Malaria

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Epidemiology

Malaria continues to contribute disproportionately to the global burden of infectious diseases, especially in sub-Saharan Africa and Southeast Asia. The World Health Organization (WHO) estimated that 80 countries had ongoing malaria transmission in 2024; of the estimated 282 million cases in 2024, approximately 245 million (94%) occurred in Africa, where HIV is the most prevalent globally.[1] Approximately 610,000 deaths were attributable to malaria in 2024, with the majority of those deaths in children younger than 5 years of age. Five countries in Africa (Nigeria, the Democratic Republic of the Congo, Uganda, Ethiopia, and Mozambique) accounted for nearly half of all malaria cases worldwide.[1]

Malaria is transmitted by the bite of an infected female *Anopheles spp*. mosquito. Reports of perinatal transmission and infection after blood transfusion or organ transplantation do exist, but these routes of transmission are uncommon, particularly in nonendemic areas.[2-6]

In humans, malaria can be caused by any one of six species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale curtisi*, *Plasmodium ovale wallikeri*, *Plasmodium malariae*, and *Plasmodium knowlesi* (a zoonotic species that also infects macaques in Southeast Asia and can cause severe disease).[6] *P. vivax* occurs in a wider geographic distribution,[7] accounting for the majority of cases in the Americas and nearly half of cases in India, but less than 10% of all malaria infections globally.[8-10] Although *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections, *P. vivax* can also cause severe disease and should not be disregarded as a risk for travelers, especially those from Latin America and Asia.[11]

People born in endemic areas who now live in the United States can develop malaria because of distant exposure before their arrival (particularly if infected with the relapsing strains *P. vivax* or *P. ovale* species, or with the late-presenting *P. malariae*), or as a result of more recent travel to endemic areas.[12-15] The absence of appropriate chemoprophylaxis is a common factor for malaria acquisition among travelers.[16,17] People who formerly lived in malaria-endemic areas may assume that they are immune and therefore do not need to take prophylaxis when traveling to an endemic area.[18] However, such people are at high risk of infection because they likely have diminished immunity within 6 months after leaving endemic regions. Although locally acquired cases of malaria in the United States are extremely rare, four states reported autochthonous cases in 2023.[19-21]

Consideration of malaria in returning travelers or recent immigrants who are febrile is critical to reducing morbidity and mortality.[22,23] Of the nearly 80 million individuals who travel from high to low- and middle-income countries each year, between 5% and 11% develop a fever during or after travel.[24-27] Malaria is a common cause of these fevers.[28]

Clinical Manifestations

People with malaria can exhibit various symptoms and a broad spectrum of severity, depending upon factors such as the infecting species and level of acquired host immunity. Partial acquired immunity

to malaria can occur after repeated exposure, though complete sterilizing immunity does not occur. In endemic regions, this can lead to lower risks of severe disease with repeated exposure. However, such immunity can be lost after leaving endemic areas. People with HIV who are immunosuppressed and reside in endemic areas can similarly lose acquired malarial immunity, and adults with HIV who are immunocompromised with little or no previous malaria exposure (e.g., travelers) may be at increased risk of severe outcomes.[29-32]

The incubation period for *P. falciparum* is typically 7 to 30 days, and rarely longer. Malaria symptoms can present later (>30 days to >1 year), but this pattern is more common with other species, especially *P. vivax*. In 2018, 99% of U.S. travelers with *P. falciparum* fell ill before or within 90 days of return, whereas 40% of those with *P. vivax* or *P. ovale* species fell ill 90 days or more following their return.[6] In nonimmune patients, typical symptoms of malaria include fever, chills, myalgia and arthralgia, headache, diarrhea, vomiting, and other nonspecific signs. Splenomegaly, anemia, thrombocytopenia, pulmonary or renal dysfunction, and neurologic findings also may be present. Classically, paroxysmal fevers occur every 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale* species, and every 72 hours for *P. malariae*. However, people with malaria often present with no pattern of fevers. *P. knowlesi*, known to cause human infection in Southeast Asia in travelers to jungle/forested areas, has a 24-hour life cycle, is clinically indistinguishable from other species of malaria, and although the large majority (~80%–90%) of affected people present with uncomplicated disease, severe disease is possible.[33,34]

