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Review

Malaria and HIV Co-Infection among Pregnant Women in Africa: Prevalence, Effect on Immunity and Clinical Management: Review

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Abstract: Malaria and HIV are geographically in the tropics and subtropics of the world, including sub-Saharan Africa. Understanding the overlapping effect of both infections, especially among pregnant women, is crucial in managing pregnant women during antenatal care visits, and postpartum babies. It was realized that the prevalence of malaria among HIV-positive pregnant women ranges between 31–61%, while for non-HIV infected pregnant women the prevalence still stands between 10 and 36%. Co-infection is between 0.52 and 56.3%. Even though the rate of mother-to-child transmission of HIV has dropped, MTCT of malaria still remains a problem. MTCT is associated with low birth-weight, anemia, and even immune dysregulation. The adoption of the Option B+ plan has proven to be effective in the fight against the MTCT of HIV. However, malaria in pregnancy still remains a problem. Concurrent administration of both antimalarial drugs and Cotrimozaxole to pregnant women is not recommended, because of the toxic effect of the interaction of both drugs. Nevertheless, studies looking at the effect of the current ART regimens on mothers and their children need to be carried out. Studies looking at exposed children over a longer period of time, to determine their susceptibility to malaria infection and also to monitor their immune response to malaria over time, are needed.

Keywords: malaria; HIV; co-infection; prevalence; interaction; immunity; treatment; Africa

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1. Introduction

Malaria and HIV are concentrated geographically in the tropics and subtropics of the world, including sub-Saharan Africa [1,2]. Around 70% of the world's HIV-infected population lives in sub-Saharan Africa, where 350 million people are at risk of malaria infection [1]. Malaria and HIV co-infection is expected, due to the overlapping distribution of both diseases [1]. Both illnesses are leading causes of morbidity and mortality, predominantly in sub-Saharan Africa [3].

Malaria during pregnancy has profound effects, including parasite sequestration in the placental vascular space [4]. It may result in increased morbidity and mortality, abortion, stillbirth [5], low birth-weight (as a result of intrauterine growth retardation and preterm birth), and mother-to-child transmission (MTCT) of parasites [6]. In areas of stable malaria transmission in sub-Saharan Africa, it is recommended that all pregnant women should receive intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) at each scheduled antenatal-care visit (at least one month apart), until delivery [7,8]. Several studies have shown that HIV during pregnancy amplifies the effects of malaria [9], which is why administering Cotrimozaxole alongside antiretroviral therapy (ART) to pregnant women is essential during every antenatal-care visit [9].

Nevertheless, there is enough evidence to show that, despite efforts such as the distribution of long-lasting insecticidal bednets (LLINs) to pregnant women [10] and the implementation of intermittent preventive treatment (IPT-p) programs to reduce the burden of these infections [11], co-infection among pregnant women remains a problem, as malaria during pregnancy persists among pregnant women [1,12–14].

The persistence of malaria during pregnancy is linked to multiple factors, such as the inappropriate use of LLINs [15], not owning a single LLIN, and drug shortages at health institutions [15,16]. Therefore, a clear understanding of the overlapping effect of malaria and HIV infections among pregnant women is fundamental to controlling and improving the clinical management of women during antenatal-care visits and of babies postpartum.

This paper reviews relevant publications on the prevalence of malaria and HIV co-infection, the impact of malaria and HIV co-infection on biological, clinical, immunological, and therapeutic outcomes (not excluding the effect on transmission), and treatment strategies for malaria and HIV co-infected patients. We finally conclude with some future perspectives.

2. Malaria and HIV co-infection during pregnancy

2.1. Epidemiological Evidence of Malaria and HIV Co-Infection among Pregnant Women in Africa

In sub-Saharan Africa (SSA) severe public health hazards such as malaria and HIV/AIDS persist. Both illnesses are widely spread in the sub-Saharan region, but their ranges overlap [1]. A parasitic disease known as malaria claimed the lives of 216 million people and resulted in 445,000, cases in 2016 [1]. The World Malaria Report suggests that African nations should emphasize support for pregnant women and children [17]. Approximately 11 million pregnant women in 38 countries in sub-Saharan Africa with moderate-to-high transmission were infected in 2018. This resulted in an estimated 872,000 babies being underweight, due to malaria in pregnancy [18]. Malaria-related maternal mortality is Nigeria's most significant public-health issue [19]. The most common malaria complications in expectant mothers are low birth-weight, high placental plasmodia load, fetal difficulties, and even newborn mortality. These are all results of malaria during pregnancy [20].

