

HIV AND MALARIA

EPIDEMIOLOGY

Malaria is endemic in Belize, the Dominican Republic, French Guiana, Guyana, Haiti, and Suriname. Other countries may also see sporadic cases of malaria infection due to migration and tourism. In endemic countries, the intensity and periodicity of malaria transmission and the predominant *Plasmodium* species vary broadly. For example, in Haiti and the Dominican Republic, nearly all malaria is caused by *P. falciparum*, and the annual parasitic index (API, or number of confirmed malaria cases per 1,000 population at risk) is 2.1. In contrast, in Suriname, where malaria transmission is more intense than anywhere else in the Americas, the API is 370.8, with cases contributed by three different species of malaria: *P. falciparum* (approximately 80% of cases), *P. vivax* (10%), and *P. malariae* (10%).ⁱ

Drug resistance patterns also vary within the region. Although chloroquine-susceptible malaria, particularly *P. vivax*, still occurs, resistance to both chloroquine and sulfadoxine-pyrimethamine (SP) has become widespread particularly in the Amazon River basin, where some degree of *P. falciparum* resistance to mefloquine and *P. vivax* resistance to primaquine have also been observed.ⁱⁱ Because antimalarial drug resistance is evolving rapidly in many sites, the Pan American Health Organization (PAHO), in conjunction with the Centers for Disease Control and Prevention (CDC) and the United States Agency for International Development (USAID), has recently established a network for ongoing evaluation of antimalarial drug resistance, for the purpose of guiding antimalarial drug policy.ⁱⁱⁱ Some countries with particularly high burdens of antimalarial drug resistance are now introducing artemisinin-based combination therapies, such as artemether/lumefantrine, as recommended by recent World Health Organisation (WHO) guidelines.^{iv,v}

CLINICAL MANIFESTATIONS

In both HIV-infected and -uninfected persons, clinical syndromes caused by malaria infection vary depending on transmission patterns (stable vs. unstable), *Plasmodium* species (*P. falciparum* vs. others), and host immunity (related to age, transmission intensity, nutritional status, and HIV infection). At its most symptomatic, malaria causes acute febrile syndromes that may be complicated by seizures, coma, renal failure, and/or death. The clinical spectrum of malaria also includes chronic, often severe, anaemia in the otherwise asymptomatic person.^{vi} Although often undiagnosed until its later stages, malaria-related anaemia is associated with more fatalities than any other malaria-related syndrome.^{vii} Because of the great variation in malaria species and transmission patterns in the Caribbean region, predominant clinical syndromes will vary by site. Increased vigilance for anaemia is warranted in HIV-infected patients at risk for malaria (especially in those who have other risk factors for anaemia, such as AZT use), and clinical suspicion of malaria is warranted in the HIV-infected patient with unexplained anaemia or fever.

DIAGNOSIS

Although rapid tests for detection of *Plasmodium* species are currently being developed and evaluated, inspection of stained blood smears for the presence of malaria is still the standard means of diagnosis. Where multiple *Plasmodium* species are endemic, laboratory diagnosis should seek both to detect malaria and to classify the infecting species. Creation of new laboratory capacity may be required in some sites.

MANAGEMENT OF THE PATIENT WITH MALARIA AND HIV INFECTION

Malaria infection can be rapidly fatal, especially in non-immune patients. Therefore, prompt diagnosis and rapid administration of effective treatment must be easily available to patients where malaria is endemic. Appropriate treatment for malaria infection depends on several factors: the severity of infection; the responsible *Plasmodium* species (bearing in mind that mixed infections may occur); the pregnancy status of the patient; local antimalarial drug-resistance patterns; national drug policy and availability; and the likelihood of interactions or

overlapping toxicities involving antimalarials and other medications the patient may be taking, including ARV agents and other medications used in the management of AIDS and its complications. Clear treatment guidelines devised to respond to varying local conditions should be created at national (or regional) levels and should be updated frequently in response to changing drug-resistance and transmission patterns.

The differential diagnoses of fever and anaemia are broad in the HIV-infected patient. In order to avoid the unnecessary prescription (with resultant risks of toxicity and resistance) of antimalarials, it is important to encourage laboratory confirmation of malaria infection prior to treatment (other than prophylaxis in pregnancy) and to discourage patients from self-treatment with antimalarials where these agents are available without prescription.

INTERACTIONS BETWEEN MALARIA AND HIV

HIV infection appears to increase both the susceptibility to and the severity of malaria infection. Most of our understanding of the interaction between malaria and HIV comes from studies performed in Africa, primarily involving infection with *P. falciparum*.

