Challenges in the concurrent management of malaria and HIV in pregnancy in sub-Saharan Africa

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Introduction

Approximately one million pregnancies per year are thought to be complicated by coinfection with malaria and HIV in sub-Saharan Africa. Maternal malaria infection has been associated with maternal anaemia, infant low birthweight, and maternal and infant mortality. Maternal HIV infection has also been associated with maternal anaemia and low birthweight, and with increased risk of maternal malaria. HIV-associated risk of maternal malaria affects women of all gravidities, thus attenuating or even eliminating the decrease in malaria parasitaemia normally seen in HIV-negative multigravidae. The prevalence of maternal anaemia and incidence of low birthweight are both higher in pregnancies affected by HIV/malaria coinfection than in pregnancies affected by malaria or HIV alone. In the presence of coinfection, anaemia prevalence and low birthweight incidence may both exceed 35% in some subgroups. Maternal malaria/HIV coinfection may also increase the incidence of mother-to-child transmission of HIV, perhaps because malaria infection is known to increase HIV viral load, although published evidence has been inconsistent.

Maternal malaria and its consequences can be substantially diminished through the use of insecticide-treated bednets (figure 1), intermittent preventive treatment with two or more doses of an antimalarial medication after the first trimester (figure 2), and effective case management of malaria and anaemia.

WHO now recommends insecticide-treated bednet use and intermittent preventive treatment for all pregnant women living in areas of stable Plasmodium falciparum transmission in Africa, along with antenatal HIV testing and antiretroviral therapy if indicated. However, malaria transmission patterns are quite heterogeneous within Africa, and intermittent preventive treatment is not as yet recommended in regions where placental malaria parasitaemia is infrequent or where Plasmodium vivax predominates. Sulfadoxine-pyrimethamine is generally regarded as the preferred antimalarial medication for intermittent preventive treatment, although its effectiveness is now threatened by rising levels of drug resistance.

Antiretroviral regimens vary, but WHO guidelines currently recommend highly active antiretroviral...
therapy (HAART) using the combination of nevirapine, lamivudine, and either stavudine or zidovudine for HIV-infected pregnant women with clinical or laboratory evidence of immunosuppression. WHO recommendations for prevention of mother-to-child transmission where women do not require or do not have access to HAART now include several different regimens involving single-dose or short-course treatment with nevirapine, zidovudine, and/or lamivudine.

Because many pregnant women would benefit from prophylaxis and/or treatment of both malaria and HIV, it is important to confirm that the concurrent use of regimens to manage both infections is safe, effective, and operationally feasible. Through review of major policy documents, the published medical literature, and our own field experiences, we sought to identify challenges to successful concurrent control of malaria and HIV in pregnant women in regions of stable *P. falciparum* transmission in sub-Saharan Africa. We focused on the three primary components of malaria control in pregnancy—insecticide-treated bednet use, intermittent preventive treatment, and case management of malaria and anaemia—and their known or potential interactions with antiretroviral regimens commonly used during pregnancy.

**Use of insecticide-treated bednets by HIV-infected pregnant women**

Insecticide-treated bednet use has been recommended for HIV-infected people living in malaria endemic regions because of the increased risk of malaria conferred by HIV infection. The use of insecticide-treated bednets alone has been found to be effective for prevention of pregnancy-related anaemia in women of unknown HIV status: in one study, the protective efficacy of insecticide-treated bednets alone was 41·6% in primigravidae, versus 55·8% for insecticide-treated bednets plus two-dose sulfadoxine-pyrimethamine, although this difference was not statistically significant. In Kenyan children, a single dose of sulfadoxine-pyrimethamine combined with regular bednet use was found to be as effective as multidose sulfadoxine-pyrimethamine for the prevention of anaemia; this approach has not yet been evaluated in pregnant women. Regular insecticide-treated bednet use, although not yet studied specifically in HIV-infected women, may be expected to reduce the burden of malaria during pregnancy even among those who do not adhere to the full course of recommended antenatal visits.

There are at least three important operational constraints to effective insecticide-treated bednet use by HIV-infected pregnant women in sub-Saharan Africa. First, where insecticide-treated bednets are not highly subsidised, the poorest families—eg, those whose resources have been eroded by chronic illness—may be unable to afford them. Second, because approximately 65% of African women do not present for antenatal care until the second or third trimester, maternal peripheral malaria parasitaemia may be well established before the first antenatal visit, thus reducing the effectiveness of insecticide-treated bednet use if not begun until afterward. Finally, where donor funds restrict provision of subsidised bednets to women known to be HIV infected, increased stigma and new health inequities may arise.

**Preventive treatment of malaria in pregnancy in HIV-infected pregnant women**

**Co-trimoxazole**

Daily prophylaxis with co-trimoxazole (trimethoprim-sulfamethoxazole) has been recommended for all HIV-infected pregnant women in sub-Saharan Africa. Co-trimoxazole has been used effectively to treat malaria in children, and daily use of co-trimoxazole by non-pregnant HIV-infected adults has been associated with reductions of over 70% in the incidence of febrile malaria parasitaemic syndromes. However, no published data yet describe the effectiveness of daily co-trimoxazole for the prevention of malaria and its consequences (specifically maternal anaemia, placental parasitaemia, etc.).
and low birthweight) during pregnancy. Nevertheless, WHO now recommends daily co-trimoxazole as an alternative to intermittent preventive treatment with sulfadoxine-pyrimethamine for immunocompromised HIV-infected women. Concurrent administration of sulfadoxine-pyrimethamine and co-trimoxazole has been associated with a substantially increased incidence of severe adverse reactions in HIV-infected patients, and is therefore not recommended.