Malaria is primarily known as a climate-sensitive disease [21]. Environmental factors such as temperature, humidity, and rainfall affect the plasmodium and its transmitters (anopheles mosquitoes) [22]. The temperature has an impact on the parasite and mosquito life-cycles. Rain provides a habitat for mosquito fertilization and reproduction [23]. The combination of humidity and temperature can influence malaria incidence. Malaria is most common during the hot seasons [24]. The prevalence of malaria in pregnancy varies as we move from one geographical area in Africa to another, as seen in Table 1.

Female anopheles mosquitos transmit malaria to humans during a blood meal [25]. Six Plasmodium species cause malaria in humans; *P. malariae, P. vivax, P. Ovale, P. Knowles,* and *P. falciparum,* which is the most virulent, and responsible for most infections in sub-Saharan Africa [26]. Recently, *P. cynomolgi,* which was familiar to the monkey, was found to be associated with human conditions [27,28]. However, studies showing the association of this species with human disease in Africa are rare.

On the other hand, HIV is caused by the human immunodeficiency virus [29,30]. Even though sub-Saharan Africa has only about 11% of the world's population, it is the epicenter of HIV/AIDS [31]. HIV can be transmitted through the exchange of infected people's body fluids such as blood, breast milk, sperm, and vaginal secretions. During pregnancy and delivery, HIV can also be passed from mother to child [32]. However, the implementation of the prevention of mother-to-child-transmission programs for HIV-positive pregnant women, has reduced the rate of vertical transmission of HIV to children [33,34].

Table 1. Few studies showing the epidemiology of Malaria and HIV co-infection among pregnant women in Africa.

Study Area	Study Design	Prevalence (%)			Conclusion	Ref.
		Malaria	HIV	MHC		
HIV-Negative Pregnant Women						
Cameroon	Prospective cohort	25%	NR	NR	Primigravida single women, and women under 20 years had a higher incidence than multigravida married women, and women over 20 years. This study only saw *Plasmodium falciparum*.	[35]
Nigeria	Cross-sectional	28.7%	NR	NR	Moderate malaria parasitemia was higher among HIV-positive pregnant women. All malaria preventive strategies should be intensified during pregnancy, as ITNs provided little protection.	[36]
Ghana	Cross-sectional	11.0%	NR	NR	The prevalence of malaria and anemia in pregnancy among pregnant women in the Akatsi South District remains a source of concern. The high use of IPTp-SP and LLIN was observed, positively affecting malaria prevalence among pregnant women.	[37]
Ethiopia	Cross-sectional	10.2%	NR	NR	Malaria is still a public health problem among pregnant women in the Sherkole district. Age, ITN-use, gravidity, gestational age, and health education had a significant association with malaria.	[38]
Malawi	Longitudinal	5.0%	NR	NR	Increased bednet coverage explains changes in parasitemia and birth weight among pregnant women better than sulfadoxine-pyrimethamine use.	[39]
DR Congo	Cross-sectional	14.97%	NR	NR	Malaria is common among Mwene Ditu's pregnant women. The ANC attendance and an appropriate organization prove to be of paramount importance.	[40]
Burkina Faso	Cross-sectional	15.7%	NR	NR	The prevalence of *P. falciparum* infection among pregnant women in Burkina Faso remains high, despite IPTp-SP and ITNs being shown to reduce the risk of disease.	[41]
Niger republic	Cross-sectional	36.52%	NR	NR	Ignorance was discovered to be a factor in the epidemiology of malaria in the area, and a mass public-enlightenment program was proposed as a control measure.	[42]
Benin	Cross-sectional	15.3%	NR	NR	This study demonstrates the higher performance of ultrasensitive RDT compared with conventional RDTs in detecting low parasite-density *P. falciparum* infections during pregnancy, particularly in the 1st trimester	[43]
Kenya	Cross-sectional	12.9%	NR	NR	The majority of the women had anemia and asymptomatic malaria pregnancy.	[44]
HIV-positive pregnant women						
Cameroon	Case study	61.5%	17.2%	18.5%	Malaria and HIV research is lacking in many locations. The extent and effects of treatment interaction between these two diseases remain unknown. Malaria and HIV programs must cover the poor and vulnerable and integrate services whenever possible.	[45]
Seven sub-Saharan Africa	Cross-sectional	31%	1.3%	0.52%	Malaria was associated with an increased prevalence of anemia during pregnancy.	[46]
Ethiopia	Cross-sectional	-	-	22.2%	With increasing duration of ART use, there was a significant improvement in the mean CD4+ T cell count, Hb level, and parasite density in HIV/malaria co-infected pregnant women.	[47]
Nigeria	Cross-sectional	-	-	56.3%	The prevalence of malaria recorded in this study is high, but with negative results for all socio-demographic variables of participants and malaria risk factors.	[48]

Abbreviations: CD4: cluster of differentiation 4; ART: antiviral therapy; Hb: hemoglobin HIV: human immunodeficiency virus.