Uncomplicated malaria infection can progress to severe disease or death within hours. Malaria with central nervous system symptoms such as seizures or altered mental status can be particularly ominous. Cerebral malaria refers to unarousable coma not attributable to any other cause in patients infected with *P. falciparum*; case fatality rates can approach 20% in adults, even with treatment.[35,36] The risk of severe and complicated illness is increased in people with high levels of parasitemia and without partial immunity.[37] Metabolic acidosis is an important manifestation of severe malaria and an indicator of poor prognosis.[38] Other acute complications include acute kidney injury, hypoglycemia, severe malarial anemia, disseminated intravascular coagulation, shock, and acute pulmonary edema.[36] *P. falciparum* is the species most commonly responsible for severe disease and death, although the other species can cause severe disease and death as well.[39,40]

Effect of HIV on Parasitemia and Clinical Severity

Malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa, such that even modest interactions between them have public health importance.[41] HIV infection alters the natural history and severity of malaria; similarly, reciprocal effects of malaria on HIV have also been demonstrated.[42,43]

HIV impairs acquired immunity to malaria that is present in older children and both pregnant and nonpregnant adults in stable endemic areas. Large cohort studies have demonstrated increased frequency (with rates one- to twofold higher) of both parasitemia and clinical malaria in adults with HIV,[29] including a higher risk of severe malaria.[30,31,44,45] In 2021, a meta-analysis reported that the odds of severe malaria were significantly higher in adults with HIV than those without HIV (odds ratio [OR] 2.68; 95% confidence interval [CI], 1.52–4.73).[30] Pregnant women with HIV are at an increased risk of severe malaria, placental malaria, and both maternal and neonatal adverse effects.[46-49] Pregnant women with HIV also do not appear to benefit from parity-associated protection seen in pregnant women without HIV.[50]

In a prospective cohort study[51] in an area with unstable malaria transmission, nonimmune adults with HIV were found to be at increased risk of severe *P. falciparum* malaria compared to nonimmune adults without HIV, and the risk was associated with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3. In a multicenter cohort study in which >97% of malaria cases were due to *P. falciparum*, adults with HIV who were hospitalized for malaria were substantially more likely to die or require an intensive care unit admission than those without HIV.[52] In a substudy of a large multinational trial in endemic Africa, children with HIV presented more frequently with severe acidosis, anemia, and respiratory distress than children without HIV, with similar nonsignificant trends seen in adults.[29] With regards to *P. vivax*, a 4-year cohort study in the Brazilian Amazon found that HIV increased the risk of acquiring *P. vivax* infection approximately sixfold but did not alter the risk of hospitalization.[53]

In general, studies have demonstrated that the odds of clinical malaria and incidence of parasitemia rise with CD4 counts below 350 cells/mm^3 and 500 cells/mm^3.[44,45,54] In a cross-sectional study of travelers returning to France from malaria-endemic areas between 2000 and 2003, those with HIV who had CD4 counts <350 cells/mm^3 were at significantly higher risk of developing severe malaria compared with those without HIV and who had CD4 counts >350 cells/mm^3.[31] Collectively, the risk of severe disease and high-grade parasitemia are increased at CD4 counts <500 cells/mm^3 with a progressive escalation of disease severity below CD4 counts of 350 cells/mm^3. More recent studies have shown that the risk of malaria for people with HIV who reside in endemic settings is significantly reduced with effective antiretroviral therapy (ART) and trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis.[42,55,56] Very few studies examine the prevalence of malaria in people with HIV on ART. Two studies show a decrease in malaria prevalence in people with HIV receiving ART compared to those who are antiretroviral naive.[56]

Effects of Malaria on HIV

Malaria infection in adults with HIV has been associated with transient CD4 cell declines as compared to those without HIV,[57,58] as well as transient rises in HIV-1 viral load for several weeks,[57,59,60] in some settings. Transient rises in viral load do not appear to affect the rate of HIV disease progression.

Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages[61] and increased viral load,[62] raising the possibility that placental malaria leads to increased perinatal HIV transmission. Fetal immune activation by malaria antigens may also increase susceptibility to HIV.[63] However, data are conflicting concerning the effect of malaria during pregnancy on the risk of perinatal transmission in the pre-ART era, and are limited since the widespread use of ART for prevention of perinatal transmission.[64-66] In 2020, a prospective observational study demonstrated that placental malaria was found to be associated with an increased risk of neonatal HIV transmission.[67]

Diagnosis

Recommendations for Diagnosing Malaria
• Malaria is life threatening. Therefore, a laboratory diagnosis should be made rapidly. • Microscopy remains the gold standard to diagnose malaria and can provide both speciation and quantification; expert microscopists are needed. • Although they are not quantitative, rapid diagnostic tests are point of care tests that can detect *Plasmodium falciparum* and non-falciparum species. However, sensitivity is lower for non-falciparum species than for *P. falciparum*.

A malaria diagnosis must be considered in all febrile patients who have traveled to or lived in malaria-endemic areas or who have received blood products, tissues, or organs from individuals who have been to such areas, irrespective of possible intercurrent infections, including HIV. Additionally, practitioners in the United States are advised to have a low threshold for testing for malaria in cases of fever of unknown origin, given reports of locally acquired *P. vivax* in Florida, Texas, and Arkansas, as well as *P. falciparum* in Maryland in 2023.[68]

Several diagnostic methods are available, including microscopic diagnosis, antigen detection tests, polymerase chain reaction–based assays, and serologic tests. Serologic tests that detect host antibodies are inappropriate for the diagnosis of acute malaria.

Direct microscopic examination of intracellular parasites on stained thick and thin blood films is the standard for definitive diagnosis in nearly all settings because it allows for identification of the species and parasite stage and provides a measure of parasite density. Microscopic diagnosis of *P. knowlesi* is difficult because it is commonly misidentified as *P. malariae*, which tends to follow a more benign course. Providers should have a high index of suspicion for *P. knowlesi* in travelers returning from Southeast Asia.[40]

In nonimmune people with all types of malaria, symptoms may develop in the setting of very low parasitemia. Microscopy (with or without concomitant rapid diagnostic testing) should be done immediately and, if negative, repeated at multiple 12- to 24-hour intervals to definitively rule out a malaria diagnosis. Urgent exclusion of malaria is indicated in all returned travelers from malaria-endemic areas who present with fever within 1 year of travel. Guidelines for laboratory diagnosis are summarized elsewhere and are available at Centers for Disease Control and Prevention (CDC) Malaria Evaluation and Diagnosis webpage. Rapid diagnostic tests are widely used in endemic settings, particularly for the diagnosis of *P. falciparum*, and can facilitate prompt diagnosis and treatment of infected patients but must be followed by microscopy. Currently, only the BinaxNOW rapid diagnostic test is approved by the U.S. Food and Drug Administration.[69] This test can detect *P. falciparum*, *P. vivax*, *P. ovale* species, and *P. malariae* but has a lower sensitivity for non-falciparum species—particularly for *P. knowlesi*—and cannot distinguish between the non-falciparum species.[70] The antigen target specific for *P. falciparum* detection, histidine-rich protein 2, has been deleted in some parasites circulating in several endemic regions, and if absent, may lower the sensitivity and specificity of BinaxNOW for detection of *P. falciparum*.[71]