Operational constraints resulting from late diagnosis may limit the use of daily co-trimoxazole for malaria prophylaxis. Women who are not diagnosed with HIV until after the first antenatal visit may not present for HIV care until late pregnancy, especially where HIV care is not offered at the antenatal clinic itself. In many settings, prescription of co-trimoxazole may also be contingent on clinical and/or laboratory staging, which may introduce further delays in initiation of co-trimoxazole prophylaxis. If co-trimoxazole is not begun until the third trimester, malaria-related maternal anaemia and fetal growth retardation may already have developed.

Many HIV-infected people are intolerant of co-trimoxazole because of its sulfonamide component. The risk of adverse reactions to co-trimoxazole in HIV-infected people has been estimated at 26.3 per 100 person-years, increasing substantially with advancing immunosuppression. The likelihood of adverse reactions also appears to vary by sex and race, and may be higher in women.

Initiation of daily antiretroviral regimens may influence the timing of co-trimoxazole initiation and the interpretation and management of adverse drug reactions. Hypersensitivity reactions to nevirapine are common and clinically indistinguishable from reactions to co-trimoxazole. Therefore, clinicians commonly stagger their introduction by 2–4 weeks, so that adverse reactions may be correctly ascribed to the offending drug. In consequence, some women who present in late pregnancy for HIV treatment may receive antiretrovirals first, because of the urgency of reducing HIV viral load before delivery, while co-trimoxazole initiation is delayed, sometimes until the postpartum period. Addition of zidovudine to co-trimoxazole prophylaxis may accentuate the adverse haematological consequences (anaemia and neutropenia) of co-trimoxazole prophylaxis, thus increasing the risk of maternal anaemia.

As yet, few published data describe resistance of malaria to co-trimoxazole in people on daily co-trimoxazole prophylaxis. However, P falciparum resistance to trimethoprim has been observed, suggesting that the protective efficacy of co-trimoxazole against malaria may eventually wane. In one study of Ugandan children who received sulfadoxine-pyrimethamine plus chloroquine for symptomatic malaria, co-trimoxazole prophylaxis was associated with treatment failure. A study of HIV-infected children in an area of low malaria prevalence in Mali did not find a relation between co-trimoxazole prophylaxis and the development of molecular markers of sulfadoxine-pyrimethamine resistance, but the number of cases of symptomatic malaria was too low to support conclusions about treatment failure. In a similar study in Kenya, co-trimoxazole prophylaxis was also not associated with increased prevalence of molecular markers of sulfadoxine-pyrimethamine resistance; but both baseline and follow-up prevalence of markers of resistance were higher in HIV-infected participants than in those who were uninfected. In general, the risks and benefits of daily co-trimoxazole prophylaxis may be expected to vary depending on local patterns of drug resistance to malaria and to common bacterial pathogens.

Concerns over the possible toxicity of co-administered co-trimoxazole and sulfadoxine-pyrimethamine and the potential for failure of sulfadoxine-pyrimethamine-based regimens for symptomatic malaria in people on co-trimoxazole prophylaxis may soon prompt revisions to WHO guidelines.

Sulfadoxine-pyrimethamine and antiretrovirals
Sulfadoxine-pyrimethamine in HIV-infected women
Sulfadoxine-pyrimethamine is the most commonly used agent for intermittent preventive treatment because of its
in HIV-negative women the regimens were equivalent.43 compared with two doses (25·6% vs 10·5%, \( p=0·015 \)), but not in HIV-negative women.44 However, a more recent study failed to document any difference in efficacy of standard versus intensive (monthly) intermittent preventive treatment use in HIV-positive women.45 Where the benefits of standard two-dose sulfadoxine-pyrimethamine in the HIV-infected woman are indeed reduced, immunosuppression and/or antimalarial drug resistance may be responsible.46

Table 1: Reported interactions and overlapping toxicities involving antimalarials, antiretrovirals, and co-trimoxazole

