HIV infection and malaria in pregnancy in western Kenya. Their interaction and effects on maternal and infant health
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General Discussion
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The main objective of the research described in this thesis was to investigate the effects of maternal malaria and HIV in pregnancy on maternal and infant health in western Kenya. First we determined the efficacy of the different regimens of intermittent preventive treatment (IPT) with sulfadoxine-pyramithamine (SP, Fansidar®) in the prevention of placental malaria. We examined whether maternal HIV infection modified the efficacy of IPT with SP, and whether the risk of adverse effects associated with SP use was enhanced in HIV-infected pregnant women (chapter 2). In a separate study, we further evaluated the effects of dual infection with malaria and HIV on HIV viral loads and the risk of perinatal mother-to-child HIV transmission (MTCT) (chapter 3). The second study presented an ideal opportunity for additional sub-studies that looked at the impact of concurrent infections with HIV and malaria on maternal and infant health (chapters 4-8). This chapter aims to assist policy makers in public health in the interpretation and extrapolation of the main findings as presented in specific research papers of this thesis, and assist researchers to identify areas of future work. The discussion will be presented under three headings: lessons learnt and conclusions, implications for public health and policy and future research.
Sulfadoxine-pyramethamine for prevention of placental malaria

Lessons learnt and conclusions

In western Kenya, a setting of intense malaria transmission and high prevalence of HIV infection, we observed that intermittent treatment with either monthly dosing or two doses of SP in the second or third trimester of pregnancy were well tolerated and were effective in reducing the frequency of placental malaria, in primigravidae and secundigravidae (chapter 2). Overall, compared with women receiving the standard of care (case management [CM] using standard treatment with SP for fever illness and parasitemia), women receiving a presumptive intermittent treatment regimen experienced an approximate three-fold reduction in placental parasitemia. The prevalence of parasitemia among women receiving one of the intermittent SP regimens was 9-11%, comparable to rates measured in similar trials using effective antimalarials in pregnant women [1,2]. Because of the large sample sizes required to sufficiently examine the effect of a single factor on low birth weight (LBW) and because of the demonstrated association between malaria and LBW, our study was designed to use placental malaria rates as a surrogate measure for LBW risk.

HIV infection in these pregnant women was accompanied by somewhat higher rates of malaria and poorer response to IPT with SP. HIV-positive women had a higher prevalence of peripheral parasitemia at enrollment and although a single initial dose of SP had a marked impact on peripheral parasitemia, its efficacy in clearing placental malaria was diminished in the presence of HIV infection. Steketee et al. also noted higher prevalence of peripheral and placental parasitemia in HIV-positive compared with
HIV-negative pregnant women in rural Malawi [3], and as did subsequent studies in Malawi by others [4] as well as our studies in western Kenya [5]. HIV-positive women required at least three doses of SP to decrease the prevalences of placental malaria to acceptable levels, and this has also been confirmed by studies from Malawi [6]. One possible explanation for the impaired response to intermittent SP treatment seen among HIV-positive women is that the response to antimalarial drugs depends on both drug efficacy and host immunity [7] and, during pregnancy; HIV infection impairs host immunity to malaria.

SP was well tolerated, with no statistically significant differences in the frequency of ADRs among HIV-positive, as compared with HIV-negative, women. This finding is also consistent with other recent studies in this region [6,8]. More importantly, even among HIV-positive women, the rate of adverse drug reactions (ADRs) reported remained very low (3%), and no severe cutaneous adverse reactions were noted. The most common concern regarding the use of SP during pregnancy is that its use in late pregnancy may displace bilirubin from albumin in the neonate and thus, contribute to kernicterus [9]. This concern stems from one study that demonstrated an increased incidence of kernicterus in neonates treated with a sulfonamide, in combination with several other drugs, within a short period before delivery [10]. Although our study was not specifically designed to address this concern (e.g. bilirubin levels were not measured) we did not find an excess risk if clinically jaundiced infants born to mothers who had received IPT, which is consistent with all other studies of IPT with SP for the control of malaria in pregnancy [6,7,11,12]. We conclude, that in areas with high P. falciparum malaria transmission, the benefit of SP in reducing malaria-associated maternal anemia...
and LBW and thus potentially, infant mortality, appears to outweigh the risk for rare, albeit serious, SP-related ADRs.

