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

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Citation for published version (APA):
INTRODUCTION

Background
Infection by HIV and malaria represents important public health problems at the present time in many developing countries. Malaria in pregnancy is a major problem in sub-Saharan Africa, affecting an estimated 24 million pregnant women, especially in early pregnancies where malaria prevalence often exceeds 50% in endemic areas [1,2]. 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 28.1 million people are infected with HIV [3]. Africa south of the Sahara thus accounts for over two-thirds of the world’s 40 million HIV-infected persons, and 80% of the world’s HIV-infected women [4], with prevalence of HIV as high as 25-45% having been reported among pregnant women [4-8]. Without intervention, it is estimated that up to 40% of the HIV infected pregnant women will pass the virus to their children through mother-to-infant transmission [9, 10], and this will substantially impact infant and early childhood morbidity and mortality [11,12]. A recent review of the available evidence for the trends in childhood mortality as a result of malaria over the last century suggests that, despite the absence of a targeted campaign, from the 1960s onwards malaria mortality in Africa was declining parallel with the overall changes in childhood mortality. However, over the past decade, this trend has reversed with an apparent increase in malaria mortality [13]. While there are other likely contributors to this worsening of malaria in Africa such as increasing chloroquine resistance, it is certainly possible that this may be due in part to the expanding HIV epidemic [14].

HUMAN IMMUNODEFIENCY VIRUS (HIV)

Structure and pathophysiology
Viruses are intracellular parasites, i.e., they need to get into host cells in order to propagate. HIV is a retrovirus, which means that it is able to make a DNA copy of its RNA viral genome in the host cell nucleus [15]. Retroviruses use their single-stranded RNA to code for the double-stranded DNA, which is integrated into the host genome, hence the name “reverse” or “retro” viruses [16]. Retroviruses are so-called because they possess a unique enzyme [reverse transcriptase (RT)], that enables them to achieve the reverse of the well-known dogma in cell biology: namely, that deoxyribonucleic acid (DNA) codes for ribonucleic acid (RNA), which in turn codes for protein. As parasites, retroviruses are unusual in that they integrate their genome into that of the host so that the viral genome is carried continuously following infection [16].

The virus that causes HIV is the most widely studied virus in the history of biomedical science. It belongs to the subfamily of the lentiviruses, which are characterized by a long incubation period, often giving rise to immunodeficiency, sometimes accompanied by neurologic complications, anaemia and pneumonia [16]. First isolated in 1983, the HIV virus has a bilayered lipid envelope that surrounds a nucleocapsid (Figure 1). It has a two surface glycoproteins envelope (gp 120 and gp 41) and two core (inner matrix) proteins (p18 and p24) [16,17]. The RNA genome of HIV virus has at least eight genes. Three of these, namely the gag gene encodes the p18 and p24 core proteins, the pol gene encodes for the enzyme RT and the env gene responsible
for ‘locking in’ to the CD4 cell receptor codes for the membrane protein gp160, which is cleaved into gp120 (outer membrane protein) and gp41 (transmembrane protein) [16,17] (Figure 1). The HIV virus is transmitted through sexual contact or through contamination by blood and blood components and is thus transmissible during the perinatal period. The HIV has a predilection for CD4 cells and macrophages. After binding to the cellular CD4 receptors, the intact HIV enters the host cell and sheds its protein coat. The single-stranded viral RNA is transcribed by HIV’s RT into double-stranded DNA. This viral DNA is then integrated into the host genome. The virus then enters a latent phase that may last several years. During this latent phase of infection, the immune system may be damaged, but the individual is asymptomatic [17].

In most infected individuals, viral replication is eventually replicated, which leads to marked destruction of CD4-positive cells [18]. Subsequent to infection with HIV, a reduction in the CD4 population is seen and a reversal of the CD4/CD8 ratio occurs. Additionally, impairment of lymphocyte production occurs and defective cytotoxic activity by natural killer cells is observed. B cell abnormalities have also been observed, including poor antibody response to new antigens and inappropriate polyclonal activation, with resultant elevated levels of serum immunoglobulins, circulating immune complexes, and various autoimmune phenomena [16]. Whatever the precise course of events may be, it is clear that as CD4 T cell numbers in HIV patients decline [19], they eventually reach a critically low level and the symptoms of AIDS begin to appear [20]. These multiple defects in the immune response render the host susceptible to the array of opportunistic infections such as tuberculosis, non-typhi Salmonella bacteraemia, S. pneumoniae and cryptococcal disease [21-23].