<table>
<thead>
<tr>
<th>References</th>
<th>Antimalarial medication</th>
<th>Co-administered with</th>
<th>Risk or known interaction, other comments re metabolism</th>
<th>Management suggestions and other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>Artemether</td>
<td>Protease inhibitors, non-nucleoside reverse transcriptase inhibitors</td>
<td>Potential reduction of dihydroartemisinin (active metabolite) and increase in artemether</td>
<td>Clinical importance unclear</td>
</tr>
<tr>
<td>71</td>
<td>Artemisinins (general)</td>
<td>Lumefantrine</td>
<td>Metabolised by cytochrome P450 3A4; induce cytochrome P450 3A4</td>
<td>Clinical importance unclear</td>
</tr>
<tr>
<td>71</td>
<td>Artemisin</td>
<td>Nevirapine</td>
<td>Metabolised rapidly to dihydromeflumetin, a “rather inactive” compound</td>
<td>Clinical importance unclear</td>
</tr>
<tr>
<td>70, 68,72</td>
<td>Atovaquone</td>
<td>Zidovudine</td>
<td>Decreases clearance of zidovudine</td>
<td>Clinical importance unclear</td>
</tr>
<tr>
<td>73</td>
<td>Chloroquine</td>
<td>Indinavir, ritonavir, or saquinavir (all in vitro)</td>
<td>The combination inhibited HIV replication. Also decreased indinavir concentration in some isolates</td>
<td>Clinical importance as yet unknown. Note that chloroquine is of little use as an antimalarial owing to widespread resistance</td>
</tr>
<tr>
<td>10</td>
<td>Co-trimoxazole</td>
<td>Lamivudine</td>
<td>Decreased clearance of lamivudine</td>
<td>Thought not to be important clinically</td>
</tr>
<tr>
<td>35</td>
<td>Co-trimoxazole</td>
<td>Nevirapine</td>
<td>Both may cause severe adverse cutaneous reactions</td>
<td>Defer nevirapine initiation until 2–4 weeks after co-trimoxazole initiation (see text)</td>
</tr>
<tr>
<td>36</td>
<td>Co-trimoxazole</td>
<td>Zidovudine</td>
<td>Anemia, neutropenia</td>
<td>Close monitoring of haematological parameters</td>
</tr>
<tr>
<td>74</td>
<td>Dapsone</td>
<td>NA</td>
<td>Some evidence suggests that HIV-infected people may be at higher risk of dapsone-associated haemolysis, especially in the presence of intercurrent infection</td>
<td>Clinical importance as yet unclear</td>
</tr>
<tr>
<td>42, 68,70,75</td>
<td>Halofantrine or lumefantrine</td>
<td>Protease inhibitors, non-nucleoside reverse transcriptase inhibitors (especially delavirdine)</td>
<td>Potential cardio toxicity, based on inhibition of cytochrome P-450 3A4. This risk is greater with halofantrine than with lumefantrine</td>
<td>Do not co-administer if better options are available (recommendation better supported for halofantrine than lumefantrine)</td>
</tr>
<tr>
<td>72</td>
<td>Mefloquine</td>
<td>Ritonavir</td>
<td>Suppression of area under curve of ritonavir</td>
<td>Probably safe to co-administer. Mefloquine has been associated with increased fetal loss</td>
</tr>
<tr>
<td>76</td>
<td>Mefloquine</td>
<td>Nelfinavir, indinavir</td>
<td>No observed drug–drug interaction</td>
<td>Probably safe to co-administer. Mefloquine has been associated with fetal loss</td>
</tr>
<tr>
<td>68,72</td>
<td>Proguanil</td>
<td>Ritonavir</td>
<td>Decreased metabolism of proguanil to cycloguanil, possible decrease in effectiveness of proguanil</td>
<td>Unclear</td>
</tr>
<tr>
<td>10, 70, 72,77</td>
<td>Quinine</td>
<td>Protease inhibitors, non-nucleoside reverse transcriptase inhibitors</td>
<td>Potential cardio toxicity based on cytochrome P450 inhibition</td>
<td>Do not co-administer if better options are available (unless cardiac monitoring available; in this case reduce loading dose and monitor carefully)</td>
</tr>
<tr>
<td>10, 37</td>
<td>Sulfadoxine-pyrimethamine</td>
<td>Co-trimoxazole</td>
<td>Increased risk (approximately 100-fold) of severe adverse cutaneous or hepatic reactions when given in combination to HIV-infected people. Also, cross-resistance of P. falciparum</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>48, 51,52,60</td>
<td>Nevirapine</td>
<td>Nevirapine</td>
<td>Both may cause severe adverse cutaneous or hepatic reactions which may not occur until 2 weeks after administration owing to long drug half-lives; unclear if risk is additive or synergistic</td>
<td>Do not initiate concurrently (see text)</td>
</tr>
<tr>
<td>66,67</td>
<td>Zidovudine</td>
<td>Zidovudine</td>
<td>Increased risk of bone marrow toxicity; may exacerbate anaemia caused by malaria and/or HIV infection</td>
<td>Unclear, co-administer with caution in presence of anaemia. Consider substituting stavudine for pregnant women who are anaemic at baseline</td>
</tr>
<tr>
<td>78</td>
<td>NA</td>
<td>Ritonavir and saquinavir (both in vitro)</td>
<td>Decrease in cytoadherence and phagocytosis of parasitised (with P. falciparum) erythrocytes</td>
<td>Clinical importance as yet unknown</td>
</tr>
<tr>
<td>79</td>
<td>NA</td>
<td>Saquinavir, ritonavir, indinavir</td>
<td>Inhibit growth of P. falciparum</td>
<td>Clinical importance as yet unknown (all in vitro)</td>
</tr>
<tr>
<td>80</td>
<td>NA</td>
<td>Multiple protease inhibitors</td>
<td>Inhibit growth of P. falciparum at “clinically relevant concentrations”</td>
<td>Clinical importance as yet unknown</td>
</tr>
<tr>
<td>81</td>
<td>NA</td>
<td>Some nucleoside reverse transcriptase inhibitors (especially zidovudine)</td>
<td>80% killing of P. falciparum after three life cycles of parasite</td>
<td>Clinical importance as yet unknown</td>
</tr>
</tbody>
</table>

NA = not applicable

low cost, ease of administration, and documented safety after the first trimester of pregnancy.19 However, both the risks and the benefits of intermittent preventive treatment with sulfadoxine-pyrimethamine appear to differ in the setting of HIV infection.