**Implications for public health and policy**

The results of this investigation, coupled with those from the study of SP’s efficacy in pregnant Malawian women [6,13], provide strong evidence that IPT with SP during pregnancy is safe and efficacious for the prevention of placental malaria in pregnant primigravidae and secundigravidae in sub-Saharan Africa. While two doses of SP provided sufficient protection in HIV-negative women even in the very high *P. falciparum* transmission area, HIV-positive women required at least three doses of SP to sufficiently clear their infections. Given that it is not yet feasible to provide informed HIV testing to all pregnant women in many circumstances in malaria-endemic developing countries, we suggest that a monthly SP regimen be provided in areas with high HIV seroprevalence in women of childbearing age.

In a decision-analysis model comparing the cost-effectiveness of the three different presumptive SP treatment regimens, which considered the factors HIV seroprevalence, placental malaria prevalence, LBW incidence, the cost of SP, medical for LBW infants, and HIV testing, we showed that in areas with an HIV seroprevalence of more than 10%, as is the case in most parts of sub-Saharan Africa, the monthly SP regimen would be the most effective strategy for reducing LBW associated with malaria, costing US $14, a cost well within the range considered cost-effective [14]. Based on the results of our study (Chapter 2), the Kenya government implemented the findings into policy and incorporated the 2-dose IPT with SP within its antenatal care delivery package.
[15], and was implemented at the Nyanza Provincial General Hospital effective from 15th March 1999.

We evaluated how well the benefits of IPT with SP can be achieved under operational conditions of public programmes within the first year after its introduction, as new policy for the control of malaria in pregnancy at the Nyanza Provincial General Hospital, in Kisumu, western Kenya. We aimed to identify amendable factor associated with incomplete IPT in order to improve the delivery of this efficacious treatment (van Eijk and others Unpublished). Our evaluation found that two-thirds of women attending ANC and delivering in this hospital received at least 1 dose, but fewer than one-in-four received the recommended full 2 dose regimen. Whereas late first antenatal clinic attendance (≥28 weeks) explained 29.4% of missed doses, we could not explain why 52.6% of 494 women who did come early and made more frequent visits to the antenatal clinic did not receive SP treatment as recommended. We concluded that it was important that pregnant women are made aware about the benefits of an early visit to the ANC, so they can report early to the ANC, start the first SP dose early in pregnancy and receive the full IPT. In addition, the training of the ANC staff on the rationale, process and documentation of IPT will also have the potential to substantially increase the proportion of women receiving 2-doses of IPT with SP.

**Future research**

Although these results are reassuring, as African countries move toward the use of SP for prevention of malaria in pregnant women, and for first-line treatment of uncomplicated malaria, it will be essential to set up surveillance systems for safety monitoring of the
effects of the long term use of these regimen. There is also the need to assess the efficacy of two doses of SP over a range of differing transmission intensities. Results from Malawi showed that most women who received 2 doses of SP during pregnancy had placental parasitaemia, and suggest that this regimen may not be adequate for areas of high malaria transmission in sub-Saharan Africa. This needs to be confirmed in a randomized controlled trial to assess the two-dose versus three or monthly doses in these intense transmission settings. Even though the use of SP in pregnancy is unlikely to contribute significantly to the emergence of drug resistance as its use in pregnancy will only form a small part of the total use and because use in pregnancy will not be continuous, the likelihood of emergence of resistance can not be overlooked.