Co-pathogenicity between Mycobacterium tuberculosis and HIV has now resulted in tuberculosis being the commonest AIDS-associated illness and the leading killer in HIV-infected persons, especially in sub-Saharan Africa [24].

**Effects of pregnancy on HIV**

Both pregnancy and HIV infection exert immunosuppressive effects independently. It has been hypothesized that pregnancy and HIV infection might operate synergistically to depress maternal immune function [25]. Studies of normal pregnancies have reported an impairment of cell-mediated immunity as well as a decrease in the number of CD4+ T lymphocytes [26-28].

Although CD4 lymphocyte counts fall in normal pregnancy, the concern that pregnancy may increase the rate of progression of HIV disease has not been proven [29, 30]. Impairment of cell-mediated immunity during pregnancy complicated by HIV-1 infection has been reported, but those findings are not consistently correlated with adverse clinical outcome [31], furthermore, the survival time of patients with AIDS was not affected by pregnancy in a small study [32]. Since pregnant women are able to mount a satisfactory response to intradermal skin antigens, and to reject skin grafts, it is likely that only certain selective functions of cell-mediated immunity are depressed during pregnancy [33]. A decline in the number of CD4+ T lymphocytes in the third trimester that returns to baseline after delivery has been observed in both HIV-infected and uninfected pregnancies [34]. Thus, the consensus is that pregnancy does not have a major adverse effect on HIV progression [35].
Effects of HIV on pregnancy outcome
The relationship between HIV infection and pregnancy outcome is well characterized [36]. HIV infection is associated with reduced dietary intake, malabsorption of nutrients, and metabolic alterations early in the infection [37], such that one might expect HIV disease to affect birth weight through its negative effect on maternal nutrition during pregnancy. However, prospective cohorts from the United States have consistently failed to reveal an increased risk of adverse pregnancy outcomes in seropositive mothers [31, 38-40].

On the other hand, prospective cohorts from sub-Saharan Africa [41-43] have demonstrated HIV infection to have numerous and serious adverse effects on pregnancy outcome, including maternal anaemia, low birth weight, prematurity and intrauterine growth retardation [43]; leading to infant mortality in excess of the norm both at delivery and during the neonatal period [41-43]. The association between maternal HIV status and significantly higher rate of adverse pregnancy outcome in African cohorts is of interest. Vertical transmission in utero appears to contribute to poor intrauterine growth, although the causal relation could also be reversed when poor growth increases susceptibility to transmission of the virus [44]. Possible explanation for the apparent significant difference in outcome for infants born to seropositive African women when compared to similar cohorts from the United States may be related to confounding effects such as socioeconomic factors, nutrition, an increased rate of other maternal infections such as malaria, or poor access to medical care or advanced HIV disease that may not have been accounted for.

Perinatal HIV transmission
The majority of HIV infections in childhood is acquired through maternal-infant transmission of the virus in utero or in the peripartum period, and infection of the newborn is currently 100% fatal [45]. Rates of perinatal transmission range from 15-40% of children born to women infected with HIV-1 in the absence of antiretrovirals, with higher rates reported from sub-Saharan Africa [46-48]. There is no doubt that the foetus can be infected in utero during pregnancy [49], though attention is now very focused on the events around delivery, as current belief is that as much as two thirds of vertical transmission may occur around this time. There is also good evidence that babies can be infected by breastfeeding; which adds another 7%-22% risk of transmission [50].

MALARIA
The malaria parasite is transmitted via the bite of the female *Anopheles* mosquito. In regions that are less optimal for mosquito breeding, and thus parasite transmission (e.g. areas at high altitude, with low rainfall, low mean annual temperatures), the number of infected bites per person is lower. This reduction in transmission can result in unstable or epidemic malaria. In these areas, people do not develop a significant level of immunity, and thus remain equally susceptible to infection, serious morbidity and mortality at all ages [51].