2.2. Effect of Malaria and HIV Co-Infection on Mother-to-Child Transmission of Malaria and HIV

Mother-to-child transmission (MTCT) is the most common way newborns and children acquire HIV-1 and malaria [49]. It can occur in utero, intrapartum, and postnatal, through nursing. Antiretroviral usage throughout pregnancy, labor/delivery, and lactation have prevented MTCT. MTCT's multiple processes remain unclear [49].

MTCT has been dramatically reduced, especially in resource-rich settings, with comprehensive testing during pregnancy, the use of anti-retroviral (ARV) drugs during pregnancy, intrapartum and postnatal for the infant, elective cesarean delivery when the HIV-1 viral load remains detectable near the end of pregnancy, and the avoidance of breastfeeding [50]. MTCT has viral and host elements playing roles (Table 2) [49].

Table 2. Genetic, co-infection, behavioral, and dietary factors influence mother-to-child HIV-1 transmission.

	Main Aspect	Factors
1	Genetic factors	• Fetal gender and HLA type
		• Maternal–fetal HLA concordance
		• SNPs for chemokines/chemokine receptors/innate immune factors
2	**Maternal or infant co-infection**	• **Malaria**
		• Tuberculosis
		• Mastitis/breast abscess
		• Oral candidiasis in the infant
		• Chorioamnionitis
		• STIs: genital ulcer disease including HSV2 and syphilis
3	Behavioral factors	• Number of sexual partners during pregnancy
		• Frequency of sexual intercourse during pregnancy
		• Illicit drug-use during pregnancy
		• Infant feeding practices: breastfeeding, mixed feeding, food premastication
4	Maternal nutritional status	• Vitamin A deficiency
		• Advanced maternal disease with immunosuppression and malnutrition
		• Other micronutrient deficiencies

Abbreviations: HLA: human leukocyte antigen, STI: sexually transmitted infections, HSV2: herpes simplex virus type 2.

Malaria affects the placenta, causing pregnancy complications [51]. HIV-positive pregnant women who get malaria are at greater risk of all pregnancy complications. Co-infected pregnant women are more likely to suffer anemia, placental malaria, and poor birth weight [9]. HIV increases the risk of malaria infection and clinical malaria in adults in places with stable malaria transmission, such as the Democratic Republic of Congo (DRC), especially those with significant immunosuppression [52]. In addition, HIV-infected people have a higher risk of severe malaria and death [53,54]. Primigravida women tend to have severe malaria [55]. There are conflicting data on malaria's influence on HIV-1 MTCT. Several studies have shown no link between malaria and MTCT. However, some studies have shown that HIV reduces the transfer of maternal antibodies against malaria, to the baby [56]. Malaria raises HIV-1 viral load, but malaria therapy diminishes it [57].

Recent studies have shown that *P. falciparum* stimulates HIV-1 replication by activating lymphocytes in order to produce IL-6 and TNF-α. *Plasmodium falciparum* increases the

number of CCR5+ placental macrophages [58]. Therefore, HIV–Plasmodium co-negative infection effects are mainly due to immunological interactions. HIV-mediated immune-system damage reduces malaria's immunological-mediated control, and malaria can drive HIV replication by activating T cells and releasing cytokines. Immune changes during pregnancy may explain some adverse effects in co-infected pregnant women [58]. In a study of HIV-1 and malaria-infected women in western Kenya, higher parasitemia levels (>10,000 parasites/l of blood) were linked to an increased probability of MTCT of HIV-1 [59].

Placental malaria has been shown to increase the RNA viral load. Haemozoin treatment of intervillous and peripheral blood-mononuclear-cells enhanced the RNA viral load and generated IFN-γ and TNF-α, two pregnancy-damaging cytokines. Malaria infection increases the expression of the HIV co-receptor c-c chemokine receptor type 5 (CCR5) on placental macrophages [60]. This shows that in such a situation, there will be an increase in mother-to-child transmission, especially with higher viral loads [60]. However, contradictory results have been obtained [60]. Inconsistent study results may be owing to changes in malaria epidemiology, which could impact maternal immunity. Malaria and MTCT need more study [49]. However, it should be noted that these two infections interact bi-directionally and synergistically. HIV infection can raise the risk and severity of malaria, and parasite loads may increase transmission rates [60].