Preventing Infection

Recommendations for Preventing Malaria
Preventing Malaria When Traveling to Endemic Areas[a] • Malaria prophylaxis recommendations are the same for people with HIV and those without and include personal protective measures to prevent mosquito bites, malaria chemoprophylaxis, and seeking care quickly if they fall ill while traveling or upon return from travel. • Specific chemoprophylaxis recommendations are based on region of travel, malaria risks, and drug susceptibility in the region. • Clinicians should refer to the CDC Yellow Book for the most up-to-date recommendations. • TMP-SMX has been shown to reduce malaria in adults with HIV who reside in Africa. However, it is not as effective as antimalarial prophylactic regimens. Therefore, travelers with HIV **should not** rely on TMP-SMX for prophylaxis against malaria (AIII). Preventing Malaria During Pregnancy When Traveling to Endemic Areas[a] • Women who are pregnant or likely to become pregnant should be advised to avoid traveling to malaria-endemic areas if possible (AIII). • If traveling to chloroquine-susceptible malaria-endemic areas is necessary, chloroquine is the drug of choice recommended for prophylaxis and can be used during all trimesters. • If traveling to chloroquine-resistant areas is necessary, mefloquine is recommended for travel during pregnancy.

[a] People with HIV who have low CD4 counts (especially if <350 cells/mm^3) and those who are pregnant should be made aware that they are at increased risk of severe malaria. Pregnant women with HIV should also be advised that malaria infection increases risk of miscarriage and fetal loss.

Key: CDC = Centers for Disease Control and Prevention; TMP-SMX = trimethoprim-sulfamethoxazole

Pre-travel evaluation by a travel medicine specialist can provide specific education about risk of exposure in various geographic locales, the utility of insecticide-impregnated bed nets and clothing in the setting where the individual will be traveling or residing, and the use of DEET (N,N-diethyl-3-methylbenzamide)-, picaridin-, or other insecticide-containing repellents (see CDC's Mosquitoes, Ticks, and Other Arthropods).

Infection with *P. falciparum* can be more severe in people with HIV who have low CD4 counts, especially in those who are not on ART or TMP-SMX prophylaxis, and in pregnant women regardless of HIV infection. Individuals with poorly controlled HIV or advanced HIV (i.e., CD4 count <200 cells/mm^3) may face increased risks of severe malaria when traveling. As such, during pre-travel assessment, people with HIV who have low CD4 counts (especially if <350 cells/mm^3) and those who are pregnant should be made aware that they are at increased risk of severe malaria should they get infected. This risk is reduced with strict adherence to chemoprophylaxis. Therefore, individuals with poorly controlled HIV or advanced HIV should be advised to consider delaying travel if possible, especially if they are unable to take preventive therapy **(AIII).** If travel to an endemic area cannot be deferred, strict adherence to malaria chemoprophylaxis is essential, along with careful attention to personal protective measures to prevent mosquito bites (see below). Additionally, individuals should be advised to rapidly seek care in case of a febrile illness while traveling or upon return from travel.

Preventing Disease—Antimalarial Chemoprophylaxis

For people traveling from the United States (including people with HIV) to endemic areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. Recommendations for prophylaxis are the same for those with HIV as for those without HIV **(AIII)** and are available at CDC's malaria website. The CDC provides specific recommendations for chemoprophylaxis based on geographic regions during travel, as well as mosquito avoidance through the use of insect repellants, loose-fitting long-sleeved shirts and pants, and bed nets (see CDC's Preventing Malaria While Traveling).

Significant drug–drug interactions (DDIs) may occur between prophylactic antimalarials and antiretrovirals (ARVs), and in particular, drug interactions that are underpinned by cytochrome P450 (CYP) induction or inhibition and/or QT interval prolongation are the most problematic. Specific drug interactions can be queried using the interactive web-based resource Liverpool HIV Drug Interactions database.

