HIV infection and malaria in pregnancy in western Kenya. Their interaction and effects on maternal and infant health
Ayisi, J.G.

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Summary

Malaria during pregnancy is a major problem in sub-Saharan Africa, affecting an estimated 24 million pregnant women each year; malaria prevalence may exceed 50% among primigravidae and secundigravidae in endemic areas. In malaria endemic areas, *Plasmodium falciparum* parasitaemia during pregnancy is associated with anaemia in pregnant women, and low birthweight (LBW) resulting from premature delivery and intrauterine growth retardation; LBW is an important risk factor for infant mortality and morbidity.

During the past two decades, HIV/AIDS has emerged as a major problem in many malaria-endemic areas of sub-Saharan Africa, where an estimated 28 million people are infected with HIV, and 80% of the world’s HIV-infected women reside. Given the wide geographical overlap between HIV and malaria, the epidemic of HIV/AIDS in areas where *Plasmodium falciparum* is endemic has generated serious concern about potential interactions between the two infections.

The research described in this thesis concerned the interaction of malaria and HIV infection in pregnancy and the effects of the two infections on maternal and infant health. The research comprised of 2 studies. The objectives of the first study (chapter 2) were to determine the efficacy and safety of the different regimens of sulfadoxine-pyrimethamine (SP) in the prevention of placental malaria, and if it is affected by HIV status. In the second study, the following specific areas were explored: the effect of placental malaria on perinatal mother-to-child transmission of HIV (MTCT) (chapter 3); an evaluation of the risk factors for HIV infection among asymptomatic women attending antenatal clinic (chapter 4); maternal malaria and HIV infection as risk factors for third trimester maternal anaemia (chapter 5); an evaluation of the effect of dual infection with HIV and malaria on pregnancy outcome (chapter 6); an evaluation of malaria and HIV infection as risk factors for anaemia in infancy (chapter 7); and the effect of HIV infection on maternal and cord antibody responses to malarial antigenic determinants and on the mother-to-infant transfer of antibodies (chapter 8).

The main findings of the research described in this thesis are summarized in relation to several topics important for mother and child health. In chapter 2, we compared the following regimens for treatment and prevention of malaria in pregnancy: fever case management (i.e., 1,500 mg sulfadoxine and 75 mg pyrimethamine for clinical malaria only), two intermittent preventive SP-treatment doses (at enrollment and again early in the third trimester) and monthly SP (a treatment dose at enrollment and then monthly through 34 weeks of gestation). Two doses SP were less effective in HIV-seropositive women for clearing placental malaria compared to HIV-seronegative women. Less than 2% of participating women reported adverse drug reactions, with no statistically significant differences between HIV-positive and HIV-negative women. Intermittent preventive treatment with SP proved safe and efficacious for the prevention of placental malaria in primigravidae and secundigravidae. It was concluded that while a two-dose SP regimen might be effective in reducing placental malaria in areas with low HIV seroprevalence, administration of SP monthly during the second and third trimester of
pregnancy should be considered in areas of high HIV seroprevalence to prevent the effects of maternal malaria on the foetus.

In a study that examined the effect of placental malaria on MTCT (chapter 3), viral load and an episiotomy or perineal tear were associated with increased MTCT, which is consistent with previous findings. MTCT was decreased among women with low density placental malaria and increased in women with high density placental malaria. This finding does not suggest altering existing recommendations for the use of intermittent preventive antimalarial treatment in pregnant women in malarious areas of Africa. The majority of dually (malaria + HIV) infected women will have low density parasitaemias, associated with a reduced MTCT, and a minority of dually infected women will have insufficiently controlled infections, associated with increased MTCT. At this point, we do not appear to be able to differentiate, in advance, which women will end up in which group. The important benefit of antimalarial treatment may be to reduce the likelihood of women having high-density PM and in also helping reduce the other known adverse effects of malaria in pregnancy, including anaemia, low birth weight and prematurity.

We evaluated if it was possible to identify risk factors for HIV infection in our study (chapter 4). The identification of risk factors associated with HIV infection would allow for the targeting of limited resources for counselling and testing in developing countries to sub-populations among the ANC attenders who will most benefit from the services. Overall, 26% of our study women were HIV seropositive. We were not able to identify a subgroup of women at risk of HIV infection in this ANC population using non-serologic information, suggesting that in this ANC population, universal access to voluntary HIV counselling and testing would be preferable to targeted screening.