2.3. HIV and Malaria Co-Infection Affects Immune Modulation during Pregnancy

Infection with HIV or malaria during pregnancy generally has negative consequences for both mother and child [61]. Co-infection raises the chances of these outcomes, including maternal anemia and low birth-weight [61]. Critical public health issues are the immunological grounds underlying HIV-infected women's greater vulnerability to malaria and the co-infection effect on HIV transmission from mother to child [61]. These heightened hazards are most significant, once again, in multigravidas. These epidemiological findings indicate a substantial impairment in acquired immunity to malaria in HIV-infected pregnant women, resulting in a reduced ability to restrict the *P. falciparum* infection. This result is supported by the discovery that the preventive efficacy of sulfadoxine-pyrimethamine in HIV-infected pregnant women is diminished [62]. Both humoral and cellular immune-responses protect against malaria infection. Unfortunately, these adaptive immune-response compartments are also profoundly altered during HIV-1 infection [61]. The available evidence in Figure 1 shows proof that co-infected pregnant women have significant changes in both humoral and cell-mediated immune responses to malaria [61].

2.4. HIV Effect on the Humoral Immunity to Malaria

Regarding humoral immunity, antibodies against malaria antigens can protect using various methods, including preventing parasite penetration into host cells, phagocytosis, and antibody-dependent suppression of cellular development [63,64]. Some studies have found that HIV infection reduces the humoral immune-response to malaria. Daniel et al. reveal that point estimates of all antigen responses were lower in HIV-infected children. However, this was only statistically significant for AMA1. HIV-infected children were less likely to respond well to AMA1. HIV was linked to a narrower range of responses to particular merozoite antigens. HIV altered the rate of age-related acquisition of antibodies against schizont extract, but not the rate of age-related development of responses to specific merozoite antigens [65]. Another study carried out in Kenya comparing humoral immune-response among pregnant women with CD4+ T-cells $\leq$ 500 and those with CD4+ T-cells > 500 when using a protein microarray revealed that 57 antigens, including CSP, MSP1, LSA1, and AMA1, were shown to be substantially more reactive in women living in the area of all-year-long malaria transmission. In a previous investigation, ten of these antigens were found to be protective. The CD4+ T-cell count did not affect humoral responses [66].

These findings were contrary to the conclusions from Ayisi and collaborators, who reported lower incidence and concentration of antibodies against the circumsporozoite protein (CSP)-repeat sequence NANP, which can prevent sporozoites from penetrating

liver cells in the pre-erythrocytic stage. Antibodies against EBA-175, a blood-stage antigen important in parasite penetration of red blood cells, showed a similar pattern. These consequences were not caused by placental malaria. There were no apparent HIV-associated alterations for the other antigenic determinants studied—MSP119kD, MSP-2, MSP-3, and RAP1—implying that HIV infection impacts antibody responses to certain, but not all, malaria antigens [67]. However, Babakhanyan et al., in Yaoundé, Cameroon, revealed that Cord IgG levels to CSP, MSP-1 and TCC were considerably lower in neonates born to HIV+ mothers. The frequency of hypergammaglobulinemia in mothers was substantially greater in HIV+ women than in HIV mothers. Maternal hypergammaglobulinemia was linked with a reduced trans-placental transfer of antibodies to CSP, MSP-1, and TTC [56].

Other studies have shown a decreased prevalence of antibodies against the variant surface antigen (VSA) among HIV-positive pregnant women, which helps to prevent parasite attachment to chondroitin surface A (CSA), which is more concentrated in the placenta [68–71]. This decrease was found in all gravidities, irrespective of the malaria infection status. These findings are critical, because HIV-related declines in antibody responses to VSA may explain some of the increased susceptibility of HIV-infected pregnant women to malaria. Anti-VSA antibody-deficiency may impair protective immunological processes in at least two ways. (1) These antibodies may prevent parasite sequestration by CSA in the placenta. (2) Anti-VSA antibodies are anticipated to play an essential role in the phagocytic uptake of CSA-binding parasites by monocytes and macrophages. As a result, decreasing this antibody response can have a deleterious impact on parasite clearance [66,71]. However, further investigations are required to understand the biological basis behind HIV-infected pregnant women's higher sensitivity to malaria infection.

