfected cohort [$p < 0.0001$]) [13]. In the only other published study that evaluated the effect of TMP–SMX on malaria incidence, in this case in HIV-uninfected children, daily TMP–SMX had a protective efficacy of 99.5% (CI: 96–100%) [9].

The protection against malaria demonstrated in these studies is an added advantage to the use of TMP–SMX that has been associated with reduction in mortality of 33% in HIV-infected children [14].

Although the available data strongly supports the implementation of these low-cost interventions for all HIV-infected children and adults in Africa, preliminary data [Dorsey G, University of California, CA, USA, Unpublished Data] suggest that even with the use of both ITNs and TMP–SMX, HIV-infected children living in Tororo, Uganda, a very high transmission area, continue to suffer a high incidence of malaria (over one episode per person per year).

Trimethoprim–sulfamethoxazole prophylaxis & antifolate resistance

While current evidence provides reason for optimism for successful malaria control in HIV-infected persons, there is some apprehension about increasing the use of TMP–SMX. Widespread TMP–SMX use may lead to selection and spread of antifolate-resistant malaria parasites, and subsequently diminish its prophylactic effects against malaria. This is particularly important as intermittent preventive therapy with sulfadoxine–pyrimethamine (SP) is a promising control measure for prevention of malaria in children [15,16] and pregnant women [17,18].

TMP–SMX acts against many microbes by the same mechanism as the antimalarial drug SP. Both drug combinations inhibit two enzymes in the folate pathway. Trimethoprim and pyrimethamine inhibit dihydrofolate reductase (DHFR); the sulfa drugs inhibit dihydropteroate synthase. In addition to their shared mechanism of action, TMP–SMX and SP likely share mechanisms of resistance, with increasing numbers of mutations in the two target enzymes mediating increasing drug resistance. However, mechanisms of resistance of malaria parasites have principally been studied for SP and, as discussed below, limited data are available to determine whether the specific

Table 1. A summary of recent studies of interventions to prevent malaria in HIV-infected populations.

Intervention	Study population	End point	Incidence rate ratio	Ref.
TMP–SMX	HIV-infected adults and children Controls: HIV-uninfected household members	Clinical malaria	0.28 (0.19–0.40)	[54]
TMP–SMX + ITN + ART	HIV-infected adults Controls: HIV-infected adults with different interventions	Clinical malaria	TMP–SMX: 0.24 (0.15–0.38) TMP–SMX + ART: 0.08 (0.04–0.17) TMP–SMX + ART + ITN: 0.05 (0.03–0.08)	[11]
TMP–SMX + ITN	HIV-infected children Controls: HIV-uninfected children	Clinical malaria	ITN: 0.57 (0.46–0.71) TMP–SMX: 0.69 (0.25–1.51) ITN + TMP–SMX: 0.03 (0.01–0.10)	[13]

ART: Antiretroviral therapy; ITN: Insecticide-treated bed net; TMP–SMX: Trimethoprim–sulfamethoxazole.

mutations that engender resistance of malaria parasites to SP similarly affect sensitivity to TMP-SMX.

Few molecular studies have evaluated the relationship between TMP-SMX use and selection of antifolate resistance-conferring mutations in malaria parasites. One study in a setting of low antifolate resistance in Malawi reported identical prevalence of known resistance-mediating DHFR and dihydropteroate synthetase (DHPS) mutations among children receiving or not receiving TMP-SMX [9]. A study in a setting of high antifolate resistance in Uganda also found no increased risk of markers of resistance among adults exposed to TMP-SMX [12]. In a study in Ugandan children [13], five DHFR/DHPS mutations strongly associated with SP malaria treatment failure were identified in parasites, causing all episodes of malaria diagnosed in HIV-infected children receiving TMP-SMX, and 75% of malaria episodes in HIV-uninfected children not receiving TMP-SMX. This difference was not statistically significant, and the overall malaria incidence in HIV-infected children receiving TMP-SMX was low.