In areas of high malaria transmission, individuals receive a large number of infective mosquito bites per year. In these areas, malaria is characterized as stable or
Holoendemic. Children suffer repeated malaria attacks and morbidity and mortality mainly occurs in children below the age of 2 years [51]. As a result of frequent exposure to the parasites, children acquire substantial immunity by the age of 5 or 6 years, resulting in milder and asymptomatic malaria in older children and adults [52]. In these areas, immune persons develop antitoxic (anti-disease) immunity because the level of parasitaemia may be reduced, but parasites are rarely completely cleared from circulation [53]. An exception is during pregnancy, when the risks of maternal anaemia [54-56] and low birth weight are increased by malaria [57-59]. The risks and severity are more pronounced especially in the first malaria-exposed pregnancies (primigravidae) [60].

**Malaria in Pregnancy**

Pregnancy is a major risk factor for malaria parasitaemia and disease. In malaria endemic areas, the incidence of malaria is increased during pregnancy compared to the non-pregnancy state [52,57]. The frequency of a patent parasitaemia and disease depend on the endemic conditions under which women are living, parity and gestational age [58]. In areas of stable *P. falciparum* transmission, infection in pregnant women is frequently asymptomatic, but what makes malaria in pregnancy unique is that parasites sequester in the placenta, where infection is often extremely heavy [61-63]. Parasites are seen in maternal erythrocytes in the intervillous space in active/acute infection. If there is longer-standing infection, haemozoin (malaria pigment) is seen in peri-villous fibrin deposits in the placenta. Thickening of syncytiotrophoblast basement membrane in association with placental malaria is a consistent feature and an intervillous inflammatory response often occurs with infiltration of mononuclear inflammatory cells resulting in altered placental integrity [1, 64].

It was a widely held belief that pregnancy attenuates the immunity established to malaria at an earlier age. However, this does not explain the unique susceptibility to malaria of primigravidae (women in their first pregnancy), compared to multigravidae. Until recently, the mechanisms through which placental parasite sequestration occurs have been unclear. Recent evidence of studies in Malawi and Kenya has identified a subset of parasites, which have the ability to adhere to chondroitin sulphate A (CSA) on syncytiotrophoblast in the placenta [65]. These parasites may differ from other *P. falciparum* strains in their pathological effects and antigenic expression, resulting in evasion of the parasite from the established immune surveillance and splenic clearance. A woman becomes highly susceptible to infection in her first pregnancy but, with successive pregnancies, organ specific immunity to this subset of parasites may develop, leading to reduced frequency and severity of malaria in pregnancy [65].

**Complications of malaria in pregnancy:**

Because in areas with high transmission, *P. falciparum* infection is generally not associated with acute symptoms such as fever, it remains undetected and untreated. Adverse complications implicating malaria as a major contributing factor include: maternal and infancy anaemia, low birth weight, premature delivery and maternal and foetal mortality [60]. The incidence and magnitude of complications vary depending on the malaria endemicity and malaria immune status of the individual.
Maternal and infant anaemia

An important complication of malaria in pregnancy is the development of anaemia [54-56]. The malaria parasite develops within red blood cells and may cause anaemia via several mechanisms including direct and indirect haemolysis, accelerated removal of red blood cells in the spleen, and suppression of erythropoiesis [52]. In the tropics, anaemia due to malaria often occurs in conjunction with other important causes of anaemia including nutritional deficiencies, HIV and hookworm infections [55,66]. In sub-Saharan Africa, it is estimated that between 50-70% of pregnant women are anaemic with 5-15% being severely anaemic. Severe anaemia is a major obstetric problem, and has been associated with maternal morbidity and mortality and premature delivery [67,68,69]. Several studies have demonstrated that protection against malaria leads to an increase in haemoglobin levels in primigravidae and generally prevents severe anaemia during pregnancy [1, 69-71].

Maternal mortality due to malaria with or without anaemia is high in non-immunes [72]. In semi-immunes, maternal mortality from malaria is increased in the presence of anaemia, and commonly results from severe postpartum haemorrhage [73,74]. In areas with unstable malaria transmission, severe disease in pregnant women has been associated with 20-30% maternal mortality, and a very high risk of spontaneous abortion, premature delivery and neonatal death, occurring in women of all gravidities [75]. In areas with high P. falciparum malaria transmission, where women may have substantial acquired antimalarial immunity, women in their first and second pregnancies are most at risk of malaria and malaria-associated complications such as maternal anaemia and low birth weight [1,64].