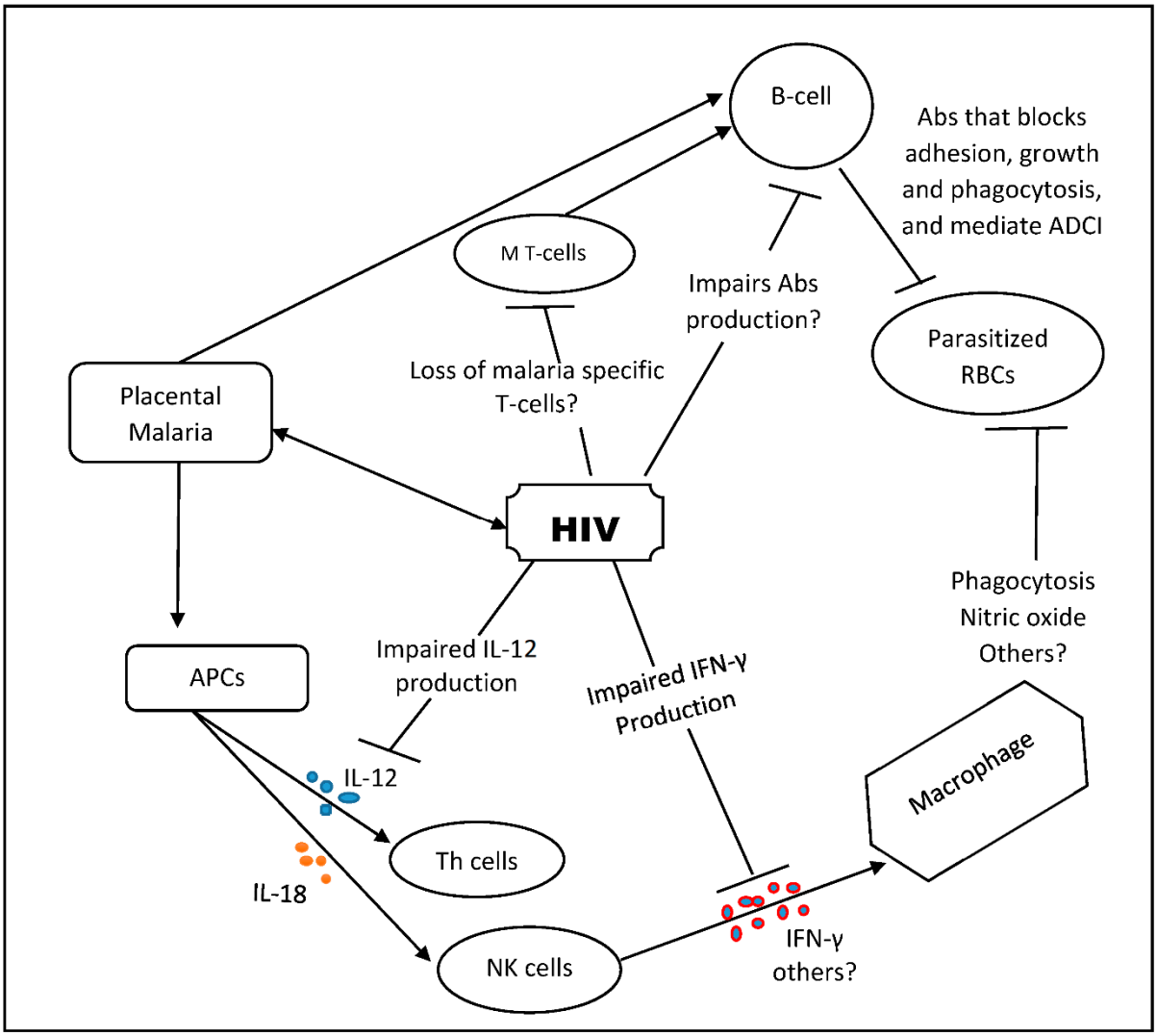

Figure 1. The image depicts how HIV-1 infection compromises various immunological mechanisms related to placental-malaria prevention [61]. Placental malaria can activate antigen-presenting cells, resulting in the release of cytokines such as IL-12, IL-18 [72], and others, as well as the presentation of antigens to T cells. This can activate T cells, particularly Th1 cells, which release IFN-γ. Furthermore, innate immune mechanisms involving natural killer (NK) cells may be activated during placental malaria infection, leading to the release of IFN-γ and other cytokines. IFN-γ can protect by activating macrophages to phagocytize malaria parasites and release nitric oxide and other mediators. HIV-1 infection has been demonstrated to affect IL-12 and IFN-γ production in pregnant women [73,74]. As a result, protective cellular immunological pathways that can limit placental malaria infection are affected. Because HIV causes memory T cell loss even before the onset of AIDS, the stimulation of malaria-antigen-specific T cells, particularly memory cells, during placental malaria infection may render these T cells attractive targets for HIV infection and death [75]. This will affect cellular and humoral immune-responses. Infection with malaria can stimulate B-cells to release malaria-specific antibodies, including VSA. Anti-VSA antibodies can prevent parasites from attaching to placental CSA receptors. Antibodies against many parasite surface antigens, including VSA, can impede parasite invasion and development and mediate phagocytosis and antibody-dependent cellular inhibition (ADCI). HIV-1 infection affects the production of antibodies in some malaria antigens, such as VSA, compromising anti-malarial immunity [71]. Abbreviations: HIV: human immunodeficiency virus, Th: T-helper cells, APCs: antigen-presenting cells, IL: interleukin, IFN: interferon, MT-cell: memory T-cells, RBCs: red blood cells, ADCI: antibody-dependent cellular inhibition.

2.5. HIV Effect on the Cellular Immune Response to Malaria

On the other hand, for cellular immunity, many immune-cell types and the soluble immunoactive substances released are critical for malaria protection. Several investigations have focused on the cytokines and chemokines that may mediate in the protection against placental malaria [76,77], and how they are altered in HIV-1 infection. Placental intervillous blood mononuclear cells (IVBMCs), cells of maternal origin found in the placental intervillous gaps, have been employed in various searches. IVBMC production of the T-helper (Th)1 cytokine interferon (IFN)-γ, which is required for activating monocytes and macrophages for parasite clearance, has been linked to protection from placental malaria [74]. Regardless of their malaria status, HIV-infected women's IVBMCs generate considerably lower amounts of IFN-γ than HIV-uninfected women, particularly in response to stimulation with crude blood-stage malaria antigens [74]. Other studies showed that IL-12, which contributes to IFN-γ regulation, was impaired to almost undetectable levels in IVBMC among HIV-infected pregnant women [73,78]. However, some studies have shown an increased level of IL-10 amongst HIV-infected pregnant women and a low likelihood of flora infection [79].