Malaria incidence has been markedly reduced in African adults with HIV who receive TMP-SMX prophylaxis.[72] An early study in Uganda demonstrated that malaria burden was reduced by 82% with TMP-SMX, subsequently reduced by another 61% when ART was provided, and finally reduced by another 40% with the provision of insecticide-treated nets.[56] More recent data in adults and children supports that TMP-SMX, alongside effective ART, continues to provide protection against malaria.[42,55,56,73] However, TMP-SMX is not as effective for malaria prophylaxis as the recommended antimalarials. Therefore, travelers with HIV **should not** rely on prophylaxis with TMP-SMX for chemoprophylaxis against malaria **(AIII).**

Treating Disease

Recommendations for Treating Malaria
Treating Malaria • Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all people who have confirmed or suspected *P. falciparum* infection should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to therapy (AIII). • When malaria is suspected, treatment should not be delayed while diagnosis is pursued if the patient is severely ill (AIII). • Treatment should also not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed (AIII). • When suspicion of malaria is low and the individual is not severely ill, antimalarial treatment can often be deferred until the diagnosis has been confirmed by laboratory investigations (AIII). • Treatment recommendations for people with HIV, regardless of CD4 count, are the same as for people without HIV (AIII). • Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the person's clinical status, and the antimalarial susceptibility profile of the local *Plasmodium* species. • For treatment recommendations for specific regions, clinicians should refer to: o CDC Clinical Guidance for Malaria o CDC Malaria Hotline: 770-488-7788; Monday through Friday, 8 a.m. to 4:30 p.m. ET. 770-488-7100 after hours.

Recommendations for Treating Malaria

Preventing Relapse

- Patients should be treated with standard antimalarials for malaria and, in addition, receive primaquine or tafenoquine to prevent relapse (AI).
- For those with normal G6PD levels, standard adult dosing (30 mg of primaquine base given daily for 14 days) should be administered (AI). For those with intermediate deficiency, consider giving primaquine at 45 mg (base) PO once per week for 8 weeks with close monitoring for hemolysis along with consultation with an expert in infectious disease and/or tropical medicine (BIII).
- Tafenoquine can only be given for anti-relapse therapy in those who have received chloroquine for treatment of the acute stage of malaria and are ≥16 years of age (AI). Tafenoquine is contraindicated for any degree of G6PD deficiency due to its long half-life and is contraindicated in pregnancy and lactation, as well as in those with psychosis. Primaquine is also contraindicated in pregnancy. Those unable to receive either primaquine or tafenoquine should be administered for weekly chloroquine (300-mg base) once a week for 1 year following treatment of the acute infection (BIII).

Pregnancy Considerations

Chloroquine-Sensitive Malaria

- For uncomplicated malaria caused by *P. malariae, P. ovale,* chloroquine-sensitive *P. vivax,* or chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended (AI).

Chloroquine-Resistant Malaria

- For uncomplicated chloroquine-resistant *P. vivax* or *P. falciparum* malaria, artemether-lumefantrine (preferred), quinine plus clindamycin (alternative), or mefloquine (alternative) is recommended (AI).

Severe Malaria

- Treatment with intravenous artesunate is recommended during all trimesters (AI).

Post-treatment Prophylaxis

- After treatment, all pregnant women with *P. vivax* and *P. ovale* should receive chloroquine prophylaxis for the duration of pregnancy to avoid relapses (AIII). Once-weekly mefloquine can be used for prophylaxis during pregnancy to treat malaria caused by *P. vivax* acquired in an area with chloroquine-resistant strains.
- Women who have normal G6PD screening tests can be treated with primaquine following delivery if not breastfeeding or the infant is known to be G6PD normal (AIII). Use of primaquine during breastfeeding depends on the G6PD status of the mother and infant. Tafenoquine is not recommended during breastfeeding.

Medications Not Recommended for Prophylaxis in Pregnancy

- Atovaquone/proguanil, doxycycline, and tafenoquine are not recommended for malaria prophylaxis during pregnancy or while breastfeeding or feeding with breastmilk.
- Primaquine is not recommended during pregnancy, even if maternal G6PD is normal due to unknown fetal G6PD status.