Low birth weight and Preterm delivery

Twenty four of the twenty five million low birth weight (LBW; weight < 2500 grams) babies born each year are from developing countries, and placental malaria has been identified as a risk factor for LBW [1,57,58], presumably through decreased nutrient transport across the placenta. Additionally, maternal anaemia is also a risk factor for LBW [76], and LBW is the single greatest risk factor for neonatal and infant mortality [77]. While in developed countries LBW usually results from preterm delivery (PTD), in developing countries, it is mostly a consequence of intrauterine growth retardation (IUGR) [78]. Malaria-associated LBW may have different causes in different epidemiologic settings. In areas with a high rate of malaria transmission, infections early in pregnancy are associated with IUGR, whereas infections later in pregnancy are associated with PTD [79]. The mechanisms through which LBW occurs include an effect of maternal anaemia, haemodynamic disturbance of utero-placental circulation [75]; placental damage leading to impaired nutrient supply [80]. An association with pre-eclampsia has been suggested [81].

Congenital malaria

Although studies have reported high rates of cord parasitaemia [82-85], the incidence of congenital malarial infection (defined as the presence of parasites in the infant within 7 days of birth) is extremely low among infants of semi-immune women in malaria endemic areas [85]; none of the reported rates exceeds 0.7%, whereas rates in newborns of non-immune mothers range between 1% to 4% [85]. The exact mechanism of parasite
passage through the placental barrier is unknown, but possibly may be due to damage of the placental barrier during delivery [85] among women with dense placental infection or untreated cases of severe *P. falciparum* infection [84].

**Perinatal and infant mortality**

Spontaneous abortion, stillbirth, premature and false labour occur in women with malaria, especially in the case of massive infection of the placenta and high fevers; such clinical manifestations are expected in severe untreated *P. falciparum* during epidemics in areas with unstable malaria transmission [72,86]. Stillbirth rates in areas with stable transmission are low, with higher rates recorded among primigravidae [57,58]. Reported rates of spontaneous abortion due to malaria in stable areas are variable and unreliable. Presumably, this is due to several confounding factors such as prior use of antimalarial drugs, failure to demonstrate a patent parasitaemia at the time of abortion even if it was the underlying cause, and under-reporting in respect of retrospective studies.

A few studies that have attempted to estimate the actual contribution of malaria to infant mortality have yielded modest estimates of 3-8%, and likely reflect the range of possible contribution [87,88]. Because the required sample size may be prohibitively large, no studies have attempted to make direct observation of contribution of malaria to infant mortality. However, because infant mortality varies widely across malaria-endemic settings (50-175 per 1000 live births), it has been approximated that globally, 75,000-200,000 infant deaths might be attributable each year to malaria during pregnancy [89]. In 1999, UNICEF estimated that infant and under-5 mortality in Kenya were at 75 and 104 per 1000 live births respectively [90]. These figures are significantly lower than those reported from Asembo Bay, in western Kenya where malaria transmission is intense and perennial. Prospective data from this area indicate infant and under-5 mortality of 176 and 257 per 1000 live births respectively [91]. Antenatal clinic surveys in this area indicate HIV infection rates of 25-30%, suggesting HIV has substantial impact on child survival in western Kenya.

**THE INTERACTION BETWEEN HIV AND MALARIA**

The epidemic of HIV/AIDS in areas where *P. falciparum* is endemic has generated serious concern about potential interactions between the two infections, especially in sub-Saharan Africa [92-101]. Although driven by very different transmission modalities and dynamics, the wide geographic overlap and the concurrent high prevalence of both HIV and malaria mean that even modest effects of one infection on the other could lead to substantial impact in populations [14].