In addition, there is concern that large-scale use of trimethoprim-sulfamethoxazole (cotrimoxazole) for opportunistic infection prophylaxis among HIV-infected individuals might accelerate the development of Plasmodium falciparum resistance to SP [16]. Conversely expanding use of SP may contribute to the development of resistance to cotrimoxazole by other pathogens, such as Streptococcus pneumoniae [17]. Cotrimoxazole is already widely used in sub-Saharan Africa as part of the integrated management of childhood illnesses for the presumptive treatment of pneumonia [17,18]. The issue is a complex one, and the extent to which the considerable short-term benefits from prophylactic use of cotrimoxazole for HIV/AIDS outweigh the long-term risks of increasing rates of resistance to both antifolates in malaria and other common infections remains to be determined [18-20]. Thus, both HIV and malaria control programmes need to carefully monitor the efficacy of these drugs.
Maternal malaria and perinatal HIV transmission

Lessons learnt and conclusions

This evaluation of perinatal HIV transmission in a malarious area of western Kenya demonstrated that 20% of infants born to HIV-infected mothers acquired HIV by 4 months of age. While it is possible that some of the observed MTCT was from breastfeeding, the 20% rate of early MTCT noted in our study is similar to rates reported in other sub-Saharan African settings [21-23] and other settings elsewhere [24]. Nevertheless the 20% MTCT risk is among the lower risks reported from sub-Saharan Africa. This is likely to be function of our study design, which excluded women with symptomatic HIV infection, resulting in a selection of women with less advanced HIV disease and lower viral loads. In the full cohort of HIV-infected women, we identified in a multivariate model that maternal viral load in peripheral blood at the time of delivery and having an episiotomy or perineal tear were risk factors for MTCT. MTCT was seen within all levels of viral load, but was associated with a 1.7-fold increased risk with each log_{10} increase in viral load. While our study may have enrolled a population of pregnant women with attention to the evaluation of malaria, our basic investigation of MTCT is consistent with other studies that did not focus on malaria.

Contrary to our apriori expectations, we observed that, overall; women with placental malaria had lower rates of MTCT than women without placental malaria. Because this was an unexpected finding, we further examined the relationship and found that only low placental parasite density (1-9999 parasites/μl of blood) was associated with protection from MTCT; and high density placental infection was either a risk factor
for MTCT (in the model evaluating only women with HIV and placental malaria) or it was not a significant risk or protective factor for MTCT (in the model evaluating all women). Further evaluation of possible confounders or interactions with gravidity, maternal age, previous antimalarial treatment, maternal anemia, birth weight or gestational age of the infant did not alter these findings.

Because we observed reduced risk of MTCT among women with low density placental malaria, we hypothesize that in this malarious African setting, HIV-infected women with malaria at the time of delivery will have responded to this infection in several different ways. The majority of these women will mount a substantial immune response to malaria (involving antibody, cytokine, and cellular responses [25, 26] and control and limit the density of placental infection, and the stimulated malaria immune response may also augment the immune response directed against HIV, and thus limit the likelihood of MTCT. Women with placental malaria who were unable to limit parasite density may have lacked the ability to mount an effective immunologic response, their high density malaria infection may have provided substantial antigen stimulus, leading to increased HIV viral replication as observed by other studies [27-29], and a comparable increased risk of MTCT. Or, their higher density parasitaemia may have altered the placental integrity, with one or more of these factors leading to higher rates of perinatal MTCT.

Implications for public health and policy

The public health implications of this protective association, if its causal association can be confirmed in further studies, will likely be small. In this study population, for the
majority of dually infected women the overall outcome may have a modest benefit for MTCT reduction, but for the minority with insufficiently controlled infections, MTCT will be increased. At this point, we do not appear to be able to differentiate, in advance, which women will end up in which group. And, 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 anemia, low birth weight and prematurity [30-32]. The observations that maternal viral load; and conditions associated with foetal exposure to maternal blood (having an episiotomy or perineal tear) stand out strongly as significant and independent predictors of peripartum MTCT points to the fact that a combination of interventions, well targeted at specific factors, could lead to a reduction in MTCT. Interventions among pregnant women using short treatment courses of zudovudine, and/or in combination with the newer, potent antiretroviral agents such as nevirapine that have been shown to decrease viral load to low levels should be able to be effective in preventing MTCT in resource poor settings such as western Kenya [33-35]. In addition, the population attributable fractions of episiotomy or perineal tear for MTCT suggests that reducing these events will substantially reduce the risk of perinatal HIV infection in this setting.

