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Exploring secure pathways: finding the most reliable malaria prophylaxis strategies for pregnant women with HIV

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Abstract

Malaria in pregnant women, particularly those infected with HIV, poses significant health risks, including adverse maternal and neonatal outcomes. This perspective examines various prophylactic strategies, emphasizing recent clinical trial findings on the efficacy and safety of newer antimalarial drugs. Sulfadoxine-pyrimethamine (SP) has been a conventional choice for intermittent preventive treatment during pregnancy (IPTp). However, its effectiveness is compromised due to its interaction with cotrimoxazole (CTX), a medication frequently used for individuals with HIV. This interaction limits it's utility. Recent research emphasizes the promise of dihydroartemisinin-piperaquine (DP) as an effective alternative, given its prolonged half-life and robust safety profile, including among HIV-infected pregnant women in regions with minimal malaria transmission. While DP did not notably lower the incidence of placental malaria, it effectively reduced the occurrence of clinical malaria and overall Plasmodium falciparum infections, indicating its potential to improve maternal health in endemic areas. Mefloquine (MQ), another alternative, though effective, is associated with severe side effects and increased HIV transmission risks, highlighting the need for cautious implementation. This narrative underscores the complexities of managing malaria prophylaxis in this vulnerable population, urging a tailored approach based on regional epidemiology and resistance patterns. The integration of these findings into health policies could significantly improve outcomes for mothers and newborns in sub-Saharan Africa, where malaria and HIV prevalently intersect. The ongoing adaptation of these interventions is critical to addressing the dynamic challenges of co-infections in pregnancy, ensuring effective and safe treatment pathways.

Keywords: *dihydroartemisinin-piperaquine, HIV-infected pregnant women, malaria prophylaxis, cotrimoxazole, mefloquine*

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Evidence in Context

• Assesses prophylaxis effectiveness, noting adverse outcomes for mother and child. • Highlights reduced efficacy of Sulfadoxine-pyrimethamine (SP) due to cotrimoxazole interactions. • Identifies Dihydroartemisinin-piperaquine (DP) as a safer, effective alternative. • Notes Mefloquine's severe side effects and HIV transmission risks. • Urges region-specific strategies and health policy integration.

To view Article

Introduction

Malaria at the time of pregnancy can cause several adverse outcomes for both mother and newborn, including spontaneous abortions, stillbirths, restricted fetal growth, premature births, low birth weight, maternal anaemia and even leading to death of newborns in certain cases [1]. A meta-analysis conducted in 2022 revealed that, on average, 32.3% of pregnant women with HIV in the Sub-Saharan Africa region were affected by malaria [2]. Thus the integration of effective malaria prophylaxis strategies for HIV-infected pregnant women becomes critical due to the high prevalence and compounded health risks posed by both malaria and HIV [3].

In areas where malaria transmission is continuous, The World Health Organization advises the use of nets treated with insecticides and the intermittent administration of preventive treatment during pregnancy (IPTp) along with sulfadoxine-pyrimethamine (SP). This treatment should begin in the second trimester and be provided during antenatal care visits [4]. Additionally, in environments where bacterial infections or malaria are prevalent, as of now daily cotrimoxazole prophylaxis (CTX) is advised for pregnant women with HIV to prevent opportunistic infections [5]. The increasing resistance of the malaria parasite to CTX is compromising its effectiveness. In 2017, the World Health Organization stated that in regions with a high level of resistance, the daily unmonitored use of co-trimoxazole offered only limited protection against malaria for pregnant women who are HIV-positive. This underscores the need to explore new approaches to prevent malaria during pregnancy [6]. On the other hand, considering the use of Intermittent Preventive Treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), which is typically administered to pregnant women without HIV, is not advisable for women on cotrimoxazole (CTX) prophylaxis. This is due to the potential risks associated with combining two similar types of antimicrobial drugs—antifolates and sulfonamides [7]. This creates a significant concern as women most vulnerable to malaria cannot use IPTp with SP, leaving them at high risk. To address these problems, many trials have been done to check how well malaria prophylaxis drugs work and their side effects in pregnant women with HIV who are on CTX prophylaxis. However very few strategies have come in recent years and most could not effectively and safely reduce the impact of malaria on this vulnerable population, enhancing health outcomes and influencing policy shifts in regions where malaria is endemic. Table 1 cites clinical trials on various malaria prevention strategies for pregnant women with HIV from 2012 to 2024. This article further delves deeper into significant trials that have produced reliable results.