Of note, SP for IPT has been shown to remain efficacious against malaria in areas of both low and high prevalence of DHFR/DHPS mutations [18]. This is similar to findings that TMP-SMX prophylaxis against bacterial infections is maintained even when resistance is high [7]. Spread of TMP-SMX-resistant bacteria such as *Escherichia coli* [19], *Streptococcus pneumoniae* [20] and *Staphylococcus aureus* [21] has been linked to increasing TMP-SMX use in HIV-infected individuals; however, this increase is not correlated with diminished efficacy of TMP-SMX for prevention of bacterial infections. This evidence suggests that increased TMP-SMX use may not substantially increase the risk of clinically relevant parasite antifolate resistance.

Higher level antifolate resistance may impact on the protective efficacy of trimethoprim-sulfamethoxazole

Current literature does not provide evidence that in the short or medium term, increasing antifolate resistance will significantly compromise the prophylactic efficacy of TMP-SMX. However, the increased drug pressure associated with expanded access to TMP-SMX prophylaxis may lead to emergence and spread of new or currently rare resistance-mediating mutations. A sixth polymorphism, the *dhfr* I164L mutation,

which is associated with high-level resistance to SP, is common in southeast Asia and South America, but has been rare in Africa. The emergence of this polymorphism in Africa might prevent any protective efficacy of TMP-SMX against malaria. The *dhfr* I164L mutation was recently seen in Uganda [13,22] and Kenya [23]. In a study in urban Uganda, one of nine diagnosed malaria episodes in HIV-infected children receiving TMP-SMX was associated with this mutation compared with zero of 440 malaria episodes in HIV-uninfected children not exposed to TMP-SMX. In a more recently published study in HIV-uninfected patients in rural Uganda [22], the *dhfr* I164L mutation was found in 14% of 51 patients in one district and 4% of 72 patients in a neighboring district in the same year (2005). TMP-SMX use was not assessed in this latter study. In the Kenyan study, *dhfr* I164L was isolated from infecting parasites in 15 out of 76 malaria episodes. A total of 14 of the 15 cases occurred in HIV-infected persons; however, presence of the polymorphism was not related to TMP-SMX use. The presence of the I164L mutation in the Kenyan study did not predict SP treatment failure; but, the study lacked adequate power to fully assess this relationship. Spread of the *dhfr* I164L mutation in southeast Asia and South America is believed to have played a major role in the loss of antimalarial activity of SP. Thus, if continued use selects for I164L or other mutations that mediate high-level antifolate resistance, TMP-SMX prophylaxis in HIV-infected patients may be faced with diminishing antimalarial protective efficacy, although the pace of loss of efficacy is unknown. In Africa, there is some reason for optimism, as the mutation appears to be unstable, perhaps due to diminished fitness and the high level immunity of local populations. In any event, the emergence of the *dhfr* I164L mutation in Africa is quite concerning, and surveillance to monitor its spread as well as studies to evaluate its implications for treatment and prophylaxis are warranted.

Concern over cross-resistance between trimethoprim-sulfamethoxazole & sulfadoxine-pyrimethamine

In vitro studies have demonstrated cross-resistance between sulfamethoxazole and sulfadoxine [24], and trimethoprim and pyrimethamine [25]. SP was widely used as first-line antimalarial therapy for treatment of uncomplicated malaria in several African countries in the 1990s and remains useful for IPT in pregnancy.

SP resistance is already widespread in many parts of sub-Saharan Africa, particularly east and central Africa [26], and this has rendered it ineffective as monotherapy. Malaria treatment policies are increasingly recommending artemisinin-based combination therapies (ACTs) for first-line treatment of uncomplicated malaria. A combination of artesunate (AS) and SP is one of four WHO-recommended artemisinin combination therapies for treatment of uncomplicated malaria in sub-Saharan Africa [27], although its efficacy was fairly low in eastern Africa [28]. Efficacy of an ACT regimen is dependent on each of the partner drugs in the combination; therefore, widespread TMP-SMX use may further accelerate spread of SP resistance, which will in turn likely compromise the longevity of AS-SP.