**The Impact of malaria on HIV**

The hypothesis that AIDS is a 'tumor necrosis factor disease' implicates TNF as a major contributor to viral replication and dissemination through-out the body [102]. Because infection with *P. falciparum* induces CD4 cell activation [103], which enhances production of proinflammatory cytokines in plasma [104], malarial infection is expected to enhance HIV replication [105,106] and thus accelerate HIV-disease progression [107]. This hypothesis is supported by studies that have shown increased HIV replication both in blood mononuclear cells exposed to malaria antigens *in vitro* [108] and in transgenic mice carrying complete DNA copies of the HIV genome and infected with *P. chabaudi*.
In a more recent study, proviral loads were shown to be significantly higher among HIV-infected persons with clinical malaria, compared to controls, and that these levels remained high for at least 4 weeks after treatment [110]. Even though these studies suggest that malaria in HIV infected person should reduce the time taken to develop AIDS, this has not been proven in longitudinal epidemiologic studies [111] or laboratory models [112].

The Impact of HIV on malaria

HIV infection is responsible for various immunological abnormalities, the hallmark of which is a qualitative and quantitative defect of CD4 T cells, leading to a decreased production of both IL-2 and IFN-γ [18]. It is hypothesized that the HIV related immunosuppression could lead to increased prevalence rates of P. falciparum infection, since cellular mechanisms play a major role in protection against malaria [113,114].

Distinguishing the effect of HIV on malaria between children and adults is essential: defective acquisition of anti-parasite immunity following exposure in the early years of childhood may manifest clinically or parasitologically in very different ways to progressive loss of established anti-parasite immunity in adults.

The burden of malaria in African children is high and it might be expected that if HIV is significantly affecting malaria, this should be the population in which to record the interaction. However, it is surprising that young children infected with HIV, either by mother-to-child transmission, or by transfusion observed in the longitudinal [111,115] or cross-sectional surveys [116-119], who presumably had not developed a significant immune response to malaria when tested for HIV [120], did not have high levels of parasites when compared to controls. The main criticism of these longitudinal studies were the short duration of follow-up due to study design and poor survival of HIV-infected children [111] and did not give characteristics of asymptomatic parasitaemia in their study population [115]. The shortcomings of the cross-sectional studies were that they used sick children [116,117] and had a problem of testing HIV that did not address the problems of HIV diagnosis in young children [117-119]. These studies also had substantial bias, and consequently, it is difficult to draw any conclusion from these studies.

Among adults, a significant feature of the diseases in African AIDS patients is the loss of resistance to endogenous parasites and infections normally controlled by macrophages, and this loss of resistance is attributed to the reduction in CD4 generated IFN-γ [114]. Thus, one would expect a reduction in macrophage killing of malaria in HIV subjects, leading to an increase in malaria disease. Laboratory studies using mice infected with P. berghei and the LP-BM5 murine leukaemia virus, which induces murine AIDS found that the ability of mice to develop experimental cerebral malaria decreased with the severity of the immunodeficiency caused by viral infection, and that IL-10 was implicated in this protection by down-regulating the secretion of inflammatory cytokines [121]. Previous epidemiologic studies among non-pregnant adults reported that HIV infection did not influence severity of malaria [122-126] or its clinical presentation [127]. Based on these studies, it was concluded that there was no biologic association between HIV and P. falciparum infection [128]. However, these studies were small, cross-sectional and suffered from substantial selection bias [101]. In addition, the hospital and clinic-sited studies were based on individuals attending when sick (patients with fevers
and/or diarrhoea), no information on pre-attendance therapy was available; and characteristics of HIV-infected persons were missing [129]. As was the case with studies among children mentioned above, it is also difficult to draw any conclusion from these studies among adults.

During the last few years, however, a different picture has begun to evolve. Recent case control [130] and longitudinal [129,131] epidemiologic studies investigating clinical pattern of malaria in HIV-infected persons have shown HIV infection to be associated with an increase in the frequency of clinical malaria and parasitaemia, particularly among individuals with advanced HIV disease (as measured by decreasing CD4 lymphocyte counts). These findings suggest an increased HIV-related public health problem in Africa, and have important implications for clinical management of HIV/AIDS patients in malaria-endemic areas. Thus, the growing optimism that somehow the critical global malaria situation, especially in Africa, was largely unaffected by the HIV epidemic may need revision [14].