Standard intermittent preventive treatment regimens may be less effective in HIV-infected women. In one study, a substantially greater reduction of placental parasitaemia was seen in HIV-infected women receiving three or more doses of sulfadoxine-pyrimethamine compared with two doses (25·6% vs 7·1%, \( p=0·051 \)), but in HIV-negative women the regimens were equivalent.19 Elsewhere, monthly intermittent preventive treatment with sulfadoxine-pyrimethamine prevented placental parasitaemia significantly more effectively than two-dose sulfadoxine-pyrimethamine in HIV-positive women (25·6% vs 10·5%, \( p=0·015 \)), but not in HIV-negative women.44 However, a more recent study failed to document any difference in efficacy of standard versus intensive (monthly) intermittent preventive treatment use in HIV-positive women.45 Where the benefits of standard two-dose sulfadoxine-pyrimethamine in the HIV-infected woman are indeed reduced, immunosuppression and/or antimalarial drug resistance may be responsible.46

The risks of adverse reactions to sulfadoxine-pyrimethamine may be increased in HIV-infected women. Sulfadoxine-pyrimethamine, like co-trimoxazole, contains a sulfonamide component, and HIV-infected people may therefore be more likely than
Adverse reactions to single-dose pyrimethamine, sulfadoxine, or the combination may occur as early as 3 days or as late as 6–7 weeks after administration.31–33 When mass administration of single-dose sulfadoxine was used as cholera prophylaxis in Mozambique, the mean interval between sulfadoxine exposure and onset of Stevens-Johnson syndrome was 22 days in affected individuals.12

Unfortunately, malarial resistance to sulfadoxine-pyrimethamine is now increasing in many settings.28 Where levels of sulfadoxine-pyrimethamine resistance are high, standard intermittent preventive treatment regimens may lose their effectiveness, and no alternative agent has yet been defined.24

Sulfadoxine-pyrimethamine and nevirapine
Both sulfadoxine-pyrimethamine and nevirapine can cause potentially fatal liver and skin toxicity.17–39 Severe cutaneous reactions, including Stevens-Johnson syndrome, have been reported in approximately 2% of patients taking daily nevirapine, and clinical hepatitis occurs in approximately 4%.46 Hepatotoxicity has been observed to be significantly more common in pregnancy (p=0.003)41 and in women with higher CD4 cell counts;42 a recent South African study documented hepatotoxicity in 20-1% of women who initiated nevirapine with baseline CD4 cell counts greater than or equal to 200 cells per μL.43 The period of highest risk for severe reactions to nevirapine is thought to last for 12–18 weeks after initiation of therapy.44 Re-challenge with nevirapine is not recommended after a severe adverse event. Fortunately, multiple clinical trials have failed to observe severe liver or skin toxicity associated with single-dose perinatal nevirapine.

Should a pregnant patient have a severe adverse cutaneous or hepatic reaction during the first few weeks after initiating both intermittent sulfadoxine-pyrimethamine and daily nevirapine, the attending clinician will be unable to discern which drug was responsible, and may therefore advise discontinuation of both nevirapine and sulfadoxine-pyrimethamine (figure 3). Where nevirapine is a component of the local first-line HAART regimen, and/or where sulfadoxine-pyrimethamine is a component of the local first-line antimalarial regimen, this decision could effectively deprive women of both AIDS and malaria treatment if alternative regimens are unavailable or unaffordable. Assuming a 4–20% risk of severe adverse reaction to nevirapine, and a 0–6·3% risk of severe adverse reaction to sulfadoxine-pyrimethamine, this situation could theoretically affect a substantial number of pregnant women concurrently initiating daily nevirapine and intermittent sulfadoxine-pyrimethamine.

Staggering the introduction of sulfadoxine-pyrimethamine and nevirapine (as in the case of co-trimoxazole and nevirapine) would reduce the potential

Panel 1: Recommendations to policy-makers
1. Individuals and agencies responsible for malaria, HIV/AIDS, and prenatal care policies should work collaboratively at local, regional, and international levels. Collaboration should include clinicians and researchers, as well as policymakers.
2. Recommendations for prevention and treatment of malaria and HIV/AIDS (both in pregnant women and in non-pregnant individuals) should be systematically harmonised at all levels of the health-care system. This will require the participation of individuals and agencies responsible for malaria control, HIV/AIDS prevention and treatment, and maternal and child health.
3. Where antenatal and HIV/AIDS care are provided in different sites, or by different health-care professionals, systems should be developed to support communication and coordination of care.
4. Local recommendations must respond to local patterns of malaria transmission, HIV prevalence, and drug resistance (antimalarial, antimicrobial, and antiretroviral). These patterns are likely to vary by site and also over time. Where data are not available to describe local conditions, efforts should be made to collect them.86
5. Systematic pharmacovigilance is essential.87
### Specific recommendations based on maternal HIV status, gestational age at diagnosis, and indications for treatment with antiretrovirals and/or co-trimoxazole