Apart from its continued use in combination therapy, SP is the only antimalarial drug currently used in IPT in pregnant women (IPTp). IPTp is the provision of drugs at therapeutic levels at predefined time points with the goal of reducing the burden of disease in susceptible populations. IPTp has been shown to be effective [18], and is being promoted as a key strategy of malaria control in Africa by several initiatives, such as the Roll Back Malaria partnership. More recently, IPT with SP in infants is being explored as a control intervention for this high-risk population. SP will continue to be widely used in Africa for IPT, as there is currently no proven alternative to SP for this purpose. However, since it has become the standard of care to use TMP-SMX prophylaxis in all HIV-infected populations, the use of SP for IPT may not be relevant for HIV-infected individuals.

Key implications for public health policy
Current evidence highlights the benefits of TMP-SMX use in prevention of malaria and supports its use in HIV-infected populations in malaria-endemic areas. As noted earlier, in a mesoendemic area of Uganda, malaria was rarely the cause of fever among HIV-infected children receiving TMP-SMX. The relatively high rates of nonmalaria causes of fever in people with HIV who receive TMP-SMX prophylaxis strongly suggest that presumptive therapy for malaria should be avoided in HIV-infected African adults and children receiving this intervention. Careful evaluation for other causes of fever should be combined with specific diagnostic testing for malaria. This highlights the importance of building capacity for malaria and other laboratory diagnostic capacities in HIV care

settings. Studies are urgently needed to determine the optimal approach to fever diagnosis and management in people with HIV on TMP-SMX in resource-limited settings. However, resistance to antifolates (TMP-SMX and SP) should be monitored and long-term implications of TMP-SMX use on malaria and other common infections should be carefully considered. In this context, alternative malaria IPT regimens also need to be studied.

Malaria treatment in HIV-infected populations

The treatment of malaria in HIV-infected populations presents another challenge. Response to antimalarial therapy is affected by the abilities of both antimalarial drugs and host immune responses to inhibit infecting parasites [29]. Malaria-specific immunity is acquired with repeated exposure to malaria parasites, and this immunity increases with age in areas endemic for malaria [30]. Similarly, response to antimalarial therapy improves as the level of acquired immunity increases [31]. Because HIV infection impairs cell-mediated immunity, it has been suggested that HIV-infected individuals may suffer poor outcomes after malaria infection. Only a few studies have examined the effect of HIV infection on response to antimalarial treatment, and these have yielded conflicting results [32–36]. Table 2 summarizes studies assessing antimalarial treatment response in HIV-infected populations.

Monotherapy & malaria treatment in HIV-infected populations

Earlier studies using monotherapies did not suggest any adverse effect of HIV on the success of therapy with antimalarial drugs, including quinine, chloroquine and SP, which were all highly effective [33]. However, subsequent studies reported different findings. In a small study in Uganda, treatment of falciparum malaria with chloroquine appeared to be less effective among HIV-infected than -uninfected children under 5 years of age [34]. A study in Kenya reported that treatment of uncomplicated malaria with SP was significantly less efficacious in HIV-infected adults, with CD4 cell counts below 200 cells/mm³, compared with those with higher counts [35]. Treatment failures in this study were primarily due to recrudescence rather than new infections. Contrary to these findings, in Uganda HIV-infected patients older than 5 years of age treated with chloroquine plus SP were less likely to have treatment failure compared with

Table 2. Summary of studies reporting antimalarial treatment response in HIV-infected individuals with uncomplicated malaria.

