

Prevention and treatment of malaria in HIV-infected patients

There are many clinically important interactions between HIV and malaria.

CHERYL COHEN, MB BCH, FCPATH (SA) (Micro)

National Institute for Communicable Diseases, National Health Laboratory Service, and School of Public Health, University of the Witwatersrand, Johannesburg

Dr Cohen is a clinical microbiologist and epidemiologist in the Epidemiology and Surveillance Unit of the National Institute for Communicable Diseases, Johannesburg. She has a particular interest in vaccine-preventable diseases, surveillance systems and opportunistic infections associated with HIV.

Human immunodeficiency virus (HIV) infection affects the clinical presentation, severity and response to treatment of malaria cases, and malaria may affect the progression and transmission of HIV. In addition, there are potential interactions between drugs used for the treatment and prevention of malaria and antiretroviral therapy. The clinical impact of these interactions varies depending on the intensity of malaria transmission in the area (and consequent level of host immunity) and the individual affected (e.g. adult, child or pregnant woman).

Unstable malaria transmission is seasonal and generally occurs at times of increased temperature and rainfall, as is the case in South Africa and much of southern Africa. In such areas clinical malaria affects all age groups, and adults have no immunity to malaria (non-immune adults). In contrast to this, in areas of stable transmission malaria occurs throughout the year, with minimal variation in levels of transmission from year to year.¹ In these areas, adults acquire significant immunity to malaria after repeated infections in childhood; the major burden of disease therefore occurs in children and pregnant women. Clinical disease is less common in semi-immune adults.

Sub-Saharan Africa experiences more than 60% of the 350 - 500 million annual malaria cases globally and 80% of all malaria deaths occur in this region.² Sub-Saharan Africa is also the most affected by the AIDS pandemic, with an estimated 22.5 million people infected with HIV in 2006.³ The prevalence of HIV infection among antenatal clinic attendees in South Africa in 2007 was 29.1%.⁴ Malaria transmission in South Africa is seasonal and limited to the north-eastern low-altitude areas of Limpopo, Mpumalanga and KwaZulu-Natal that border Zimbabwe and Mozambique.⁵

Mathematical models suggest that the greatest increase in malaria cases and deaths due to HIV will be experienced in South Africa and its neighbouring countries, because they have a high HIV prevalence and mostly unstable malaria transmission. In these areas relatively more cases of malaria occur in adults – the age group most affected by HIV.⁶

There are sound immunological reasons why we might expect a negative interaction between HIV and malaria. HIV infection leads to impaired T-cell immunity – an essential component of the antimalarial immune response. Conversely, malaria infection leads to T-cell activation which promotes HIV replication and could lead to increased HIV progression and transmission.¹

This article reviews the important clinical interactions between malaria and HIV infection and concludes with a discussion of the clinical implications of these interactions for the prevention and treatment of malaria in HIV-infected individuals. Particular focus is placed on issues of relevance for adults and children in South

Africa, and interactions in areas of stable malaria transmission are mentioned briefly.

Interaction between HIV and malaria (Table I)

Malaria in HIV-infected adults

Non-immune adults have been shown to have at least double the risk of developing severe malaria in rural and urban settings in South Africa, and to have an approximately five-fold increased risk of death in rural areas where there is limited access to intensive care facilities. This risk increases with decreasing CD4 T-cell count.^{1,7-9}

In areas of stable malaria transmission, HIV-infected adults have an increased risk of clinical illness (including fever) and increased parasite density compared with HIV-uninfected adults. This risk increases with decreasing CD4 T-cell count. There is no evidence of an increased risk of severe malaria in this group of patients. Recent studies have suggested that clinical treatment failure may be more common in HIV-infected individuals because of new infections as opposed to recrudescence of the original infection.^{1,7,10}

Malaria in HIV-infected children

In areas of unstable transmission, HIV is a risk factor for severe malaria in young children.¹¹ HIV-infected children in areas of stable malaria transmission are more likely to die within 7 days of diagnosis and to have more frequent re-admissions for malaria than HIV-uninfected children.^{10,12}

Effect of malaria on HIV viral load and CD4 T-cell count

Acute malaria is associated with an increase in viral load and a decrease in CD4 T-cell count, but this generally returns to pre-infection levels a few weeks after successful malaria therapy. This could theoretically lead to increased HIV transmission or more rapid disease progression, but has not been demonstrated prospectively.⁷

HIV and malaria infection in pregnant women

No studies have been conducted to evaluate the interaction between HIV and malaria in pregnant women in areas of unstable malaria transmission. It is, however, reasonable to assume that such women would experience the increased risk of severe malaria and death seen in non-pregnant adults and that this might be compounded by the increased risk of severe malaria associated with pregnancy.