Efficacy and Tolerability of Mefloquine (MQ) in HIV-Positive Pregnant Women

In a research study with a placebo group carried out in Kenya, Mozambique, and Tanzania, adding MQ to the daily CTX regimen for pregnant women significantly enhanced malaria protection and overall health of mothers. This was evident from the reduced number of hospital visits [8]. However, MQ was associated with increased risks of HIV transmission from mother to child and was generally poorly tolerated, with notable side effects such as dizziness and vomiting. Studies comparing IPTp treatments in four countries found that both MQ and SP had similar effects on low birth weight, but MQ was more effective in reducing parasitemia, anemia, clinical malaria, and outpatient visits, though it was less well-tolerated with higher instances of dizziness and vomiting [9]. The open-label design may affect the reliability of the safety assessments. The effectiveness of CTX alone versus MQ-IPTp showed that while CTX alone protected against malaria effectively, MQ-IPTp was superior in preventing placental infections [10]. In a study involving both HIV-positive and negative pregnant women, side effects like dizziness and vomiting were common with mefloquine IPTp; however, these adverse reactions occurred less frequently in HIV-infected participants. The likelihood of experiencing these side effects increased with factors such as a detectable viral load, initial dose of MQ, older age, and higher educational level. Despite these challenges, adherence to MQ IPTp remained high among the participants [11]. While MQ is more effective in preventing malaria compared to CTX, its adverse effects are concerning. Therefore, its application in HIV-positive pregnant women needs careful evaluation, with a focus on identifying safer options. Furthermore, the existing data doesn't provide a definite path for required modifications in policy.

Efficacy of Dihydroartemisinin-piperaquine (DP) in HIV-Positive Pregnant Women

Among many Dihydroartemisinin-piperaquine (DP) has stood out as one of the most promising

Antimalarial drug candidates due to its long half-life that allows for monthly IPTp dosing. Even though it's not the primary treatments for malaria in sub-Saharan Africa, it's generally well accepted [12]. Studies have shown that when used as IPTp in women who do not have HIV, DP is effective in preventing malaria and has a strong safety record [13,14]. A recent study among pregnant women with HIV in areas of low malaria transmission found that adding IPTp with DP to CTX prophylaxis did not decrease parasitemia at the time of delivery. However, this approach was secure and linked with a reduced rate of clinical malaria and total Plasmodium falciparum infections [14]. Research conducted in Kenya and Malawi showed that adding a monthly preventive treatment with DP to daily unsupervised co-trimoxazole, particularly in areas with high antifolate resistance, greatly improves malaria prevention in pregnant women with HIV who were following a dolutegravir-based cART regimen [15]. Considering the facts taken from two RCT's [14,15] it can be said that DP, added to standard prophylaxis, offers a safe method to reduce clinical malaria among HIV-infected pregnant women in low-transmission regions. However, its impact on reducing placental malaria is limited, potentially due to the low prevalence of the disease. Therefore, its use should be tailored based on regional malaria epidemiology and resistance patterns. The results are highly promising and should lead to a significant policy shift that would enhance maternal and newborn health in Africa. Research has shown that combining DP with CTX is not only safe and prevents instances of malaria during pregnancy, but it is also well accepted by pregnant women. This acceptability is crucial when a drug is used for preventative purposes, allowing for the true effectiveness of the intervention to be observed.

Conclusions

There exist complexities and challenges in managing malaria in HIV-infected pregnant women through various prophylactic strategies and clinical trials. While traditional treatments like SP face limitations due to potential adverse interactions with other drugs like cotrimoxazole (CTX), alternative medications such as mefloquine (MQ) present viable options despite their own set of challenges, including tolerability and effectiveness issues. Additionally, newer drugs like dihydroartemisinin-piperaquine (DP) offer promise due to their efficacy and safety profiles, although their implementation might vary based on regional malaria transmission rates and antifolate resistance. The integration of these findings into public health policies requires careful consideration of local malaria prevalence, antimalarial resistance patterns, and HIV status prevalence. Furthermore, the studies underscore the necessity for ongoing research to refine treatment protocols that maximize health outcomes for both mother and child without worsening HIV transmission or drug resistance. Ultimately the goal is to support the development of nuanced health policies that can adapt to the evolving landscape of co-infections in pregnancy, ensuring that vulnerable populations receive the most effective and safe interventions available.