Study site and transmission	Year and study population	Sample size	Drug regimens	Duration of follow-up (days)	Treatment outcome	Comments	Ref.
Congo Intense malaria transmission	1986 Adults	n = 59 HIV+: 25 HIV-: 34	Oral quinine	7	Proportion with a negative blood film on day 7: HIV+: 23/25 (92%) HIV-: 28/34 (82%)	No direct interaction of major clinical importance	[33]
Ethiopia Seasonal malaria transmission	2002 Adults	n = 19 HIV+: 7 HIV-: 12	Artemisinin	28	Mean parasite clearance time HIV+: 37.7 h HIV-: 30.0 h Mean fever clearance time HIV+: 40.6 h HIV-: 28.7 h	Delayed parasite clearance in HIV+ patients	[37]
Uganda Varying malaria transmission	2002–2004 Adults and children	n = 1965 HIV+: 95 HIV-: 1870	SP + CQ SP + AQ AQ + AS	28	>threefold 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	[32]
Kenya Intense and perennial malaria transmission	2002–2004 Adults	n = 508 HIV+: 378 HIV-: 130	SP	28	Failure rates HIV+: 12.3% HIV- with high CD4 count: 17.2% HIV- with low CD4 count: 32%	HIV infection with CD4 count <200 cells/ μ l predicted treatment failure	[35]
Zambia Mesoendemic malaria transmission	2003–2005 Adults	n = 795 HIV+: 266 HIV-: 529	SP	45	Increased risk of early treatment failure in patients with CD count <300 cells/ μ l	No increased risk of recurrent parasitemia in HIV+ children	[38]
Uganda Mesoendemic malaria transmission	2005–2006 Children	n = 160 HIV+: 26 (on TMP-SMX) HIV-: 134	AQ/AS	28	Proportion with adequate response HIV+: 94% HIV-: 84%	AQ/AS equally efficacious in both cohorts	[5]

AQ: Amodiaquine; AS: Artesunate; CI: Confidence interval; CQ: Chloroquine; HIV: HIV negative; HIV+: HIV positive; HR: Hazard ratio; SP: Sulfadoxine-pyrimethamine; TMP-SMX: Trimethoprim-sulfamethoxazole.

HIV-uninfected patients in the same age group (rate ratio: 0.59; 95% CI: 0.4–0.8; $p < 0.001$). In this study it was found that the use of TMP–SMX prophylaxis was associated with a lower risk of malaria treatment failure in HIV-infected children and adults compared with HIV-uninfected controls [36]. However, this study did not consider the immunological status of these patients in the interpretation of treatment outcomes. In Ethiopia, artemisinin monotherapy was effective in both HIV-infected and -uninfected adults with uncomplicated malaria, but prolonged parasite and fever clearance times were seen in HIV-infected adults [37].

Impact of combination therapy on malaria treatment in HIV-infected populations

ACTs have now been adopted as first-line drugs for the treatment of uncomplicated malaria in almost all African countries. Despite these recommendations, there are limited data on the safety and efficacy of these drugs among HIV-infected populations. Evidence suggests that even with these more efficacious combination drugs, treatment failure may be common in HIV-infected individuals. The impact of HIV-associated immunosuppression on antimalarial treatment response was further assessed in a trial of artemether–lumefantrine versus SP for the treatment of uncomplicated malaria in adults in Zambia; the frequency of malaria treatment failure with either therapy increased significantly with advancing immunosuppression [38]. In Uganda, HIV infection was associated with an increased risk of new malarial infections after treatment with SP plus chloroquine, SP plus amodiaquine (AQ) and AQ/AS, but it was not associated with recrudescence after therapy. Thus, HIV infection appeared to lead to worse treatment outcomes owing to a predilection for recurrent infections after therapy, rather than failure of initial therapy. These results were contrary to those from the Zambian study [38], but similar to those from Malawi [39], which did not show an association between HIV infection and antimalarial therapeutic efficacy, as measured by the ability to clear parasites. Differences between studies may have been due to differences in overall drug efficacies and/or the immune competence of study populations.

