Preventing Malaria in HIV-Infected Pregnant Women

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(See the Major Article by Klement et al on pages 651–9.)

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Efforts to curb or eliminate malaria incidence in areas with a high prevalence of human immunodeficiency virus (HIV) face many challenges, chief among which are inconsistent access to proven interventions and limited resources of prevention and control programs. These challenges are compounded by the fact that HIV and malaria interact synergistically, with HIV increasing the risk and severity of clinical malaria and malaria increasing the viral load and hence transmission of HIV [1]. Coinfection with malaria and HIV is of special concern for pregnant women. In sub-Saharan Africa, where more than three-quarters of the world’s HIV-infected women reside, an estimated 30 million women are at risk of acquiring Plasmodium falciparum malaria every year [2]. Coinfection during pregnancy impairs both maternal and newborn health outcomes. HIV-infected pregnant women are at increased risk of parasitemia and clinical malaria throughout their pregnancy, and this increased risk is particularly apparent in multiparous women who in the setting of HIV infection do not develop the parity-dependent antimalarial immunity typically observed in areas of high malaria transmission. Coinfected women are also at increased risk of developing severe anemia and placental malaria. Placental malaria and HIV coinfection has been shown to predispose to higher rates of neonatal mortality, preterm delivery, low birth weight, and, in some settings, increased risk of mother-to-child transmission of HIV [3, 4], highlighting the critical need for evaluation and delivery of effective prevention strategies.

Prevention of malaria in HIV-infected pregnant women in areas of stable malaria transmission currently relies upon a combination of insecticide-treated bednet (ITN) use, intermittent preventive therapy with sulfadoxine-pyrimethamine (IPT-SP), and prompt management of clinical malaria episodes and anemia. ITNs and IPT-SP have been shown to be highly efficacious in preventing malaria among pregnant women, but coverage levels for both interventions have been inadequate, despite high attendance at antenatal care centers [5]. Alarmingl, IPT coverage rates appear to be lowest in regions of high-intensity malaria transmission. The World Health Organization (WHO) recently released new guidelines simplifying and reinforcing their recommendation to give IPT-SP to all pregnant women not on co-trimoxazole (CTX) prophylaxis in an effort to improve coverage [6]. WHO currently recommends a daily double-strength tablet of CTX (800 mg sulfamethoxazole + 160 mg trimethoprim) for all HIV-infected pregnant women who meet adult eligibility criteria to prevent opportunistic infections [7, 8]. In previous studies, CTX was found to be efficacious in preventing clinical malaria [9, 10], leading to the hypothesis that CTX could serve as an alternative to IPT-SP. However, efficacy relative to standard IPT, toxicity, and birth outcomes associated with CTX chemoprophylaxis for P. falciparum have not been adequately assessed in HIV-infected pregnant women [11].

In this issue of Clinical Infectious Diseases, Klement and colleagues report the results of a randomized noninferiority trial conducted in Togo comparing the effect of daily CTX vs IPT-SP on the risk of maternal malaria, parasitemia, placental malaria, anemia, and birth outcomes among HIV-infected pregnant women [12]. In the study, 126 women were randomly assigned to receive daily CTX and 124 to receive IPT-SP in an area of high P. falciparum transmission. Over the course of the study, there was no significant difference in malaria incidence rate during pregnancy between the 2 groups; however, CTX prophylaxis failed to reach...
the prespecified criterion for noninferiority to gold standard IPT-SP. A trend toward increased asymptomatic parasiteemia was found in the IPT-SP group, but there was no significant difference in risk and severity of placental malaria or birth outcomes.