Table 1 - Clinical studies on various malaria prevention methods for pregnant women over the last 15 years

Study	Study Characteristics	Interpretation - Main findings
Denoeud-Ndam et. al., 2012 [11]	This study involved a comparison between 103 HIV-positive women from the PACOME trial and 421 HIV-negative women. The aim was to assess the performance and acceptability of MQ IPTp (15 mg/kg). The investigation centered on examining the negative reactions and identifying the elements that impact these reactions using multilevel logistic regression.	MQ IPTp often led to dizziness and vomiting, though less so in women with HIV. Adverse reactions were linked to viral load, first use, age, and education level. Using antiretrovirals with MQ intensified reactions.
Klement et. al., 2013 [16]	From 2009 to 2011, a trial in Togo randomized HIV-positive pregnant women to receive CMX or IPT-SP. The study aimed for pregnancies without malaria and measured indicators like malaria occurrence, parasitemia, placental malaria, anemia, and infant birth weight.	In the research conducted in Togo, IPT-SP outperformed CMX in maintaining malaria-free conditions among women, but both failed to meet the non-inferiority standards. CMX was linked to a decrease in parasitemia rates, an increase in severe anemia, and comparable levels of placental malaria and birth weights.
Mofenson et. al., 2014 [9]	This study included 1,071 HIV-positive women from Kenya, Mozambique, and Tanzania, the women were randomly selected to receive either three doses of IPTp-MQ (15 mg/kg) or a placebo. These were given at minimum one-month intervals. Furthermore, all the women received CTX prophylaxis and a long-lasting insecticidal net (LLITN).	Women given MQ IPTp (15 mg/kg) with insecticide-treated nets had rates of low birth weight akin to those who received SP IPTp. Yet, fewer instances of clinical malaria were observed in the MQ treated group. Pregnancy outcomes and safety profiles showed similarity in both groups. However, MQ showed less tolerance, even with a two-day dose division.
Denoeud-Ndam et. al., 2014 [10]	In Benin, two studies evaluated HIV-positive women using CTX and MQ-IPTp. One study, where CTX was required, involved women with CD4 counts less than 350/mm³. The other, where CTX was not required, included women with CD4 counts greater than 350/mm³. Both focused mainly on microscopic placental parasitemia.	CTX on its own was as effective as other treatments in preventing placental parasitemia, but the addition of MQ reduced its occurrence. The trial where CTX was not required did not have enough data for a clear conclusion. MQ led to increased instances of dizziness and vomiting, but no severe negative events were associated with either treatment.
González et. al., 2024 [14]	In thissS double-blind, placebo-controlled trial HIV-positive pregnant women up to 28 weeks gestational age received either IPTp with DP plus daily CTX or placebo plus CTX. The study aimed to assess malaria parasitaemia at delivery and track safety and pregnancy outcomes.	Between 2019 and 2021, a study involving 666 HIV-positive pregnant women in Gabon and Mozambique found that IPTp with DP significantly reduced the incidence of clinical malaria and overall malaria infections during pregnancy compared to placebo, with no increase in serious adverse events or poor pregnancy outcomes.
Barsosio et. al., 2024 [15]	In Kenya and Malawi, a randomized trial tested malaria prevention in pregnant women with HIV using DP versus placebo, alongside standard CTX. Results focused on Plasmodium infection rates from first dose to delivery, assessed through various diagnostic methods.	The trial showed that adding DP to CTX significantly reduced malaria infection rates during pregnancy, with minimal risk increase in adverse events. Similar incidences of serious events and adverse pregnancy outcomes were observed by both groups.