<table>
<thead>
<tr>
<th>Pregnant woman is HIV negative or HIV status is unknown</th>
<th>Proceed with intermittent preventive treatment per WHO/national guidelines. HIV counselling and testing if indicated and available. If HIV testing subsequently reveals that the pregnant woman is HIV positive, follow recommendations below.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1: co-trimoxazole prophylaxis is readily available and is locally recommended for use in pregnancy. Recommendation: initiate intermittent preventive treatment per WHO/national guidelines.</td>
<td></td>
</tr>
<tr>
<td>Scenario 2: co-trimoxazole prophylaxis is readily available and is locally recommended for use in pregnancy. Recommendation: stop or do not start intermittent preventive treatment, and communicate this to other members of the antenatal team. Start co-trimoxazole prophylaxis at least 4 weeks after last sulfadoxine-pyrimethamine dose. Do clinical and laboratory assessments of HIV disease (or refer).</td>
<td></td>
</tr>
<tr>
<td>Pregnant woman is HIV positive but daily antiretroviral therapy is not indicated, is unavailable, or has not yet been prescribed</td>
<td>Intermittent preventive treatment has been associated with prevention of maternal anaemia, infant low birthweight, and malaria-related mortality and morbidity in mothers and infants where malaria transmission is stable and P falciparum is susceptible to sulfadoxine-pyrimethamine. Intermittent preventive treatment with sulfadoxine-pyrimethamine should prevent malaria and its complications where local P falciparum is still susceptible. It may also prevent certain other opportunistic infections—eg., Pneumocystis jiroveci and Toxoplasma gondii—although two to three monthly doses are likely to be inadequate for this indication. Co-trimoxazole has been shown effective for prevention of malaria in non-pregnant HIV-infected people in Cote d’Ivoire. Co-trimoxazole should also prevent other bacterial and protozoal complications of HIV where local pathogens retain their susceptibility to sulfonamides. Delay of co-trimoxazole initiation will reduce likelihood of adverse reaction due to combination of sulfadoxine-pyrimethamine and co-trimoxazole.</td>
</tr>
<tr>
<td>No recommendation for intermittent preventive treatment where malaria transmission is low level, where P vivax predominates, or where P falciparum is known to be resistant to sulfadoxine-pyrimethamine</td>
<td></td>
</tr>
<tr>
<td>Monthly sulfadoxine-pyrimethamine will not prevent many other HIV-related bacterial and protozoal infections.</td>
<td></td>
</tr>
<tr>
<td>HIV-infected people, particularly those with low CD4 cell counts, are commonly intolerant of sulfonamides. Some adverse reactions to sulfadoxine-pyrimethamine may occur more than 4 weeks after administration; thus the 4 week interval may not be adequate to eliminate all diagnostic confusion in the event of an adverse reaction to co-trimoxazole or sulfadoxine-pyrimethamine (or the combination).</td>
<td></td>
</tr>
<tr>
<td>No published data describe the effect of daily co-trimoxazole prophylaxis on maternal anaemia, placental parasitaemia, or infant birth weight.</td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole may or may not be equivalent to sulfadoxine-pyrimethamine in this regard. Widespread use of prophylactic co-trimoxazole may promote sulfadoxine-pyrimethamine (and co-trimoxazole) resistance in malaria, and co-trimoxazole resistance in local bacterial pathogens. If administered during the first trimester, co-trimoxazole may be teratogenic.</td>
<td></td>
</tr>
<tr>
<td>Current WHO recommendation that all pregnant women receive co-trimoxazole is undergoing review and may change.</td>
<td></td>
</tr>
<tr>
<td>Antiretroviral therapy is available to improve the mother’s health and/or to prevent vertical transmission of HIV, and has been prescribed</td>
<td>Proceed with intermittent preventive treatment per WHO/national guidelines. HIV counselling and testing if indicated and available. If HIV testing subsequently reveals that the pregnant woman is HIV positive, follow recommendations below.</td>
</tr>
<tr>
<td>Scenario 1: single-dose nevirapine will be given at delivery only. No other antiretrovirals will be prescribed to the mother. Recommendation: proceed with intermittent preventive treatment or prophylactic co-trimoxazole, as above.</td>
<td></td>
</tr>
<tr>
<td>Scenario 2: short course daily zidovudine will be given, with or without short-course lamivudine and/or single-dose nevirapine. Recommendation: proceed with intermittent preventive treatment or prophylactic co-trimoxazole, as above. Measure maternal haemoglobin (or complete blood count) at time of zidovudine initiation and 4–6 weeks afterward.</td>
<td></td>
</tr>
<tr>
<td>Nevirapine when given as a single dose at delivery has not been associated with severe adverse reactions in the mother. Hence, the likelihood of diagnostic confusion in the event of an important adverse reaction is much less. Combination antiretroviral therapy will prevent vertical transmission of HIV more effectively than single-dose nevirapine alone.</td>
<td></td>
</tr>
</tbody>
</table>

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### Review

For all pregnant women at risk of HIV/malaria coinfection, regardless of HIV status (preferably at first prenatal consult)