Recent studies from Uganda show interesting differences between HIV-infected children and adults. Both HIV-infected and -uninfected children responded well to treatment for uncomplicated malaria with AQ/AS. Times to fever and

parasite clearance were also similar for the two groups [5]. In another study from Uganda, outcomes were compared in pediatric and adult patients. The risk of clinical treatment failure in adults was more than threefold higher for HIV-infected patients than for HIV-uninfected patients [32]. By contrast, for children in this study, the risk of clinical treatment failure was not significantly higher for HIV-infected patients than for HIV-uninfected patients [32]. Thus, in pediatric populations, the immune dysregulatory effects of HIV on malaria may be less important than in adults, as in young children with or without HIV infection, antimalarial immunity may play a relatively small role in treatment outcomes. Further studies examining the effects of HIV infection on antimalarial treatment outcomes are needed. The impact of ART on malaria treatment outcomes will also need further study as most findings reported are in adults and children not yet on antiretrovirals (ARVs).

Anti-HIV effects of antimalarial drugs

Some studies have reported potential anti-HIV activity of certain antimalarial drugs. Chloroquine was reported to have an inhibitory effect on the growth of HIV *in vitro*, suggesting a dual benefit of malaria treatment and action on HIV [40]. A clinical trial that compared chloroquine to zidovudine (AZT) in asymptomatic patients reported equivalent reductions in recoverable HIV after 16 weeks [41]. Possible direct effects of chloroquine and SP on HIV are potentially very important, but these results have not been confirmed in further studies.

Antimalarial drug safety in HIV-infected populations

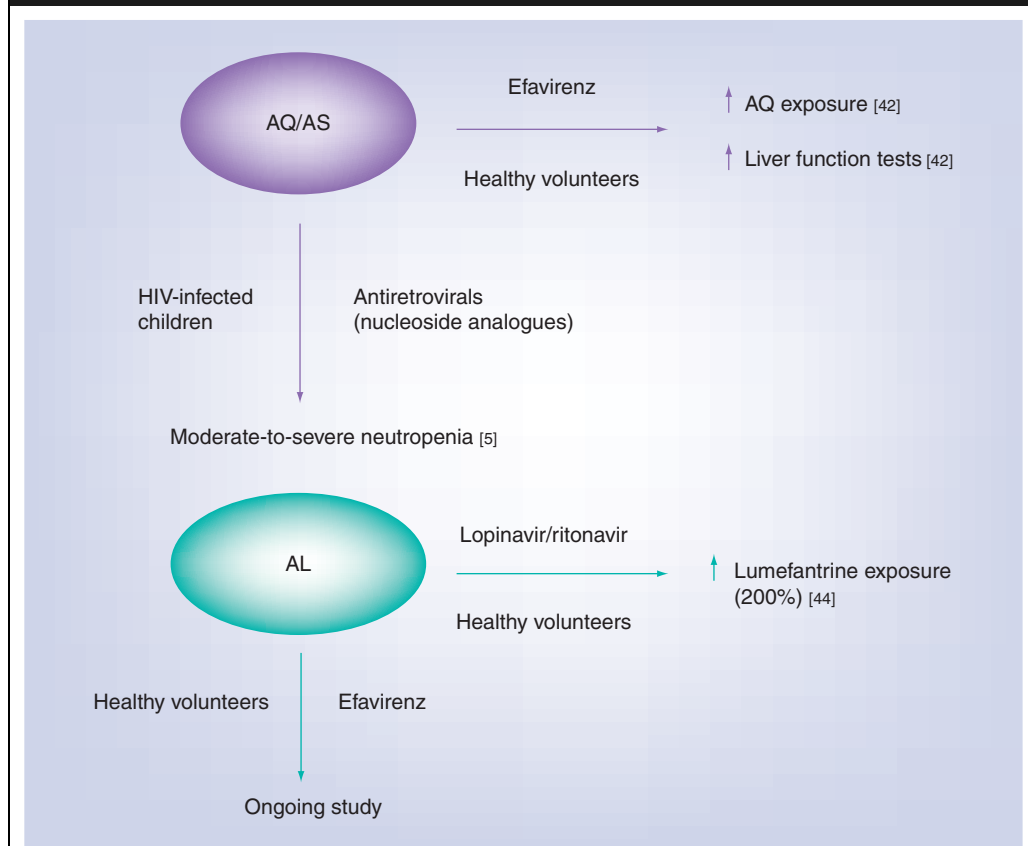
Despite the encouraging results regarding antimalarial treatment responses, concerns remain about the safety of antimalarial drugs in HIV-infected populations. Currently, there is little published information on the risk of co-administration of ART and antimalarials. This is particularly important with the rapid scale-up of ART in Africa, with standard first- and second-line ART regimens that include: lamivudine, emtricitabine, stavudine, AZT, tenofovir, didanosine, nevirapine (NVP), efavirenz and lopinavir/ritonavir. Any interactions between these ARV and antimalarial drugs may be of great clinical importance. In a recent study of uncomplicated malaria in Uganda, treatment of HIV-infected children with AQ plus AS (AQ/AS) was associated with a