International literature suggests that HIV-infected patients appear to be more susceptible to acquiring malaria infection,^{viii} particularly if they are pregnant. Both the prevalence of malaria parasitaemia and the incidence of clinical attacks of malaria are greater in patients with HIV-induced immunosuppression. Furthermore, the risks of severe malaria and malaria-related death appear to be increased significantly in HIV-infected patients of all ages who live in regions where malaria transmission is unstable.^{ix}

The influence of malaria on HIV infection is not as well characterised, but malaria infection appears to increase the HIV viral load, which could result in an increased rate of HIV disease progression as well as an increased risk of HIV transmission to others.^x

CONSIDERATIONS FOR PREGNANT PATIENTS WITH MALARIA AND HIV OR AT RISK FOR CO-INFECTION

Malaria infection is more common in pregnancy, especially in primigravidae and in the HIV-infected of any gravidity.^{xi} Although malaria in pregnancy is commonly asymptomatic, its consequences may include severe maternal anaemia, maternal death, and low infant birth weight, regardless of maternal HIV status. Infants born to HIV-infected mothers with malaria are more likely to die^{xii} and are approximately twice as likely to be infected perinatally with HIV if a high placental burden of malaria exists in the mother.^{xiii} Intermittent preventive treatment (IPT) with antimalarial agents (usually SP) during pregnancy improves pregnancy outcomes in regions of intense transmission of *P. falciparum*, probably by reducing maternal malaria parasitaemia and placental malaria burden. The WHO now recommends IPT for malaria in pregnancy in countries with high burdens of *P. falciparum* malaria.^{xiv}

IPT regimens are not yet well-defined in regions where *P. falciparum* is not the predominant strain of malaria, where transmission is infrequent, or where there are high levels of resistance to SP and chloroquine. Where the risk of malaria is low, WHO recommends aggressive management of symptomatic malaria cases and regular use of insecticide-treated bednets (ITNs), rather than IPT. The safety of many newer antimalarials has not yet been well-established for use in pregnancy.^{xv} Therefore, guidelines for treatment of symptomatic malaria in pregnancy may require frequent revision as new data become available.

Prophylactic co-trimoxazole (TMP-SMX) has been shown to reduce the prevalence of malaria parasitaemia and the incidence of symptomatic malaria in non-pregnant adults in some settings.^{xvi} Therefore, the WHO now recommends that preventive SP not be given to HIV-infected pregnant women who take daily TMP-SMX.^{xvii} However, no studies have yet demonstrated the effectiveness of daily TMP-SMX prophylaxis for prevention of malaria complications in pregnancy, and the eventual development of malaria resistance to TMP-SMX could limit the durability of this drug's usefulness for malaria prevention.

OTHER TREATMENT CONSIDERATIONS FOR PATIENTS WITH MALARIA AND HIV

SP Treatment in Patients Taking Daily TMP-SMX

As noted above, TMP-SMX has antimalarial activity with an efficacy similar to that of chloroquine or SP in some studies.^{xviii} Unfortunately, TMP-SMX and SP are chemically similar enough that clinically significant cross-resistance between the two agents is common. Hence, patients on prophylactic TMP-SMX probably should not be treated with SP for symptomatic malaria where better options exist. Some fear that cross-resistance could hasten the loss of SP as an effective antimalarial agent in regions where TMP-SMX use becomes widespread.^{xix,xx} However, as artemisinin-containing combination regimens supplant chloroquine and SP as first-line antimalarial agents, this issue may become less important.

Management of Fever in Children

Current WHO Integrated Management of Childhood Illness (IMCI) guidelines for malaria-endemic regions recommend presumptive treatment of fever in children age five years or younger. TMP-SMX is endorsed because of its effectiveness for treatment of both pneumonia and malaria.^{xxi} Where TMP-SMX is being used prophylactically in large populations over a long period of time, it may lose its efficacy in treating pneumonia, otitis, and malaria due to the development of drug resistance.^{xxii,xxiii} The introduction of new paediatric AIDS treatment initiatives may require revision of local IMCI algorithms.

Drug-Drug Interactions and Overlapping Toxicities

Some ARVs and antimalarials are known to have overlapping side effect profiles. For example, both nevirapine (NVP) and SP have been associated with Stevens-Johnson syndrome and hepatic necrosis.^{xxiv,xxv,xxvi} SP and AZT have both been associated with bone marrow suppression, and the manufacturers of pyrimethamine (PZA) note that severe anaemia may result from co-administration of PZA and AZT.^{xxvii} There is little published or anecdotal information on drug interactions between newer antimalarials and ARVs, although concerns about potential drug-drug interactions have been raised regarding the co-administration of lumefantrine or halofantrine with many protease inhibitors (PIs). Similar concerns exist regarding the co-administration of quinine or atovaquone with various PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs).^{xxviii} Increased vigilance for adverse drug reactions is advisable when treating malaria in the patient who is also taking ARVs.

PREVENTION CONSIDERATIONS

Use of ITNs prevents malaria-related morbidity and mortality.^{xxix} ITN use is strongly recommended by the WHO and others for children age five years or younger and pregnant women in areas where malaria is endemic.^{xxx} In malaria-endemic regions, ITN use should also be recommended to all HIV-infected persons. Where feasible, indoor residual spraying of insecticides should also be considered to prevent malaria transmission.

POLICY RECOMMENDATIONS

In malaria-endemic regions, management guidelines and policies must be based upon regional incidence, prevalence, and transmission patterns, as well as patterns of antimalarial drug resistance. Where these data do not exist, efforts should be made to collect them. Close collaboration between national and regional malaria and HIV control programs is essential for effective, evidence-based policy making. This collaboration will be especially critical in developing diagnostic and management guidelines for HIV-infected persons who develop febrile syndromes and/or anaemia, and for HIV-infected pregnant women who are simultaneously eligible for prophylactic antimalarial regimens and long-term ART. Because of the paucity of available information on drug interactions involving newer antimalarial drugs, ARVs, and other medications involved in management of AIDS, pharmacovigilance directed toward detection of drug interactions involving these agents is also strongly advised.

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