Key: CD4 = CD4 T lymphocyte; CDC = the Centers for Disease Control and Prevention; G6PD = glucose-6-phosphate dehydrogenase; PO = orally

Because *P. falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all persons with HIV who have confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment **(AIII).** Diagnosis prior to treatment should always be pursued; however, treatment should not be delayed when malaria is strongly suspected if the patient is severely ill **(AIII)** or when laboratory services are unavailable or results will be delayed **(AIII).** When suspicion

of malaria is low, and the individual is not severely ill, antimalarial treatment can often be deferred until the diagnosis has been confirmed by laboratory investigations **(AIII).**

The choice of treatment is guided by the severity of malaria infection; severe malaria requires intravenous (IV) artesunate, whereas uncomplicated malaria can be treated with oral therapy. Artemether-lumefantrine is approved by the U.S. Food and Drug Administration (FDA) as the preferred first-line treatment for uncomplicated malaria. The criteria of severe malaria should be reviewed in each case, and severe malaria is diagnosed based on the degree of parasitemia as well as clinical and laboratory findings. Selection of an antimalarial is based on the likely drug susceptibility of the infecting species (as determined by where the infection was acquired).

For people with HIV who acquire malaria infection, treatment recommendations are the same as for those without HIV, regardless of CD4 count **(AIII).** CDC publishes malaria treatment recommendations and has clinicians on call 24 hours to provide advice to health care providers on diagnosing and treating malaria (CDC Malaria Hotline: 770-488-7788; Monday through Friday, 8 a.m. to 4:30 p.m. EST. 770-488-7100 after hours).

Monitoring of Response to Therapy

Careful monitoring of people with malaria (especially those with *P. falciparum* malaria) is necessary, including measurement of peripheral parasitemia, both hemoglobin and blood glucose levels, and assessment of cerebral, pulmonary, and renal function. Frequency of monitoring depends on the severity of disease, a person's immune status, and the species of *Plasmodium* and does not differ for people with HIV. Additionally, to reduce the risk of relapse from dormant liver stage hypnozoites of *P. vivax* and *P. ovale* species, anti-relapse therapy (also known as radical cure; see Preventing Relapse below) with an 8-aminoquinoline medication (primaquine or tafenoquine) should be given.[74]

Preventing Relapse

Both *P. vivax* and *P. ovale* species can cause recurrence due to the dormant hepatic phase of infection (hypnozoite). Patients should be treated with standard antimalarials for malaria and, in addition, receive primaquine or tafenoquine to prevent relapse **(AI).** Guidelines for primaquine or tafenoquine treatment do not differ in individuals with HIV. The FDA approved tafenoquine for the prevention of *P. vivax* and *P. ovale* species relapse infections in 2018.[75] Primaquine has a short half-life (~6 hours) and is given daily for 2 weeks for relapse prevention, whereas tafenoquine has a long half-life (~12 days) and requires only a single dose.

Treatment with primaquine or tafenoquine can result in hemolysis if the patient has glucose-6-phosphate dehydrogenase (G6PD) deficiency. Therefore, G6PD deficiency should be screened for prior to the administration of primaquine or tafenoquine. G6PD deficiency is classified based on the level of residual enzyme activity in the red blood cells, and cut-offs for defining moderate and severe deficiency can vary by test and laboratory. For those with normal G6PD levels, standard adult dosing (30 mg of primaquine base given daily for 14 days) should be administered **(AI).** For those with intermediate deficiency, consider giving primaquine at 45 mg (base) PO once per week for 8 weeks with close monitoring for hemolysis along with consultation with an expert in infectious disease and/or tropical medicine **(BIII).**[76] Tafenoquine can only be given for anti-relapse therapy in those who have received chloroquine for treatment of the acute stage of malaria and are ≥16 years of age **(AI).** Tafenoquine **is contraindicated** for any degree of G6PD deficiency due to its long half-life and **is contraindicated** in pregnancy and lactation, as well as in those with psychosis. Primaquine **is also**

contraindicated in pregnancy. Those with G6PD deficiency who are unable to receive either primaquine or tafenoquine should be administered weekly chloroquine (300-mg base) once a week for 1 year following treatment of the acute infection **(BIII).**[76]