Supporting information

None

Ethical Considerations

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References

1. Desai M, Hill J, Fernandes S, Walker P, Pell C, Gutman J, et al. Prevention of malaria in pregnancy. Lancet Infect Dis. *2018;18(4):e119-e32 [Crossref][PubMed][Google Scholar]*

2. Mirzohreh S-T, Safarpour H, Pagheh AS, Bangoura B, Barac A, Ahmadpour E. Malaria prevalence in HIV-positive children, pregnant women, and adults: a systematic review and meta-analysis. Parasit Vectors. *2022;15(1):324 [Crossref][PubMed][Google Scholar]*

3. Flateau C, Le Loup G, Pialoux G. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. Lancet Infect Dis. *2011;11(7):541-56 [Crossref][PubMed][Google Scholar]*

4. World Health O. Intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP): updated WHO policy recommendation. Geneva: World Health Organization; 2012 2012. *Contract No.: WHO/HTM/GMP.2012.05 [Crossref][PubMed][Google Scholar]*

5. World Health O. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, 2nd ed. 2016. *[Crossref][PubMed][Google Scholar]*

6. WHO. Meeting report of the Evidence Review Group on malaria in pregnancy. 2017. *[Crossref][PubMed][Google Scholar]*

7. González R, Sevene E, Jagoe G, Slutsker L, Menéndez C. A Public Health Paradox: The Women Most Vulnerable to Malaria Are the Least Protected. (1549-1676 (Electronic). *[Crossref][PubMed][Google Scholar]*

8. González R, Mombo-Ngoma G, Ouédraogo S, Kakolwa MA, Abdulla S, Accrombessi M, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. (1549-1676 (Electronic)). *[Crossref][PubMed][Google Scholar]*

9. Mofenson LM, González R, Desai M, Macete E, Ouma P, Kakolwa MA, et al. Intermittent Preventive Treatment of Malaria in Pregnancy with Mefloquine in HIV-Infected Women Receiving Cotrimoxazole Prophylaxis: A Multicenter Randomized Placebo-Controlled Trial. PLoS Med. *2014;11(9) [Crossref][PubMed][Google Scholar]*

10. Denoeud-Ndam L, Zannou D-M, Fourcade C, Taron-Brocard C, Porcher R, Atadokpede F, et al. Cotrimoxazole Prophylaxis Versus Mefloquine Intermittent Preventive Treatment to Prevent Malaria in HIV-Infected Pregnant Women. JAIDS J Acquir Immune Defic Syndr. *2014;65(2):198-206 [Crossref][PubMed][Google Scholar]*

11. Denoeud-Ndam L, Clément M-C, Briand V, Akakpo J, Agossou VK, Atadokpédé F, et al. Tolerability of Mefloquine Intermittent Preventive Treatment for Malaria in HIV-Infected Pregnant Women in Benin. JAIDS J Acquir Immune Defic Syndr. *2012;61(1):64-72 [Crossref][PubMed][Google Scholar]*

12. World Health O. WHO Guidelines for malaria. 2023. *[Crossref][PubMed][Google Scholar]*

13. Kakuru A, Jagannathan P, Muhindo MK, Natureeba P, Awori P, Nakalembe M, et al. Dihydroartemisinin–Piperaquine for the Prevention of Malaria in Pregnancy. N Engl J Med. *2016;374(10):928-39 [Crossref][PubMed][Google Scholar]*

14. González R, Nhampossa T, Mombo-Ngoma G, Mischlinger J, Esen M, Tchouatieu A-M, et al. Safety and efficacy of dihydroartemisinin–piperaquine for intermittent preventive treatment of malaria in pregnant women with HIV from Gabon and Mozambique: a randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. *2024;24(5):476-87 [Crossref][PubMed][Google Scholar]*

15. Barsosio HC, Madanitsa M, Ondieki ED, Dodd J, Onyango ED, Otieno K, et al. Chemoprevention for malaria with monthly intermittent preventive treatment with dihydroartemisinin–piperaquine in pregnant women living with HIV on daily co-trimoxazole in Kenya and Malawi: a randomised, double-blind, placebo-controlled trial. Lancet. *2024;403(10424):365-78 [Crossref][PubMed][Google Scholar]*

16. Klement, E. , et al. , Effectiveness of Co-trimoxazole to Prevent Plasmodium falciparum Malaria in HIV-Positive Pregnant Women in Sub-Saharan Africa: An Open-Label, Randomized Controlled Trial. *Clin Infect Dis. 2013. 58(5): p. 651-659 [Crossref][PubMed][Google Scholar]*

. . , et al. , Effectiveness of Co-trimoxazole to Prevent Plasmodium falciparum Malaria in HIV-Positive Pregnant Women in Sub-Saharan Africa: An Open-Label, Randomized Controlled Trial. *Clin Infect Dis. 2013. 58(5): p. 651-659 [Crossref][PubMed][Google Scholar] [Crossref][PubMed][Google Scholar]*

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