Table I. The impact of HIV infection on clinical presentation, severity and adverse outcomes of malaria in adults, children and pregnant women in areas of stable and unstable malaria transmission

Patient group	Unstable transmission (non-immune)*	Stable transmission
Non-pregnant adults	<ul style="list-style-type: none"> • Increased risk of severe malaria • Increased risk of death in rural areas 	<ul style="list-style-type: none"> • Increased risk of clinical malaria (including fever) • Increased parasite density • Increased risk of clinical treatment failure (re-infection)
Children	<ul style="list-style-type: none"> • Increased risk of severe malaria 	<ul style="list-style-type: none"> • Increased risk of death and re-admission for malaria
Pregnant women	<ul style="list-style-type: none"> • No data but increased risk of severe malaria likely 	<ul style="list-style-type: none"> • Increased risk of malaria infection • Increased risk of placental malaria • Higher parasite density • Increased risk of anaemia • Decreased response to antimalarial therapy • Loss of gravidity-dependent immunity • Increased risk of low birthweight, preterm birth, intra-uterine growth retardation and higher postnatal infant mortality rate

*Risks to travellers are thought to be similar to those described in individuals from areas of unstable malaria transmission.

Studies in areas of stable malaria transmission have found that HIV-infected pregnant women have higher rates of malaria infection and placental malaria, higher parasite density, more clinical illness, more anaemia and decreased response to antimalarial therapy.¹³

¹⁵ Malaria infection leads to higher maternal HIV viral load, but evidence is contradictory as to whether this translates into increased risk of mother-to-child HIV transmission. HIV infection decreases or eliminates the reduction in malarial parasitaemia normally seen with increasing gravidity. Babies born to dual-infected women are more likely to experience low birthweight, preterm birth, and intrauterine growth retardation and have a higher postnatal infant mortality rate than those born to women affected by HIV or malaria alone. There are no data available on the effect of HIV on severe malaria or death in pregnancy.¹⁵

Clinical implications for malaria treatment and prevention

Prevention of malaria in the HIV-infected non-immune traveller

HIV-positive non-immune adults are at increased risk of severe malaria and death and therefore they should be meticulous about adhering to precautions to prevent malaria should they be unable to avoid travelling to malaria areas. Travellers should utilise personal protection measures such as permethrin-coated bednets and clothes, avoidance of mosquitoes, and use of diethyltoluamide (DEET)-containing insect repellants.

Chemoprophylaxis should be started in good time before travelling, as adverse events may necessitate a change of regimen. Overlapping adverse effect profiles and potential drug interactions between antiretrovirals and antimalarials should be considered. Options for chemoprophylaxis include mefloquine, atovaquone/proguanil (Malaril) and doxycycline.¹⁶ Doxycycline is recommended as the prophylaxis of choice in HIV-infected individuals in the South African guidelines for prevention of malaria,⁵ as it has no significant drug interactions with antiretroviral medications. Adverse effects such as photosensitivity and vaginal candidiasis may occur. Mefloquine may be associated with neuropsychiatric side-effects, especially if co-administered with efavirenz which also has a risk of central nervous system toxicity. Mefloquine use may lead to decreased ritonavir levels. The induction of cytochrome P450 3A by non-nucleoside reverse transcriptase inhibitors (NNRTIs) could lead to low levels of mefloquine, but it is unclear if this is clinically significant. Atovaquone/proguanil may be suitable in patients using a regimen that includes NNRTIs. However, protease inhibitors decrease atovaquone levels and, although the clinical significance is uncertain, co-administration is not recommended. HIV-infected pregnant women and young children should, if possible, avoid travelling to malaria areas owing to increased risk of severe disease and lack of effective safe prophylaxis.