Special Considerations Regarding Antiretroviral Therapy Initiation

There is no reason to defer ART initiation after patients have recovered from acute malaria. No immune reconstitution inflammatory syndrome has been described in association with malaria.

Drug–Drug Interactions

Chemoprophylaxis or treatment for malaria in patients receiving ARV agents requires attention to potential drug–drug interactions. Several potential drug interactions can occur between antimalarial and HIV drugs, as well as other medications used to treat HIV-associated opportunistic infections (see Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines).[77,78] Providers are also encouraged to check for drug–drug interactions using Liverpool HIV Drug Interactions database.

Managing Treatment Failure

Individuals with HIV and CD4 counts <300 cells/mm^3 are at increased risk of recurrent parasitemia.[79] Management of treatment failure is the same in people with or without HIV, aside from considerations about drug interactions between ART and antimalarial drugs. Drug-resistant malaria, suboptimal adherence, drug–drug interactions, and possible concomitant infections should be considered in people with HIV whose malaria fails to respond to therapy. Partial resistance to the artemisinin component of artemisinin-based combination therapy (ACT) is widespread in Southeast Asia and increasingly reported in multiple countries in East Africa.[80-82] Testing for suspected drug-resistant malaria is not routinely available, and treatment with ACTs remains effective in most cases. If drug resistance is suspected, consultation with CDC Malaria Hotline is recommended.

Special Considerations During Pregnancy

Malaria during pregnancy can lead to disease in the pregnant woman as well as the placenta, which can be associated with intrauterine growth restriction, low birth weight, and increased infant mortality. In endemic areas, women acquire partial immunity with each pregnancy, reducing risks associated with malaria infection.[83,84]

Preventing Infection and Disease

Data are conflicting concerning the effect of malaria during pregnancy on the risk of perinatal transmission in the pre-ART era and are limited since the widespread use of ART for the prevention of perinatal transmission.[64-66] During pregnancy, malaria affects both the pregnant woman and her fetus. When acute malaria is developed during pregnancy in areas of unstable transmission, the consequences may include spontaneous abortion and stillbirth. In more stable transmission areas, pregnant women, particularly primigravidas, may lose some acquired immunity. Although malaria infections may continue to be asymptomatic, placental malaria may be acquired, contributing to intrauterine growth restriction, low birth weight, and increased infant mortality. Pregnant women are three times more likely to develop severe disease than nonpregnant women.[85] Infection with

P. falciparum during pregnancy can increase maternal risk of severe disease and anemia, as well as risk for stillbirth, preterm birth, and low birth weight.[85-87] Therefore, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible **(AIII).** If travel to an endemic area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

When traveling to chloroquine-susceptible malaria-endemic areas during pregnancy, chloroquine is recommended for prophylaxis and can be used during all trimesters. Mefloquine is recommended for travel to areas with chloroquine resistance during pregnancy. Atovaquone/proguanil, doxycycline, and tafenoquine **are not recommended** for malaria prophylaxis during pregnancy or while breastfeeding. Primaquine **is not recommended** during pregnancy even if maternal G6PD is normal due to unknown fetal G6PD status.