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommendation</th>
<th>Potential benefits of this recommendation</th>
<th>Exceptions, precautions, costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnant women at risk of HIV/malaria coinfection</td>
<td>Long-lasting insecticide-treated bednets for all women, to be provided free of charge or at highly subsidised prices</td>
<td>Provision of nets to all women (regardless of HIV status) may avoid HIV-related stigma and promote both equity and “community-level protection” of insecticide-treated bednets. Insecticide-treated bednets should reduce malaria transmission even where high levels of antimalarial drug resistance occur.</td>
<td>Cost of bednets.</td>
</tr>
<tr>
<td>Iron supplementation and multivitamins</td>
<td>Where mother is HIV-infected: provision of multivitamins (in addition to ferrous sulphate) has led to improvements in postnatal child growth, reductions in child mortality, possible reduction in vertical HIV transmission, increase in birthweight, reduction in perinatal deliveries, improved survival of HIV-infected mothers, and slowing of progression of HIV-related maternal illness. Prevention of maternal anaemia is important because of the association of maternal anaemia with adverse outcomes for mother and infant.</td>
<td>Negligible.</td>
<td></td>
</tr>
<tr>
<td>Assessment of HIV status, including counselling and testing for women of unknown status</td>
<td>Where services are available, early diagnosis of HIV infection during pregnancy may afford the opportunity to prevent vertical (and horizontal) transmission of HIV, and to provide appropriate management of HIV-related maternal illness.</td>
<td>HIV-related stigma.</td>
<td></td>
</tr>
</tbody>
</table>

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### Review (continues)

Network meta-analysis using a Bayesian hierarchical model indicated that antenatal zidovudine is associated with improved outcomes for mother and infant.88–92 Prevention of maternal anaemia is important because of the association of maternal anaemia with adverse outcomes for mother and infant.88–92

Antenatal zidovudine therapy has also been shown to improve growth and survival in HIV-exposed, uninfected infants.89–92

### Antenatal zidovudine therapy

**Scenario 1:** single-dose nevirapine will be given at delivery only. No other antiretrovirals will be prescribed to the mother. **Recommendation:** proceed with intermittent preventive treatment or prophylactic co-trimoxazole, as above. Measure maternal haemoglobin (or complete blood count) at time of zidovudine initiation and 4–6 weeks afterward.

Nevirapine when given as a single dose at delivery has not been associated with severe adverse reactions in the mother. Hence, the likelihood of diagnostic confusion in the event of an important adverse reaction is much less. Combination antiretroviral therapy will prevent vertical transmission of HIV more effectively than single-dose nevirapine alone.

As above. Addition of short-course zidovudine increases risk of maternal anaemia. Co-administration of zidovudine and sulfadoxine-pyrimethamine has been associated with bone marrow toxicity. The likelihood of this complication has not been quantified, but appears to be greater in patients who are anaemic at baseline.
for diagnostic confusion should an adverse event occur. However, because both drugs have long half-lives, their introduction may need to be separated in time by a month or more.

Intermittent preventive treatment using antimalarial agents that are shorter-acting and/or have more favourable side-effect profiles should eventually eliminate this problem, but adequate alternative regimens have not yet been defined. Other candidate drugs or combinations (thought possibly or probably safe in pregnancy but not yet evaluated or approved as intermittent preventive treatment agents in HIV-infected women) include chlorproguanil-dapsone, mefloquine, artesunate, amodiaquine, azithromycin, and arteether-lumefantrine.68,69

Sulfadoxine-pyrimethamine and zidovudine
Zidovudine is another mainstream of antiretroviral therapy for prevention of mother-to-child transmission and treatment of HIV infection. Its use has been associated with bone marrow suppression, particularly anaemia.44 Haematological adverse reactions to daily zidovudine have been reported to occur at a rate of 16.2 per 100 person-years.13 Zidovudine-related anaemia generally occurs after 4–6 weeks of therapy.15 Where daily zidovudine therapy is initiated in mid-pregnancy, the period of highest risk of zidovudine-related anaemia may coincide both with the period of highest risk of malaria-associated anaemia and with the estimated delivery date, thus increasing the parturient woman’s vulnerability to haemorrhage (figure 3).

Effective malaria prevention may increase the pregnant woman’s ability to tolerate the adverse haematological effects of both HIV and zidovudine. However, concurrent administration of pyrimethamine and zidovudine has been associated with increased mortality in HIV-infected people in clinical trials, particularly in study subjects with anaemia at study entry.16,67 The risk of bone marrow suppression in patients using daily zidovudine and monthly sulfadoxine-pyrimethamine has not been quantified.

Sulfadoxine-pyrimethamine and other antiretrovirals
Little is known about interactions or overlapping toxicities involving sulfadoxine-pyrimethamine and other antiretrovirals, although some anecdotal evidence and theoretical concerns have been reported (figure 4).18

Case management of malaria and anaemia
Malaria
Because many other conditions may cause signs and symptoms suggestive of malaria in people with AIDS, and because laboratory capacity to confirm the diagnosis of malaria is often limited, people with AIDS may receive presumptive antimalarial treatment more frequently than immunocompetent individuals. Indeed, presumptive prescription of antimalarial medications to treat fevers of uncertain origin has been observed to decrease mortality in some HIV-infected African patients not on HAART.19 Prevention of malaria through insecticide-treated bednet use and intermittent preventive treatment may or may not decrease the HIV-

Table 2: Provisional recommendations for malaria and anaemia prevention in pregnant women at risk for HIV/malaria coinfection