Prevention of malaria in areas of stable malaria transmission

The use of insecticide-treated bednets (ITNs), antiretroviral therapy and daily co-

trimoxazole prophylaxis as recommended by the World Health Organization (WHO) Guidelines has been shown to decrease the risk of clinical malaria in HIV-infected adults and children in areas of stable malaria transmission. In addition, a high index of suspicion for malaria, with prompt, effective treatment of acute malaria and early evaluation for the initiation of antiretroviral therapy, is recommended, especially in HIV-infected children.^{7,10}

Recommended preventive measures for pregnant women in stable malaria transmission areas include the use of ITNs, intermittent preventive treatment (IPT) with three or more doses of an effective antimalarial after the first trimester, and prompt, effective management of malaria and anaemia.¹³ All pregnant women should be offered HIV testing, and highly active antiretroviral therapy (HAART) should be initiated when indicated. The WHO now recommends daily co-trimoxazole as an alternative to IPT. Some concerns have been raised as to possible adverse effects associated with this practice, including the risk of folate deficiency and the potential for the development of resistance in *Plasmodium falciparum*.¹⁰

Diagnostic challenges in co-infected patients

The clinical presentation of malaria may mimic that of many other opportunistic infections. This may lead to a missed or delayed diagnosis of malaria, and clinicians should have a high index of suspicion for malaria in HIV-infected individuals who have travelled to a malaria-endemic area. A blood smear and/or antigen test should always be performed (and repeated) until the diagnosis of malaria is confirmed or excluded.⁷

The reverse may also be true, particularly in semi-immune individuals, where pyrexia may be treated as malaria without further investigation. This could lead to a missed or delayed diagnosis of other infections. In semi-immune patients asymptomatic parasitaemia may occur concurrently with other treatable causes of fever; thus the finding of a malaria parasitaemia does not exclude other co-morbid diagnoses.¹

Acute malaria infection leads to decreased CD4 T-cell count and increased viral load measurements; therefore these should be re-checked several weeks after the patient has recovered in order to ensure that measurements are reliable for staging of HIV-infection.

Therapeutic challenges in co-infected patients

HIV-infected individuals may be malnourished or wasted or they may experience gastrointestinal infections which may lead to decreased absorption of antimalarial drugs.

Although there are no reports of increased adverse reactions in HIV-infected individuals to the currently recommended first-line treatment, artemether-lumefantrine, the risk of adverse effects to other antimalarials may be increased in these individuals. They are at a higher risk of developing adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis after treatment with sulfadoxine-pyrimethamine (which is no longer recommended owing to widespread resistance). The observed increased risk of clinical treatment failure means that HIV-infected individuals may be more likely to be treated with 2nd- and 3rd-line antimalarials, which may have a less favourable side-effect profile.¹

A number of potential drug interactions between antiretrovirals and antimalarials may occur in co-infected patients.

• Effect of anti-HIV drugs on antimalarial treatment regimens

Potential drug interactions with malaria prophylactic agents have been discussed above.

The WHO does not recommend any specific modifications to the general guidelines for the management of acute malaria in HIV-infected individuals.¹⁷ Antiretrovirals may be suspended in the setting of severe malaria. HIV protease inhibitors inhibit cytochrome P450 enzymes; therefore co-administration of antimalarials may increase the risk of adverse effects (cardiotoxicity, arrhythmias and hypoglycaemia with quinine, and hepatotoxicity with artesunate). The NNRTIs induce the cytochrome P450 enzyme system and may lead to decreased efficacy of quinine therapy. However, there are very

few studies evaluating interactions between antimalarials and antiretrovirals.^{7,16}

• Overlapping adverse effects profiles

Antimalarials and antiretrovirals may have overlapping adverse effect profiles that may lead to difficulties in identifying which drug to discontinue, e.g. both nevirapine and sulfadoxine/pyrimethamine can cause severe liver damage and skin toxicity. Excellent up-to-date references for HIV malaria drug interactions can be found at <http://www.hiv-druginteractions.org/>¹⁸ as well as in recent articles by Brentlinger *et al.*⁷ and Khoo *et al.*¹⁹