We evaluated the prevalence of anaemia in women visiting the ANC in the third trimester, and assessed the contribution of malaria and HIV infection to this anaemia (chapter 5). In primigravidae and secundigravidae, malaria and HIV infection were important risk factors for anaemia; documented fever at the time of the antenatal clinic visit and HIV infection were associated with severe anaemia. In multigravidae (gravidae ≥3), HIV infection was the most important determinant of anaemia, and this was independent of the presence of parasitaemia. Thus, HIV infection adds another cause to the long list of etiological factors of anaemia in pregnancy in developing countries. It will be important to confirm if treatment of anaemia efficacious in HIV-negative women will be efficacious in HIV-positive women as well.

In chapter 6, we evaluated the effect of dual malaria and HIV infection on adverse birth outcome. When compared to uninfected women, dual infection among primigravidae was associated with a 3-fold increased risk of LBW, almost a 3-fold increased risk of prematurity, and about a 2-fold increased risk of SGA. In addition, dual infection more than doubled the risk of moderate-to-severe anaemia (Hb < 8 g/dl) in both primigravidae and multigravidae. Comparison of dually infected women with women infected with HIV-alone showed that the risks of LBW and prematurity among primigravidae, and moderate-to-severe anaemia among multigravidae were exacerbated by co-existent malaria. Similarly, when compared to women infected with malaria-alone, dual infection substantially increased the risk of moderate-to-severe anaemia over and above that among primigravidae and multigravidae women infected with malaria-alone.
Thus, dual infection increases adverse birth outcomes mainly in primigravidae, and increases anaemia considerably in all gravidae.

In chapter 7, we report on anaemia in 661 infants (467 born to HIV-seropositive and 194 born to HIV-seronegative mothers) who were monitored monthly from birth, until they attained the age of one year. Anaemia was common, with haemoglobin levels decreasing after birth and reaching the nadir at approximately 32 weeks of age. HIV-positive infants had lower mean haemoglobin levels than HIV-negative infants. HIV-negative infants born to HIV-positive mothers had slightly lower haemoglobin levels at the end of the first year of life compared to infants born to HIV-negative mothers. Placental malaria was a risk factor for anaemia in early infancy. HIV-infected infants with co-existent parasitaemia had lower haemoglobin levels than HIV-uninfected infants with or without parasitaemia, or HIV-infected infants without parasitaemia. Close monitoring, malaria treatment with an effective antimalarial, and haematinic supplementation did not prevent anaemia in most infants, with anaemia prevalence remaining high throughout the second half of infancy.

In chapter 8, we assessed whether HIV alters maternal and cord plasma malarial antibody responses and the mother-to-infant transfer of the antibodies to recombinant malarial proteins [merozoite surface protein 1 (MSP-119kD), the erythrocyte binding antigen (EBA-175)], the synthetic peptides [(MSP-2, MSP-3), rhoptry associated protein 1 (RAP-1), and the pre-erythrocytic stage, circumsporozoite protein (NANP)5], antigenic determinants of *Plasmodium falciparum*, and tetanus toxoid (TT). The prevalence of maternal antibodies to the malarial antigenic determinants was high, and HIV infection was only associated with reduced antibodies to (NANP)5 in maternal and cord plasma, and reduced mother-to-infant antibody transfer to (NANP)5. No consistent HIV-associated differences were observed for other antigenic determinants, suggesting that the increased susceptibility to malaria among HIV-infected pregnant women may not be explained on the basis of their reduced antibody response to malaria antigens.

In conclusion: the studies described in this thesis suggest that HIV and malaria interact and together form a major public health problem in sub-Saharan Africa. The high rates of antenatal clinic attendance in Africa imply that the impact of HIV and malaria in pregnancy can be reduced by incorporating malaria prevention, through intermittent chemoprophylaxis and the use of insecticide-treated bed nets, and access to HIV diagnosis and antiretrovirals into routine antenatal care. While the scientific communities concerned with malaria and HIV may have developed the basis for these interventions, incorporating these tools into service delivery will be critical. The studies described in this thesis were carried out in a changing environment of perinatal HIV and malaria prevention and have been transformed into a programme of delivery of nevirapine to HIV-infected women and their infants to prevent vertical transmission at birth, and a system to support the provision of intermittent preventive antimalarial treatment in pregnancy according to newly adopted national policy. Efforts are underway to develop and expand this prevention programme more widely in Kenya, with HIV counseling and testing, community education, the provision of antimalarials to prevent the consequences of malaria and antiretrovirals for MTCT prevention. Continued investigation into the nature of the HIV-malaria interaction, combined with joint programming of key intervention strategies, could lead to both immediate and long-term benefits.