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
<th>Potential benefits of this recommendation</th>
<th>Exceptions, precautions, costs</th>
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<tr>
<td>Scenario 3: nevirapine-based HAART will be given daily throughout pregnancy and thereafter. Estimated gestational age at anticipated time of nevirapine initiation is &lt;32 weeks. Recommendation: stop sulfadoxine-pyrimethamine, begin prophylactic co-trimoxazole at least 4 weeks after last sulfadoxine-pyrimethamine dose. Delay initiation of HAART for at least 2 weeks after start of co-trimoxazole. If the regimen includes zidovudine, monitor haemoglobin levels, as above.</td>
<td>Because of the overlapping toxicities of these agents, staggering of sulfadoxine-pyrimethamine, co-trimoxazole, and HAART should reduce the likelihood of diagnostic confusion should an adverse drug reaction occur.</td>
<td>As above. The intervals between sulfadoxine-pyrimethamine, co-trimoxazole, and nevirapine administration may not be adequate to avoid all cases of diagnostic confusion related to cutaneous or hepatic adverse events. Staggering of sulfadoxine-pyrimethamine, co-trimoxazole, and HAART may delay HAART initiation. However, if pregnancy is not advanced, sufficient time should still remain to reduce HIV viral load before delivery. Reduction of interval between sulfadoxine-pyrimethamine and HAART initiation may result in increased incidence of adverse events of uncertain aetiology.</td>
<td></td>
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<tr>
<td>Scenario 4: same as scenario 3, but estimated gestational age at anticipated time of nevirapine initiation is ≥32 weeks. Recommendation: stop sulfadoxine-pyrimethamine. Initiate HAART as soon as possible, regardless of interval since last sulfadoxine-pyrimethamine dose. Defer initiation of co-trimoxazole prophylaxis until after nevirapine initiation.</td>
<td>When delivery is thought to be imminent, prompt reduction of HIV viral load should have the highest priority to minimise the risk of vertical HIV transmission. Suspension of preventive sulfadoxine-pyrimethamine and/or deferral of co-trimoxazole initiation in the late third trimester may not result in increased incidence of malaria-related adverse effects for mother or infant, because malaria-related reductions in maternal haemoglobin and infant birthweight are likely to be determined earlier in gestation. As above.</td>
<td></td>
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<tr>
<td>Scenario 5: pregnant woman initiates co-trimoxazole prophylaxis and/or HAART before entering prenatal care. Recommendation: continue co-trimoxazole prophylaxis, do not proceed with intermittent preventive treatment.</td>
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infected pregnant woman’s likelihood of being treated with antimalarials, depending on local thresholds for empiric treatment.

As in the case of sulfadoxine-pyrimethamine, there is little published information on the risks of co-administration of antiretrovirals and other antimalarials (table 1). The paucity of data on risks of co-administration of antiretrovirals and other antimalarials when given in early pregnancy, animal studies have suggested a risk of fetal toxicity, and more data are urgently needed. Co-administration of quinine with several protease inhibitors and non-nucleoside reverse transcriptase inhibitors is considered hazardous, which is worrisome given the importance of quinine for treatment of severe malaria and/or malaria during the first trimester of pregnancy. Halofantrine and lumefantrine (a component of the most widely available artemisinin-based combination regimen) have been used successfully in many sites where drug resistance limits other options. In all cases, (A) the clinical presentation of malaria in pregnancy is variable, and may not include such “classic” signs as fever. Whenever possible, the diagnosis of malaria should be confirmed by laboratory means before treatment. However, the absence of laboratory capacity should not result in the withholding of necessary treatment. (B) Because malaria may be lethal for both mother and infant, and prompt treatment is essential to avoid complications, the safest and most effective (based on prevailing patterns of drug resistance) available antimalarial should be used to treat symptomatic malaria in pregnancy, even if its safety profile is not ideal. Antiretroviral or artemether appear to be the best alternatives to quinine in this situation. 

Intriguingly, chloroquine apparently inhibits HIV replication, and several antiretrovirals inhibit P. falciparum growth, cytoadherence, or phagocytosis in vitro—but the clinical importance of these observations is as yet undefined. Anaemia Capacity for diagnosis and case management of anaemia in HIV-infected pregnant women must be enhanced where both malaria and HIV are prevalent. HIV-infected pregnant women are at higher risk of anaemia because erythropoiesis may be suppressed by opportunistic infections, zidovudine, and HIV itself.