This study raises challenging questions regarding the use of CTX to prevent malaria in HIV-infected pregnant women. Is there sufficient evidence to consider CTX as a first-choice malaria prophylactic in this population? Although the study could not demonstrate noninferiority to IPT-SP, it is noteworthy that the point estimate of difference in malaria rates between the 2 arms lies within the noninferiority margin; hence, a larger sample size might have allowed demonstration of noninferiority. All other outcomes appeared to be similar between the 2 study arms, supporting the notion that CTX effectively prevents malaria in HIV-infected pregnant women. It is important to note that, despite randomization, there were significant baseline differences between the groups in CD4 cell count and proportion of women undergoing antiretroviral therapy. These discrepancies complicate the interpretation of the results, as baseline differences may have altered susceptibility to \textit{P. falciparum} infection and risk of anemia. Nonetheless, the results provide a compelling argument for the consideration of CTX as a viable alternative to IPT-SP for the prevention of malaria in HIV-infected pregnant women, particularly in settings where high IPT-SP coverage is difficult to achieve or is inaccessible.

It has been known for some time that CTX, in addition to providing empiric prophylactic coverage for opportunistic infections in HIV patients, has antimalarial activity \cite{11}. Both CTX and SP act via interception of the folate synthesis pathway: trimethoprim and pyrimethamine both target dihydrofolate reductase (DHFR), and sulfamethoxazole and sulfadiazine target dihydropteroate synthase (DHPS). The antimalarial activity of CTX raises the attractive possibility of repurposing the relatively accessible and inexpensive CTX for malaria prophylaxis in addition to opportunistic infection prevention. The WHO guidelines recommend that women on CTX not receive IPT-SP due to the increased risk of toxicity seen with coadministration of these drugs \cite{13}. However, if HIV and malaria programs do not communicate, it is possible that many women receive both CTX and IPT-SP. How often does this occur, and how can programs work together to ensure women do not receive both? These are important questions, and it is important that HIV control programs work with national malaria control programs, reproductive health programs, and birth defects programs to ensure consistency across program guidelines and documents, particularly as these are updated in response to the new WHO policy.

One issue related to efficacy that was not addressed in this study, but which should be addressed, is the effect of high-dose folic acid, which is commonly, but inappropriately, administered to pregnant women in place of the WHO-recommended 0.4 mg/day dose \cite{14}, on the efficacy of CTX prophylaxis. It has been shown that high-dose folic acid (5 mg/day) diminishes the efficacy of IPT-SP \cite{15}. It stands to reason that the same is likely true of CTX, regarding prevention of malaria, although this requires investigation.

Another important issue to consider is the safety of CTX use during pregnancy. In this study, CTX and IPT-SP were found to have a comparable safety profile. The study did find an increased rate of maternal anemia and opportunistic infections in the CTX group, but this may have been related to lower CD4 cell counts in the CTX group at baseline. One case of polydactyly was found in each group, but no other congenital abnormalities were reported. Although trimethoprim use during the first trimester has been associated with an increased risk of neural tube and other defects \cite{16, 17}, among HIV-infected women, provision of CTX during pregnancy has been shown to reduce preterm delivery and neonatal mortality \cite{18}. Given the proven benefits, the WHO guidelines on CTX use state that when CTX is indicated for HIV-infected women, the benefits outweigh the risks and it should be given, regardless of the stage of pregnancy \cite{7}. Case-control studies within a birth defects surveillance system may be the best approach to assess the risk of congenital defects potentially associated with CTX; such surveillance systems are currently under development in Malawi and Uganda.

Finally, the shared mode of action of CTX and IPT-SP raises concerns regarding selection of DHFR and DHPS mutations that confer antifolate drug resistance. As rates of antifolate drug resistance continue to increase, will both CTX and IPT-SP become less effective? Data from previous studies suggest that CTX does not commonly select for SP-resistant parasites, and in most settings it appears that concerns regarding selection of SP resistance are outweighed by the clear benefits of CTX prophylaxis \cite{9}. Ongoing monitoring of this issue is critical. Studies like the one by Klement and colleagues are crucial to developing effective guidelines that will ensure the intelligent, safe, and cost-effective use of existing interventions, and should inspire further inquiry and discussion on how to best prevent the adverse consequences of malaria in HIV-infected pregnant women and their newborns.

**Note**

**Potential conflicts of interest.** All authors: No reported conflicts.

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