remarkably higher risk of neutropenia compared with treatment of HIV-uninfected children. The risk of neutropenia was higher in participants with concurrent ARV use (especially AZT), and in those with history of repeated doses of AQ/AS [5]. Neutropenia appeared to have clinical consequences, as HIV-infected study participants had an increased risk of pneumonia during neutropenic episodes compared with matched controls. These findings will need to be confirmed in another setting; however, the current observations suggest that in HIV-infected individuals, particularly among those receiving AZT-containing ART, the treatment of malaria with AQ/AS should be avoided if possible. Another common side effect of AZT is anemia, which may be particularly problematic in the context of concurrent malaria.

Concerns also exist about the potential hepatotoxicity of antimalarial drugs when combined with ART. In a study of healthy adult volunteers, a combination of AQ/AS in the presence of

efavirenz led to significant elevations in liver transaminases as well as a substantial increase in AQ pharmacokinetic exposure (Figure 1) [42]. However, in a cohort of HIV-infected children receiving AQ/AS and efavirenz, no significant elevations in liver transaminases were observed in ten patients followed-up for 42 days [5]. This observation stresses the importance of conducting drug interaction studies in populations with disease and not only in healthy populations. Despite the lack of frequent toxicity in the cohort study, interactions of the magnitude seen in healthy volunteers are concerning. Based on the neutropenia in African children and hepatotoxicity in volunteers described above, artemether–lumefantrine should probably be considered as the preferred regimen over AQ/AS for treatment of HIV and malaria co-infected patients receiving ART. Despite these recommendations, it is important to note that interactions between lumefantrine and ARVs also exist as detailed below.

Figure 1. Summary of potential interactions between commonly used artemisinin-based combination therapies and antiretroviral drugs.



AL: Artemether–lumefantrine; AQ: Amodiaquine; AS: Artesunate.
Data from [5,42,44].

Ritonavir or lopinavir/ritonavir may boost levels of quinine or lumefantrine, perhaps to dangerous levels [43,101]; the clinical implications of these elevations need further study. Recently, a study in healthy adults indicated an increase of 200% in lumefantrine area under the concentration versus time curve (AUC) when co-administered with lopinavir/ritonavir (Figure 1), presumably due to inhibition of CYP450-mediated drug metabolism [44].

On the other hand, non-nucleoside reverse transcriptase inhibitors such as NVP or efavirenz may lower concentrations and effectiveness of both quinine and lumefantrine [102] owing to induction of metabolic enzymes.

Conversely, the impact of antimalarial drugs on the pharmacokinetics of ARV agents is less of a concern. Artemisinin combination therapy is administered for only 3 days. Therefore, adjustments of ARV dosing for this short period of time is not clinically practical nor warranted, even if an interaction occurs affecting ARV exposure. In our study in healthy adult volunteers, we observed that the AUC₀₋₁₂ and maximum concentration of lopinavir/ritonavir was not altered in the presence of artemether–lumefantrine relative to lopinavir/ritonavir administration by itself [44], further indicating dosage adjustment is unnecessary.