**HIV and malaria in pregnancy**

Pregnancy establishes an extremely vascular organ which shields the parasite from destruction by extraterine immune effector mechanisms, and which permits parasite replication within its confines [1]. This happens within an otherwise effectively immune host. Pregnant women have an immune system, which is biased towards type 2 humoral defense mechanisms and away from type 1 cellular response because the latter may compromise the viability of the foetal-placental unit [132]. There is evidence to suggest that cell-mediated but not antibody responses to malaria parasites are suppressed during pregnancy [133,134].

Pregnancy is thus an important pre-disposing risk factor for malaria, and infection with HIV appears to increase this risk. Studies among pregnant women in sub-Saharan Africa provided the first evidence to suggest an important public health problem arising from the interaction of HIV and malaria. HIV infection appears to impair malarial immunity among pregnant women, such that HIV infected pregnant women demonstrate more frequent and higher density parasitaemias than HIV uninfected pregnant women [6-8, 135]. This was initially thought to be a problem principally in multigravidae due to presumed HIV-1-associated alterations in the immune memory mechanisms responsible for the parity-dependent acquisition of antimalarial immunity [6]. However, subsequent studies in western Kenya, where one-in-four pregnant women have HIV infection, showed HIV infection to be directly responsible for one-third of all malarial infections in primigravidae and as much as one-half of malarial infections in multigravidae [135].

**Malaria chemoprophylaxis during pregnancy**

Because of the consequences of *P. falciparum* infection during pregnancy in areas of high endemicity, the World Health Organization (WHO) recommends women living in such areas to receive chemoprophylaxis during pregnancy with safe antimalarial agents to protect the mother and her child from the harmful effects described [136]. However, WHO did not specify which agents to be used, allowing each country to develop its own protocol for malaria chemoprophylaxis in pregnancy [137].

Historically, the mainstay of this prevention has been the weekly chloroquine prophylaxis. The efficacy of any antimalarial policy depends on the susceptibility of the
parasite to the drug used and on the adherence of the patient to the drug regimen. The choice of an efficacious and safe regimen has, however, become increasingly challenging because of widespread chloroquine (CQ) resistance and poor adherence [138-141], prompting some countries in malaria endemic areas of sub-Saharan Africa to change their first line malaria treatment and prevention drug from chloroquine to sulfadoxine-pyrimethamine (SP, Fansidar®) [142-144]. If an antimalarial is effective when taken periodically in doses sufficient to clear parasitaemia, and needs only be given twice during pregnancy, it would be a safer alternative to regular daily or weekly prophylaxis. This would also mean it could be given when women come to the antenatal clinic, thereby improving adherence.

Scope of the thesis
This thesis is based on two main studies, which were designed to complement findings of two studies carried out in Malawi [145,146].

Intermittent preventive treatment of placental malaria with sulfadoxine-pyrimethamine (SP)
In 1994, Schultz et al [145] demonstrated that two treatment doses of SP, administered once in the second and once in the third trimester, was efficacious in decreasing placental malaria in an area where persons receive, on average, 50 infective mosquito bites/year. Important remaining questions included whether such a two-dose SP regimen would be sufficiently efficacious in an area with even higher malaria transmission and where malaria transmission is less seasonal than at the Malawi study site and, additionally, whether SP would be effective in an area with a high prevalence of HIV infection.

In western Kenya, where women receive 200-300 infective mosquito bites/year [147], the standard of care at the time of this study was to provide fever case management (CM), that is, antimalarial treatment for febrile episodes accompanied by parasitaemia during pregnancy. In the first investigation which was conducted from December 1994 through July 1996, we compared CM to two presumptive (preventive) intermittent SP-treatment regimens, namely: (1) two-dose SP, with treatment doses (1,500 mg sulfadoxine and 75 mg pyrimethamine) at enrollment and again early in the third trimester; (2) monthly SP, with treatment doses at enrollment and then monthly through 34 weeks of gestation. The objectives of the study were to determine the efficacy of the different regimens in the prevention of placental malaria, to examine for adverse effects associated with SP use, and to assess the effect of HIV infection on antimalarial efficacy and adverse drug reactions (Chapter 2).