Future research

The findings in this study were unexpected and the association and protective mechanisms of low density placental malaria observed in our investigation needs to be confirmed and evaluated in further studies.
Effects of malaria and HIV in pregnancy on maternal and infant health

Lessons learnt and conclusions

The sub-studies presented in this thesis (chapters 2 and 5) show that, consistent with other studies [3,4], HIV-seropositive women were more likely to have malaria parasites than HIV-seronegative women, and to have significantly higher geometric mean parasite densities. Anaemia was highly prevalent among pregnant women and their infants after delivery (chapters 4-7), and both HIV and malaria were found to be key risk factors. In a multivariate analysis, for primi- and secundigravidae women, HIV-seropositivity and documented fever were associated with severe anemia (Hb < 7 g/dL) in the third trimester. In women of higher gravidities, HIV seropositivity was the only statistically significant factor associated with any anemia or with severe anemia. The relative impact of HIV on maternal anemia was found to be consistently greater among multigravidae women than among women in their first or second pregnancy in the third trimester (chapter 5) and at delivery (Chapter 6). As presented elsewhere, the HIV-seropositive women were more likely to have documented fever or history of fever than were HIV-seronegative women (chapters 4 and 5).

At delivery, when compared to uninfected women, dual infection with HIV and maternal malaria 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 small for gestational age (SGA); and in addition, dual infection more than doubled the risk of moderate to severe anaemia (Hb < 8 g/dl) in both primigravidae and multigravidae (chapter 6). 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 the multigravidae were exacerbated by co-existent malaria. Similarly, when compared to women infected with malaria-alone, dual infection increased the risk of moderate to severe anaemia over and above that among primigravidae and multigravidae women infected with malaria-alone (Chapter 6). Thus, compared to women with either malaria or HIV alone, women with dual infections are more likely to develop severe maternal anaemia, and deliver a preterm or low birth weight newborn, and given that birth weight is one of the major predictors of neonatal and infant mortality, this in turn will affect infant survival. Thus our finding helps explain part of the increased infant mortality risk observed in the previous analysis of data Malawi [36]. Although, iron and folic acid supplementation is recommended as part of prenatal care services in Kenya, only 1 of every 20 pregnant women in our study hospital was receiving the recommended doses of iron and folate. This low coverage of hematinics supplementation in this prenatal clinic clinic population demonstrates the importance of developing strategies to improve delivery and compliance of routine interventions that have already been shown to reduce anemia in pregnancy [37, 38].

Malaria and HIV were also found to be predominant risk factors for anemia in infants (chapter 7). We estimated that in the HIV-infected infants participating in this study, 16 to 17% of the anemia could be attributed to the presence of HIV (attributable fraction). Similarly to pregnant women, malaria and HIV were found to interact; HIV-infected infants with malaria had lower mean hemoglobin levels from age 16 weeks onwards compared with HIV-uninfected infants with and without malaria, or HIV-
infected infants without malaria, suggesting that HIV-infected infants are particularly vulnerable to the adverse consequence of malaria at this age.

This study also showed that maternal factors play an important role in infant anemia. Maternal HIV was an additional risk factor, not only directly, through MTCT, but also indirectly, as suggested by the finding that infant anemia was worse in HIV-uninfected infants when born to HIV-seropositive mothers compared with those born to HIV-seronegative mothers. Placental malaria was a risk factor for early infant anemia independent of prematurity and SGA. The observation that this association was present only in the first few month of life and absent in the last 6 months of infancy, suggests that this can not only be explained by mere environmental associations (e.g. both mother and newborn live in the same high malaria transmission households). It suggests, that a biological association may play a role reflecting the inability of mothers to provide an in utero optimal environment for foetal growth that affects infant health postpartum. Brabin and colleagues suggested that exposure of the fetus to malaria antigens due to damage of the placental barrier may make the newborn more susceptible to immunologically mediated haemolysis or to dyserythropoiesis [39]. Of note is the fact that despite all infants were regularly examined by a physician and treated free of charge for anemia, malaria (any parasitemia, regardless of symptoms) and other infectious diseases, close monitoring, combined with early detection and prompt treatment of infant malaria apparently failed to prevent most of the infants from becoming anemic.
Implications for public health and policy