Some studies evaluating levels of the cytokine tumor necrosis factor (TNF)-α, IL-4, IL-10, and macrophage migration inhibitory factor (MIF), as well as the chemokine macrophage inflammatory protein (MIP)-1α and MIP-1β, showed no generalized suppression of cytokines due to HIV-1 or HIV-placental malaria co-infection [73,74]. Interestingly, other studies showed a complex immune response, with an elevated level of MIP-1β in co-infected pregnant women, compared with non-pregnant HIV-infected women [4,80]. This indicates that cellular immune-response to malaria in co-infected women has a complex alteration level, including the loss of the protective pathway that involves IFN-γ, and the potential up-regulation of other chemokines and cytokines [61]. Other studies have shown that the immune alteration becomes severe with decreased levels of CD4+ T-cells, and reduces inversely with increased levels of viral load [73,74].

3. Clinical Management of Malaria and HIV Co-Infection

3.1. The Clinical Management of Malaria

Chloroquine has been the first-line medicine for treating mild malaria in sub-Saharan Africa, followed by sulfadoxine-pyrimethamine (SP) as the most cost-effective second-line therapy. However, recent studies show that the clinical efficacy of both drugs has been significantly diminished, due to *Plasmodium parasite* resistance [81]. Using the World Health Organization's standardized technique, twenty-five surveys were conducted in Cameroon between 1997 and 2004, to examine the effective therapeutic and second-line anti-malarial medicines (WHO). In the southern and central areas, chloroquine was ineffective, with a treatment failure rate of more than 25% [82]. Sulfadoxine-pyrimethamine (SP) failure rates varied from 8.6% to 14.1%. Despite being used as a first-line antimalarial treatment from 2002 to 2004, amodiaquine remained effective across the country, with a failure rate of around 4% [83].

The World Health Organization (WHO) advises pregnant women to take sulfadoxine-pyrimethamine (SP) and use insecticidal nets (ITNs) for the successful management of clinical malaria and anemia [18]. Any interaction between malaria parasites and HIV might result in an additional health burden, especially in pregnant women, with poor birth outcomes and the potential transmission of these intracellular diseases from mother to child [84]. HIV-infected women using Cotrimozaxole to decrease opportunistic infections should not receive IPTp, due to the increased risk of significant skin reactions such as Stevens–Johnson syndrome (unless otherwise indicated). Mefloquine increased the chance of HIV transmission from mother to child, while decreasing parasite incidence in HIV-infected women [85].