Concurrent use of NVP and SP also raises safety concerns, as hypersensitivity reactions to NVP are fairly common and clinically indistinguishable from reactions to SP [45]. Severe cutaneous reactions, including Stevens–Johnson syndrome, have been reported in approximately 2% of patients taking daily NVP, and clinical hepatitis occurs in approximately 4%; both events have been previously described in patients taking SP [46]. Serum levels of artemether and dihydroartemesinin may also be affected by ARV protease inhibitors or non-nucleoside reverse transcriptase inhibitors, but data are limited and clinical implications unclear [43].

Any interactions of ARV and antimalarial drugs could have major implications regarding malaria treatment recommendations in Africa, as artemether–lumefantrine and AQ/AS have been chosen as first-line antimalarial therapy in most countries in Africa. More studies are urgently needed to better characterize potential interactions between ACTs and ARVs and further investigate the clinical significance of these interactions; this underscores the need for pharmacovigilance. Figure 1 summarizes the potential interactions between commonly used ACTs and ARVs.

Impact of antiretroviral drugs on

malaria: implications for malaria control

The expanding use of ARVs could have implications for malaria control if these drugs have antimalarial activity. HIV [47] and malaria parasites [48] both encode aspartic-class proteases, raising the possibility that HIV protease inhibitors (PIs) may have antimalarial activity. A number of groups showed recently that HIV protease inhibitors blocked the development of cultured malaria parasites at concentrations that, for many of the drugs, are clinically achievable [49,50]. In particular, lopinavir inhibited four strains of *Plasmodium falciparum* at concentrations well below serum levels of the drug after standard dosing [49]. HIV PIs also inhibited *P. falciparum* cytoadherence and phagocytosis by macrophages [51]. *In vitro* synergy was demonstrated between the antimalarials chloroquine and mefloquine and HIV PIs [40,52]. Biochemical studies also demonstrated inhibition of the presumed targets of the aspartic PIs, the *P. falciparum* plasmepsins, by HIV PIs [49,52]. In *ex vivo* studies, sera from HIV patients treated with saquinavir–ritonavir or lopinavir/ritonavir inhibited the *in vitro* growth of *P. falciparum* [53]. In summary, a wealth of data collected over the last few years demonstrates that ARV PIs exert antimalarial activity. Thus, the use of PI-based ART in HIV-infected individuals living in areas of high malaria transmission may help to prevent malaria in this vulnerable population. However, clinical trials testing the impact of PIs on malaria incidence are not yet available.

Conclusion

Interactions between HIV and malaria remain a major public health concern in most areas affected by the two diseases. Increased incidence and severity of malaria has been well documented in HIV-infected populations, with resulting increased morbidity and mortality. These data suggest that malaria is a particular risk for those with HIV infection, and call for the strengthening of programs for the prevention of malaria in this population. The available data are strong and support immediate implementation of low-cost interventions to prevent malaria, including use of ITNs and TMP–SMX prophylaxis, for all HIV-infected individuals at risk of malaria in Africa. The long-term efficacy of TMP–SMX will, however, need further evaluation and study given increasing rates of resistance to the related drug SP. Available data also suggest that, although malaria is somewhat more

common in HIV-infected populations, the malaria treatment policy in these individuals can follow the standard malaria treatment policy; however, until further data are available, AQ regimens should be avoided in patients on ART. ACTs are generally effective in treating malaria in HIV-infected patients, although concerns about potential interactions with ARVs exist. In light of the challenges presented, we advocate for the linkage of antimalarial and HIV treatment programs. Ongoing surveillance using both active and passive pharmacovigilance systems will also be needed to document adverse events that result from the different therapies used to manage malaria and HIV infection.