### References

<table>
<thead>
<tr>
<th>Classifications</th>
<th>Symptomatic malaria</th>
<th>Gestational age</th>
<th>Concurrent medications</th>
<th>Treatment options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>93–98</td>
<td>Severe malaria</td>
<td>Any</td>
<td>No PIs or NNRTIs</td>
<td>Parenteral quinine and dextrose a clindamycin. Parenteral artemesine and artemether are alternatives; parenteral artemesine was observed to confer a survival benefit when compared with parenteral quinine in one recent randomised trial.</td>
<td>If coma or convulsions are present, consider treatment for pre-eclampsia/eclampsia as well, because of clinical overlap in these syndromes. As above. Data on safety of artemisinin derivatives in pregnancy are still scanty; there are concerns about teratogenicity based on animal studies.</td>
</tr>
<tr>
<td>82, 91–98</td>
<td>Any</td>
<td>HAART regimen including PIs and/ or NNRTIs</td>
<td>Quinine may be considered where cardiac monitoring is available. Lumefantrine is not recommended in this situation because it may cause cardiac toxicity, but the magnitude of risk is not well-defined. Parenteral artemesine or artemether appear to be the best alternatives to quinine in this situation.</td>
<td>Data on safety of artemisinin derivatives in pregnancy are still scanty; there are concerns about teratogenicity based on animal studies.</td>
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<tr>
<td>94, 99</td>
<td>Uncomplicated malaria</td>
<td>First trimester</td>
<td>No PIs or NNRTIs</td>
<td>Quinine. Consider chloroquine if still effective locally. As above. Quinine may be considered if adequate cardiac monitoring is available. The combination of lumefantrine with these antiretroviral may cause cardiac toxicity and its use in this situation is therefore not recommended, but the magnitude of risk is not yet defined. Artesunate or artemether appear to be the best alternatives to quinine in this situation.</td>
<td>Data on safety of artemisinin derivatives in pregnancy are still scanty; there are concerns about teratogenicity based on animal studies.</td>
</tr>
<tr>
<td>94, 99, 100</td>
<td>Current co-trimoxazole prophylaxis or sulfadoxine-pyrimethamine within the preceding month</td>
<td>HAART regimen containing PIs or NNRTIs</td>
<td>Artesunate (with or without clindamycin, mefloquine, or the combination of atovaquone-proguanil) has been used successfully in some women infected with drug-resistant malaria. The combination of arteether-lumefantrine is now being used more frequently because it is the most readily available artemisinin preparation in many sites where drug resistance limits other options.</td>
<td>Local patterns of drug availability and antimalarial drug resistance should be taken into account. Data on safety of artemisinin derivatives in pregnancy are still scanty; concerns exist regarding teratogenicity based on animal studies.</td>
<td></td>
</tr>
<tr>
<td>99–101</td>
<td>Second and third trimesters</td>
<td>No PIs or NNRTIs</td>
<td>No recent preventive or therapeutic sulfadoxine-pyrimethamine or co-trimoxazole</td>
<td>As above, but avoid sulfadoxine-pyrimethamine (or combinations that include it) if better options are available because of the risk of cross-resistance: As above, but avoid quinine and lumefantrine if better options are available because of concerns over cardiotoxicity.</td>
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</table>
Panel 2: Suggested priorities for future research and surveillance

1. Documentation of effectiveness of daily co-trimoxazole prophylaxis for prevention of clinical malaria, placental parasitaemia, maternal anaemia, and infant low birthweight.

2. Systematic surveillance for adverse effects (for mother and infant) related to co-administration of antimalarials and antiretrovirals in pregnancy, including newer antimalarials. All health-care providers who are regularly involved in the care of HIV-infected pregnant women should be included in pharmacovigilance networks.87

3. Systematic surveillance for antimalarial drug resistance (including agents used for intermittent preventive treatment), and for resistance of malaria (and common bacterial pathogens) to co-trimoxazole.

4. Clinical trials to evaluate the safety and effectiveness of a broader range of preventive and therapeutic antimalarials in HIV-infected pregnant women, with special attention to the following: artemisinin-based combination regimens; regimens to be used during the first trimester and/or for treatment of severe-complicated malaria; and alternatives to sulfadoxine-pyrimethamine for intermittent preventive treatment in regions where sulfadoxine-pyrimethamine resistance is substantial (or in individuals who have had adverse reactions to sulfonamides).

5. Improved identification of populations at higher risk of malaria in pregnancy to identify high-priority sites more efficiently.

6. Definition of optimal intermittent preventive treatment regimens for HIV-infected women who use insecticide-treated bednets regularly.

7. Assessment of effect of intermittent preventive treatment (or antimalarial chemoprophylaxis) on vertical transmission of HIV.

8. Assessment of effect of antiretroviral therapy on maternal malaria and its consequences for the infant.

Summary and recommendations

Because HIV infection increases the risk of malaria in pregnancy, and because both HIV infection and malaria increase the burden of maternal and infant mortality, it is urgent that antenatal programmes for both HIV and malaria control be implemented in a coordinated fashion for at-risk populations. This coordination attains even greater importance where late presentation for antenatal care may oblige clinicians to manage HIV, malaria, and all other common complications of pregnancy in a period of only a few weeks or months. Although gaps in the existing data represent a serious hindrance to sound policymaking, we believe that the following recommendations are reasonable at present.

First, policies for management of HIV, malaria, and other complications of pregnancy must be harmonised, at local, regional, and international levels. Recommendations for policymakers are given in panel 1.

Second, strategies for prevention of malaria in HIV-infected pregnant women must be tailored to suit each woman’s clinical situation and HIV treatment regimen. Our suggested protocol is described in table 2. Third, treatment of symptomatic malaria in HIV-infected pregnant women must also be adapted in response to medication regimens used for malaria prevention and/or HIV treatment. We have attempted to synthesise recent—and rapidly evolving—recommendations regarding treatment of malaria in pregnancy with data on antimalarial-antiretroviral incompatibilities in table 3. Finally, research and systematic surveillance are urgently needed to fill existing gaps in the available data, and to respond to changes in prevalence of antimalarial, antimicrobial, and antiretroviral drug resistance. Priority topics for research and surveillance are suggested in panel 2.

We hope that these recommendations—in addition to those recently published by WHO—will provide some practical guidance to the many clinicians who now care for pregnant women at risk for malaria/HIV coinfection, and that they will stimulate the further research and discussion that will be required to define sound, evidence-based guidelines in the future.

Conflicts of interest

We declare that we have no conflicts of interest.

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