In malaria-endemic areas, the WHO recommends that pregnant women of all gravidities and regardless of HIV status be given antimalarial medicine at predetermined intervals, an approach termed intermittent preventive treatment of malaria during pregnancy (IPTp) to reduce disease burden in pregnancy, as well as adverse pregnancy and birth outcomes.[87,88] Sulfadoxine-pyrimethamine (SP) has been widely used for malaria chemoprevention during pregnancy; with the IPTp approach, SP is started as soon as possible in the second trimester (not before 13 weeks gestation) with a goal of at least three doses administered 1 month apart during pregnancy. In 2024, two studies showed that monthly administration of dihydroartemisinin–piperaquine, a long-acting ACT, significantly reduces malaria incidence in pregnant women with HIV living in endemic areas when given in addition to daily cotrimoxazole.[89,90]

Treating Disease

In the setting of pregnancy with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale* species, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended **(AI).**[91] During all trimesters with a diagnosis of uncomplicated malaria due to chloroquine-resistant *P. falciparum* or *P. vivax*, treatment with an ACT (preferably artemether-lumefantrine) is preferred,[92] with quinine plus clindamycin, or mefloquine (least preferred) as alternatives **(AI).**[88,93] For severe malaria, treatment with IV artesunate is recommended during all trimesters **(AI).**[93,94] Previously artemether-lumefantrine was recommended in the second and third trimesters of pregnancy for malaria treatment, but after re-evaluation of available evidence, this recommendation has been expanded to all trimesters of pregnancy in line with WHO recommendations.[88]

Although quinine at high doses has been associated with an increased risk of birth defects (especially deafness) in some animal species and humans, use of therapeutic doses in pregnancy is considered safe.[95,96] Because of the potential for hypoglycemia, glucose levels should be monitored in pregnant women treated with quinine and their neonates. Clindamycin use has not been associated with birth defects. Animal and human data on the use of prophylactic and treatment doses of mefloquine do not suggest teratogenicity and the drug can be used safely during all trimesters.[93]

Although experience is limited, available data on artemether-lumefantrine during pregnancy suggest that use is not associated with increased adverse events or birth defects.[97] A systematic review and meta-analysis of 19 studies reporting 4,968 episodes of uncomplicated malaria in pregnant women receiving artemisinin-based and quinine-based treatments—including 33 (0.7%) episodes in the first

trimester—demonstrated no adverse pregnancy-related safety or tolerability outcomes.[98] A pharmacokinetic study in people without HIV found no difference in artemether-lumefantrine levels between pregnant and nonpregnant subjects except for small differences in the elimination half-life of lumefantrine.[99] Data on pharmacokinetics during pregnancy with HIV were not included.[89,90]

Because of limited data, atovaquone-proguanil **is not recommended** for treatment in pregnancy and should be used only if an ACT, quinine plus clindamycin, or mefloquine are unavailable or not tolerated.[96] Tetracyclines **are not recommended** in pregnancy due to an increased risk of maternal hepatotoxicity and staining of fetal teeth and bones. For those with HIV, artesunate-SP is not a suitable ACT for treatment if TMP-SMX is used for prophylaxis.[88,92,100,101]

For pregnant women with either *P. vivax* or *P. ovale* species, treatment of dormant hypnozoites is also needed to prevent relapse. However, neither primaquine nor tafenoquine use is recommended during pregnancy because of potential toxic effects on the fetus. Therefore, following treatment of the initial infection with *P. vivax* and *P. ovale* species, chloroquine prophylaxis should be administered for the duration of pregnancy to avoid relapses **(AIII).** Women who have normal G6PD screening tests can be treated with primaquine following delivery if not breastfeeding or the infant is known to be G6PD normal **(AIII).** Use of primaquine during breastfeeding depends on the G6PD status of the mother and infant. Tafenoquine **is not recommended** during breastfeeding.

Based on extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria during pregnancy. For travel to regions with chloroquine-resistant malaria, mefloquine (administered once weekly) is currently the only medication recommended for prophylaxis.[102] Of note, one randomized trial of mefloquine used with daily cotrimoxazole for malaria prophylaxis in pregnant women on ART (most of which were nevirapine-based regimens) demonstrated an increased risk of perinatal HIV transmission in the mefloquine arm, potentially because of drug interactions.[103]

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