Inadequate prevention and control of malaria leads to excess malaria-associated severe anaemia, which often requires blood transfusion [40]. However, the issue of blood safety in the face of malaria-induced anaemia continues to cause concern. Although identified repeatedly as an important public health measure, the attention to blood safety in many sub Saharan African countries is not well documented and inadequate HIV screening is likely to remain a widespread problem [41]. The high prevalence of anaemia in association with HIV infection is an important finding. For all pregnant women and their infants, asymptomatic HIV infection is an important additional risk factor to be considered in the differential diagnosis of anemia. In addition, dual infection may have important detrimental impact on maternal morbidity through its association with increased risk of maternal anaemia, and on infant survival through its direct and indirect association with restriction on infant growth (chapter 6). The association between placental malaria and early infant anemia found in this study (chapter 7) suggests that prevention of maternal malaria might be beneficial in preventing anemia in the first 6 months of life, particularly when combined with other interventions that impact beneficially on birth weight and the maternal micronutrient status [42].

Because of increased vulnerability of infants to develop anemia, in particular in the presence of malaria, infants born to HIV-seropositive mothers, and particularly if HIV-infected themselves may need to be targeted specifically for intervention. In areas with moderate or high prevalence of HIV and malaria, all pregnant women should be the targeted for malaria control efforts to improve maternal and infant health. Prevention of
anemia may thus be particularly important for HIV-seropositive pregnant women and their infants, in whom the value of blood transfusions may be more limited [43,44].

**Future research**

Optimal growth is an important health goal, as impaired growth is associated with poor health, increased risk of morbidity and mortality and delayed psychomotor and mental development. Thus, more research is needed to identify the factors involved in the growth impairment in utero in HIV and malaria co-infection. Because of our failure to control anaemia in infancy despite close clinical monitoring and early treatment with effective drugs, our studies suggest that for populations where micronutrient supplementation is considered; often nutriment of more than one micronutrient is inadequate. There is need to evaluate whether programs to deliver haematinics, antimalarials and micronutrient supplementation in an effort to prevent anemia during pregnancy will be as effective for HIV-seropositive women as has been proven to be for HIV-seronegative women.
Risk factors for HIV among pregnant women in Kenya

Lessons learnt and conclusions

The identification of risk factors for HIV infection has the potential to allow targeting of ANC counselling and testing services to women with the greatest risk and has the potential for significant cost savings in a resource-poor environment such as western Kenya. Analysis of risk factors for HIV infection in our study population identified five significant factors independently associated with HIV seropositivity, namely: anaemia, malarial parasitaemia, a history of being treated for vaginal discharge, documented fever, and reported alcohol consumption (chapter 4). Multigravidae women whose most recent child had died were also more likely to be HIV seropositive.

Although risk factors for HIV infection were discernible from our study by Poisson regression, the model containing the five identified risk factors had low positive predictive value for HIV infection. In addition, only 5.5% of the women had none of the identified risk factors.

Implications for public health and policy

Because of the high prevalence of HIV and high prevalence of factors associated with HIV infection in our entire study population, it was not possible based on our data to identify a well-defined sub-population of women to whom counselling and testing for HIV should be targeted. As observed elsewhere in sub-Saharan Africa [45-55], the overall population of pregnant women attending this ANC must be considered at high risk of HIV infection.
Maternal HIV and antibodies to malaria

In chapter 5, we report that HIV seropositive pregnant women are more susceptible to malaria infection than HIV seronegative women. The precise immunological mechanism of this increased risk is unclear. We previously reported an HIV-mediated dysregulation of cytokine responses at the level of the placenta, affecting protective cellular immune responses to placental malaria [56]. Although our current study showed a high prevalence of maternal total IgG to various malarial antigenic determinants (chapter 8), we did not find a consistent modulation of antibody responses associated with maternal HIV infection, suggesting the absence of an additional impairment of the humoral immune response. These findings are consistent with those of earlier studies in non-pregnant adults, and support previous reports that levels of total IgG to malarial antigens are not affected by asymptomatic HIV infection [57-59].

Overall recommendations

The high rates of antenatal clinic attendance in Africa imply that the impact of HIV and malaria in pregnancy can be minimised 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 short course antenatal antiretroviral therapy to HIV-infected women 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, and 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.