• Antimalarial effect of antiretrovirals and vice versa

Recent studies have suggested that some antiretroviral agents may have antimalarial effects and, conversely, chloroquine has been shown to inhibit HIV replication, but these effects have not been evaluated in clinical trials.^{7,13}

Conclusions

There are many clinically significant interactions between malaria and HIV. Treatment guidelines specifically addressing interactions between these infections are needed. Clinicians should be aware of the potential for drug interactions and misdiagnosis due to heterogeneous clinical presentations.

References

- Hewitt K, Steketee R, Mwapasa V, Whitworth J, French N. Interactions between HIV and malaria in non-pregnant adults: evidence and implications. *AIDS* 2006; 20(16): 1993-2004.
- World Health Organization. *World Malaria Report 2005*. Geneva: World Health Organization, 2006.
- Joint United Nations Programme on HIV/AIDS (UNAIDS). *Report on the Global AIDS Epidemic*. Geneva: UNAIDS, 2006.
- Department of Health. *National HIV and Syphilis Antenatal Seroprevalence Survey in South Africa*. Pretoria: National Department of Health, 2007.
- National Department of Health. *Guidelines for the Prevention of Malaria in South Africa*. Pretoria: National Department of Health, 2007.
- Korenromp EL, Williams BG, de Vlas SJ, *et al.* Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. *Emerg Infect Dis* 2005; 11(9): 1410-1419.
- Brentlinger PE, Behrens CB, Kublin JG. Challenges in the prevention, diagnosis, and treatment of malaria in human immunodeficiency virus infected adults in sub-Saharan Africa. *Arch Intern Med* 2007; 167(17): 1827-1836.
- Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS* 2004; 18(3): 547-554.
- Cohen C, Karstaedt A, Frean J, *et al.* Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis* 2005; 41(11): 1631-1637.
- Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases. I. Protozoal pathogens. *Clin Infect Dis* 2007; 45(9): 1208-1213.
- Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. Childhood malaria in a region of unstable transmission and high human immunodeficiency virus prevalence. *Pediatr Infect Dis J* 2003; 22(12): 1057-1063.
- Malamba S, Hladik W, Reingold A, *et al.* The effect of HIV on morbidity and mortality in children with severe malarial anaemia. *Malaria Journal* 2007; 6(1): 143.
- Brentlinger PE, Behrens CB, Micek MA. Challenges in the concurrent management of malaria and HIV in pregnancy in sub-Saharan Africa. *Lancet Infect Dis* 2006; 6(2): 100-111.
- ter Kuile FO, Parise ME, Verhoeff FH, *et al.* The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-Saharan Africa. *Am J Trop Med Hyg* 2004; 71(2 Suppl): 41-54.
- Desai M, ter Kuile FO, Nosten F, *et al.* Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007; 7(2): 93-104.
- Bhadelia N, Klotman M, Caplivski D. The HIV-positive traveler. *Am J Med* 2007; 120(7): 574-580.
- World Health Organization. *Guidelines for the Treatment of Malaria*. Geneva: World Health Organization, 2007.
- Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. *AIDS* 2005; 19(10): 995-1005.
- University of Liverpool. <http://www.hiv-druginteractions.org/> (accessed 5 January 2008).

In a nutshell

- HIV-infected adults and children in South Africa have an increased risk of developing severe malaria.
- Acute malaria leads to an increase in viral load and a decrease in CD4 T-cell count, but this resolves after successful treatment.
- Antiretroviral agents may have potential drug interactions with agents used for the prevention and treatment of malaria.
- Antimalarials and antiretrovirals may have overlapping adverse effect profiles.
- HIV-infected travellers to areas of malaria transmission should use strict personal protective measures to avoid mosquito bites.
- Doxycycline is recommended for chemoprophylaxis in HIV-infected non-pregnant adults.
- Clinicians should have a high index of suspicion for malaria in HIV-infected patients who have visited, or are resident in, a malaria-endemic area, as the clinical presentation may be confused with that of other opportunistic infections.