Future perspective

Recent studies have demonstrated that prophylactic TMP–SMX in combination with ITNs can markedly decrease the incidence of malaria in HIV-infected adults and children. However, in high transmission regions, malaria remains

common even with these two interventions. The relationship between malaria transmission intensity and the protective effect of TMP–SMX needs to be determined. In determining policies for prophylaxis, one must also consider other factors, such as the prevention of other diseases (e.g., bacterial infections), potential for adverse events due to TMP–SMX and the selection of drug resistance. More research is needed to determine whether continuing TMP–SMX prophylaxis may be beneficial even among HIV-infected people who have experienced immune recovery in response to ART, and whether there are any risks of increased rates of malaria if TMP/SMX is discontinued after an extended period of use. Although progress has been made in preventing malaria in HIV-infected populations, additional interventions are needed to protect HIV-infected people that reside in high malaria transmission areas. ARV PIs exert antimalarial activity *in vitro* and animal models, but clinical

Executive summary

Malaria & HIV interactions

- Malaria and HIV infection are two of the most important infectious diseases worldwide.
- HIV infection may impair the acquired immune response to malaria and increase incidence and severity of malaria.
- Acute malaria elevates HIV viral load and so may increase the risk of HIV transmission and accelerate disease progression.
- HIV infection may be associated with reduced efficacy of older antimalarial treatment regimens.
- Therapies for each infection may impact upon the other, leading to unanticipated effects on drug efficacy or toxicity.

Malaria prevention in HIV-infected populations

- Daily trimethoprim–sulfamethoxazole (TMP–SMX) has led to significant reduction in malaria incidence in HIV-infected populations.
- A synergistic effect is seen with a combination of interventions: TMP–SMX, insecticide-treated bed nets (ITNs) and antiretroviral therapy.
- Widespread TMP–SMX use may lead to selection and spread of antifolate-resistant malaria parasites.
- Higher level antifolate resistance may subsequently diminish protective efficacy of TMP–SMX.
- Cross-resistance between TMP–SMX and sulfadoxine–pyrimethamine (SP) may potentially impact on the long-term efficacy of SP for both intermittent presumptive treatment and treatment as combination therapy.

Malaria treatment in HIV-infected populations

- Presumptive therapy for malaria should be avoided in HIV-infected individuals on TMP–SMX prophylaxis.
- The impact of HIV-induced immunosuppression on antimalarial treatment outcomes progressively increases as antimalarial drug efficacy decreases.
- Artemisinin-based combination therapies are generally effective in management of malaria in HIV-infected individuals, although there is an increased risk of new malaria infections after treatment.
- Recrudescence malaria seems to occur more commonly in adults with advanced immunosuppression.
- Concerns exist about the potential interactions between antimalarial drugs and antiretroviral agents.

Conclusions

- TMP–SMX prophylaxis and ITNs are critical components for malaria prevention in the HIV-infected population.
- Treatment for malaria in the HIV-infected population should follow current guidelines for the HIV-uninfected population.
- There is a need for further studies to monitor the resistance to both TMP–SMX and SP and the effect on protective efficacy.
- Ongoing surveillance and clinical studies are needed to evaluate for potential interactions and adverse events that result from co-administration of therapies used to manage malaria and HIV infection.

evidence that HIV PIs will protect against malaria is lacking. Should their efficacy be confirmed, this may change the balance towards using more PI-based regimens in resource-poor settings. If this evidence becomes available, HIV PIs will 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. Progress in malaria vaccine research has been slow, but a candidate vaccine recently provided modest protection in infants and children. Large-scale Phase III trials have yet to be initiated, and it is likely that a vaccine for routine use is at least 5–10 years away; in any event, this vaccine will provide only partial protection against malaria. The efficacy of these vaccines in HIV-infected populations will need further study.

Available data show that effective antimalarial regimens are efficacious for 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 efficacy of potent antimalarial drugs such as ACTs. Limited data exist on the safety and efficacy of ACTs in HIV-infected populations, including HIV-infected pregnant women. If HIV infection reduces the ability to clear malaria parasites, this may hasten the development of antimalarial drug resistance. In addition, antimalarial drug combinations may lead to toxicity owing to HIV-specific factors or drug interactions, and research on the safety of malaria therapies in HIV-infected Africans is an urgent priority.

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