Placental malaria and perinatal vertical transmission of HIV
Our second study was based on findings of retrospective analysis of data in Malawi [146] which suggested that exposure to both placental malaria and maternal HIV infection increased the risk of post-neonatal mortality by 3-8 fold when compared with infants born to mothers with either HIV infection or malaria alone. A possible explanation for this association could be that PM either stimulates HIV viral replication or it disturbs the placental architecture, thereby facilitating transfer of HIV-infected cells or free virus in utero. Confirmation of this association would have enormous implications, especially in sub-Saharan Africa where endemicity of malaria and HIV overlap. If confirmed, malaria
chemoprophylaxis during pregnancy could then be a practical, inexpensive, and widely applicable preventive strategy in reducing mother-to-child transmission of HIV. Consequently, we carried out a study in western Kenya between June 1996 through July 2001, whose primary aim was to determine the effect of placental malaria on perinatal transmission of HIV (Chapter 3).

Other studies of the interaction between malaria and HIV in pregnancy
The second study presented an ideal opportunity for additional sub-studies that looked at the impact of both HIV and malarial infections on maternal and infant health. Specific areas explored the following: an evaluation of the risk factors for HIV infection among asymptomatic women attending antenatal clinic (chapter 4); maternal malaria and HIV infections 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); maternal malaria and HIV infections 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).

Description of the study site
These studies were conducted at the Nyanza Provincial General Hospital (NPGH), a large publicly funded hospital, in Kisumu, a city with a population of approximately 320,000 people located on the shores of Lake Victoria in western Kenya [148], while most of the laboratory investigations took place at the Centers for Disease Control and Prevention (CDC), Kenya Field station, based at the Centre for Vector Biology and Control Research of the Kenya Medical Research Institute (CVBCR/KEMRI) at Kisian (Figure 2).

The main ethnic groups in this area are the Luo, followed by the Luhya and the Kisii. The climate is tropical with a distinct wet and dry season. Malaria is endemic and transmission occurs all year round although transmission intensifies during rainy season, which includes the months of April, May and June (long rains) and October and November (short rains). *P. falciparum* is the predominant species, accounting for 98% of malaria cases. The remaining 2% are caused by *P. malariae* and *P. ovale*. Chloroquine resistance is prevalent in the area with 75-80% of *P. falciparum* strains showing RII/RTfl resistance pattern [141]. HIV infection is also highly prevalent in the area, with 25% of the women attending antenatal care (ANC) clinic being HIV seropositive [7, 149]. NPGH with 400 beds provides health care mostly to the low-income population in this area. On average, about 30 pregnant women present each day for their first antenatal care visit to the ANC service.

Kenya is one of the poorest countries in the world with a rapid population growth due to a high fertility rate (6.4 birth per woman). The estimated maternal mortality rate is 620 per 100,000 births and infant mortality rate is 134 per 1000 live births, rates which are among the highest in the world [148]. Malnutrition, malaria and anaemia are the main three causes of mortality in the under-5's in our study area, whilst in the older age groups AIDS-related infections are the main causes of mortality.
FIG. 1. Schematic representation of the HIV. The cylindrical inner core shows the RNA strand closely associated with the RT, and surrounded by the p24 and p18 core proteins. While the \textit{gag} gene codes for the p24 and p18 core proteins, the RT is encoded for by the \textit{pol} gene. The envelope, encoded by the \textit{env} gene, makes up the surface of the virus. It has about 80 knob-like structures of glycoprotein (gp120) each connected to a transmembrane protein component (gp41). In addition to the structural genes mentioned, the HIV genome is made up of a number of regulatory genes (\textit{vif, vpr, rev, tat, vpu, and nef}).

Fig. 2. Study site
References:


60. Brabin BJ. The risks and severity of malaria in pregnant women. *UNDP/World Bank/WHO programme for Research and Training in Tropical Diseases Research (TDR).* Applied Field Research in Malaria Reports No. 1; 1991


90. UNICEF. United Nations Population Division, United Nations Statistical Division; 1999


108. Xiao L, Owen SM, Rudolph DL, Lal RB & Lal AA. Plasmodium falciparum antigen-induced human immunodeficiency virus type 1 replication


142. Malawi Guidelines for Managements of Malaria. Malaria Control Programme, Community Health Sciences Unit, Ministry of Health, Lilongwe, Malawi, 1992


Population and housing census. Nairobi, Kenya

infection among asymptomatic pregnant women attending an antenatal clinic 