Houmsou et al. advised the following in a study of malaria infection in HIV-infected pregnant women visiting a rural prenatal clinic in neighboring Nigeria: (i) HIV-infected pregnant women in their first trimester should be administered sulfadoxine-pyrimethamine

(SP) like their counterparts in the second and third trimesters, or they should be given daily Cotrimozaxole, which has been used with HIV patients for malaria prophylaxis [86]. (ii) Iron deficiency, the most common cause of anemia, should be adequately examined, and pregnant women should be treated as soon as possible to prevent anemia, from both malaria and HIV in pregnancy [86] as well as receiving HIV follow-up care among pregnant women [86]. (iii) To reduce the detrimental impacts of malaria throughout their pregnancies, HIV-infected pregnant women in rural areas should be effectively and comprehensively informed of prophylactic malaria measures [86]. (iv) Health nongovernmental organizations (NGOs) should enter into memorandums of understanding (MoU) with both public and private hospitals in remote areas that are already underfunded and underserved by stakeholders. These non-governmental organizations may help organize effective malaria and HIV screening, control programs, and follow-up HIV care among pregnant women [86].

Recently, the World Health Organization (WHO) has recommended that the malaria vaccine RTS, S/AS01 (RTS, S) be extensively administered to children in sub-Saharan Africa and other countries where Plasmodium falciparum, the most fatal of malaria parasites, is endemic. This advice was based on the findings of 11 pilot studies in sub-Saharan Africa, with varying levels of endemicity [87,88].

3.2. Role of Malaria Vaccine in the Management of Malaria during Pregnancy

Despite significant progress in malaria vaccine development in recent years, no trials of malaria vaccines have ever been conducted in pregnant women [89]. In December 2016, an expert meeting was convened at the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Health (NIH), in Rockville, Maryland, to deliberate on the rationale and design of malaria vaccine trials in pregnant women [89]. Even though human trials on these vaccines have not been conducted yet on pregnant women, studies testing the potential of some of these vaccine markers have been carried out [87,90,91]. Nevertheless, Table 3 outlines some of the malaria vaccines to be considered for human trials on pregnant women [89].

Table 3. Malaria vaccines currently in clinical development which may be considered for testing in pregnant women.

Vaccine (Type)	Status	Target	Activity	Indication	Developer
RTS,S/Mosquirix (subunit)	Phase 3 complete	Sporozoite/liver stage	Prevent disease	Reduce childhood disease	GlaxoSmithKline
PfSPZ Vaccine (whole organism)	Phase 2	Sporozoite/liver stage	Prevent infection	Elimination; travelers	Sanaria
VAR2CSA (subunit)	Phase 1	Infected red cell	Control infection	Prevent placental disease	Various(EVI)
Pfs25/Pfs230 (subunit)	Phase 1	Mosquito stages	Block transmission	Elimination	NIAID

In a study conducted in Mali on PfSPZ-CVac malaria vaccine safety in malaria-experienced adults, it was realized that the efficacy of PfSPZ-CVac was 33.6%. PfSPZ-CVac (CQ) was tolerated well. The tested dosing-regimen failed to protect significantly against *P. falciparum* infection in this high transmission setting [90]. Another study showed that the efficacy of PfSPZ-CVac increases to 75% when the dose is doubled [92].

Furthermore, studies have shown that in subsequent pregnancies, women develop protective immunity against pregnancy-associated malaria, which is thought to be due to the acquisition of antibodies for the parasite variant surface antigen VAR2CSA [93]. Multiple studies have been conducted on this marker to evaluate its suitability as a vaccine candidate [94,95]. Nevertheless, studies looking at the efficacy of this vaccine are rare.

Other studies have shown that Pfs230-C is a suitable candidate vaccine marker, with an efficacy of 83.5% and 99.7% anti-Pfs25 in preventing malaria. The effectiveness of vaccines targeting either Pfs25 or Pfs230 may increase as malaria transmission declines [96].

RTS, also known as Mosquirix, is the only vaccine that has reached the clinical trial phase, and was approved for use in children by the World Health Organization [87]. Compared with the control group, the larger, extensive trial of the RTS S/AS01 vaccine showed efficacy estimates of 28.3% against all malaria episodes over a median of four years of follow-up in the group that received three doses of the RTS, S/AS01 vaccine [97].

3.3. Clinical Management of HIV-Infected Pregnant Women

Over the last two decades, international health programs and interventions have been implemented regarding human immunodeficiency virus transmission from mother to child (HIV) [98]. The World Health Organization revised its recommendations for using antiretroviral drugs in pregnant women and preventing HIV infection in infants in 2004, stating that pregnant women who require highly active antiretroviral therapy (HAART) for their health should start first-line ART regimens as soon as possible during pregnancy. HIV-infected pregnant women who do not need antiretroviral medication should start on Zidovudine (ZDV) at 28 weeks, ZDV throughout labor, and single-dose Nevirapine (sd-NVP) plus ZDV for one week after the child is delivered [99,100].

For example, Cameroon and some African countries [92] are transitioning from Efavirenz to Dolutegravir (DTG). Some studies have demonstrated that Efavirenz, a first-line treatment, is sluggish in lowering the viral load. This reduces the chances of safeguarding the baby from HIV infection during birth [101]. According to a study that used data from a trial in Cameroon, the Dolutegravir-based regimen, a low-cost, generic, fixed-dose antiretroviral therapy (ART) combination containing Tenofovir, Lamivudine, and Dolutegravir, is the preferred first-line treatment for patients with HIV-1 infection [102,103]. However, there are concerns about the overall risks and benefits of using Dolutegravir monotherapy in women of childbearing potential, given the increased risk of neural tube defects in those who already have resistance to Tenofovir and Lamivudine [104].

3.4. Guidelines for Monitoring and Prophylaxis of HIV-Exposed Children

All children born to HIV-positive mothers, commonly known as exposed children, are routinely examined at a health facility until the danger period of postpartum HIV transmission has passed (18–24 months postpartum) [105]. Children born to HIV-positive mothers should undergo thorough clinical and biological testing after birth and before being discharged from the hospital. Results should be noted in their medical records. Efforts are also being made to identify children born to HIV+ mothers at child entrance sites (immunization, pediatric, antiretroviral therapy service) [105]. Cotrimozaxole should begin six weeks after birth for all newborn/HIV-exposed children, and continue until weaning and HIV infection is eliminated. NVP prophylaxis should be given to newborns delivered to HIV-positive mothers as follows: (i) for six weeks if the mother receives antiretroviral therapy, regardless of the feeding method chosen by the mother; (ii) for 12 weeks if the infant is breastfed or if the mother did not receive treatment during pregnancy, or received it for less than four weeks; and (iii) for the duration of breastfeeding, if the mother received antiretroviral therapy during pregnancy (option A) [105].

Nevirapine is prescribed in Cameroon as a single daily dosage. Table 4 shows the dose of preventive Nevirapine to give to infants delivered to HIV+ mothers, based on their birth weight [105]. ARV regimen for infants delivered to mothers with ARV drug-resistant virus is unclear. Although some studies have shown that ARV drug-resistant viruses may have diminished replicative capacity (reduced viral fitness) and transmissibility [106], there is the perinatal transmission of multidrug-resistant viruses [106–108]. Maraviroc (MVC) was recently licensed for infants weighing 2 kg, and may give an alternative treatment option for neonates of mothers with multidrug-resistant HIV-1 that remains CCR5-trophic [109].

Table 4. Nevirapine (NVP) dosages in exposed children born to HIV-positive mothers in Cameroon.

	DOSAGE
From birth to 6 weeks	
• Weight: 2000 to 2499 g	• 10 mg in a single dose (1 mL)
• Weight ≥ 2500 g	• 15 mg in a single dose (1.5 mL)
1 mL = 10 mg NVP	

Note: For newborns with low birth weight (<2000 g), start with 2 mg/kg (0.2 mL/kg) daily until they reach 2000 g. All asymptomatic HIV-exposed children should take BCG, yellow fever, and measles vaccines only when the child is immunocompetent (CD4 > 25%).

4. Conclusions

Malaria during pregnancy remains a problem in Africa. Mother-to-child transmission is associated with several adverse outcomes, such as low birth-weight, stillbirth, anemia, and immune dysregulation. Even though the current option B+ treatment plan effectively prevents MTCT of HIV, mother-to-child malaria transmission remains a problem. Studies in other areas have shown that HIV-exposed children are more susceptible to opportunistic infection when compared to unexposed children. Therefore, studies examining exposed children over a more extended period, to determine their susceptibility to malaria infection and their immune response to malaria over time, need to be carried out. Nonetheless, studies looking at the efficacy of vaccine candidates for malaria in pregnancy need to be carried out.

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Data Availability Statement: Due to confidentiality, data will not be made public but will be provided to coauthors upon request. However, this will be upon the validation of the study protocol to ensure it meets all the necessary ethical consideration.

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