

# Malaria and HIV co-infection: available evidence, gaps and possible interventions

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## Abstract

**Objectives:** To review the evidence of association between malaria and HIV/AIDS co-infection for purposes of developing strategies for malaria control.

**Design:** Desktop review of literature.

**Setting:** Harare, Zimbabwe.

**Main Outcome Measures:** Response to treatment, development of severe malaria, malarial immunological response in HIV/AIDS positive people and incidence of malaria in HIV/AIDS positive individuals.

**Results:** HIV-1 infection increases the incidence of *Plasmodium falciparum* parasitaemia and is associated with the development of severe malaria, commonly anaemia, cerebral malaria and high parasite density (OR=2.56; 95% CI=1.53 to 4.29; p<0.001). The efficacy of chloroquine and sulphadoxine-pyrimethamine in reducing placental malaria in HIV-1 positive pregnant women was impaired compared to HIV-1 negative pregnant women. However, the situation in non-gravid HIV-1 positive people as regards efficacy of chloroquine and sulphadoxine-pyrimethamine prophylaxis is not known. Also not known is the relationship between malaria parasitaemia without symptoms and HIV-1 infection, the results of which may provide useful information regarding malaria control and prevention in HIV-1 positive people.

**Conclusions:** HIV-1 positive people staying in malaria endemic areas are at risk of developing severe malaria. Malaria prevention using insecticide-treated bednets and indoor residual house spraying may be the best available options for these people. Chloroquine and sulphadoxine-pyrimethamine prophylaxis require further studies to verify their efficacy, in the presence of HIV-1/AIDS infection.

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## Introduction

Malaria still remains a major public health problem in southern Africa and Zimbabwe, where it causes severe morbidity and mortality. The World Health Organization (WHO) estimated that more than 88 million people worldwide were at risk of malaria in 1998 alone.<sup>1</sup> In 1998, the estimated malaria prevalence in Zimbabwe was 15%

and more than 1.7 million clinical malaria cases were reported with 2 040 hospital deaths (Hospital Crude Fatality Ratio of 4.03).<sup>2</sup> Malaria is characterized by an acute febrile illness that is associated with headache, joint pains and vomiting. The actual pathophysiology of malaria is complex and not well understood.<sup>3,4</sup> It is believed that the malaria parasite merozoite adheres to the erythrocyte membrane's

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glycophorin A receptor to trigger a series of immunological responses.<sup>3,4</sup> Infection with malaria results in the reduction in the T-helper cells and CD4 lymphocytes. The presence of HIV infection is believed to alter this immunological response due to *Plasmodium falciparum* infection and therefore promotes the development of severe malaria. Complications occur commonly with *Plasmodium falciparum* infection and usually in young children, pregnant women, debilitated persons, adults in epidemic prone areas and people moving from non-endemic to endemic areas including immunosuppressed patients.<sup>5</sup> The commonest complications include cerebral malaria, hypoglycaemia, renal failure and anaemia. The mainstay of malaria prevention and control in Zimbabwe includes indoor residual spraying, passive case finding, accurate diagnosis and adequate treatment.

Malaria and HIV-1 infection share a few similarities and differences. The similarities are that both infections are prevalent in southern Africa where poverty is also prevalent. The infecting agent enters the body system through binding to a cellular receptor, the two infections cause a reduction in T-helper and CD4 cells in the circulation and fever is a common symptom.<sup>6,8</sup> The few differences are that the focus in malaria control is on both the vector through spraying and insecticide treated bed-nets and on the host through adequate case management.<sup>7</sup> The main focus in the management of HIV-1 infection and AIDS is on the host through promoting behavior change. The other difference is that the emergence of HIV/AIDS pandemic has been associated with the emergence of other diseases that were previously under control, like tuberculosis and cancers. There are no known disease conditions that are modified by malaria infection. The pathophysiological interaction of malaria and HIV-1 is of public health interest in Africa and more importantly southern Africa. Several studies have made conclusions which have not affected the management of either malaria or HIV/AIDS. The aim of this literature review was to document the available evidence and gaps so that possible strategies may be recommended for malaria prevention and control in Zimbabwe.

#### Specific Objectives.

1. To conduct a literature review on the information between malaria and HIV-1 co-infection
2. To document the available evidence and gaps between malaria and HIV/AIDS association
3. To recommend strategies for malaria prevention and control in the presence of HIV/AIDS based on the review of the literature.

### Materials and Methods

#### Types of studies.

All cohort, case control, randomized control trials and cross sectional studies done between the years 1985 to 2000 were reviewed.

#### Search strategy.

The Cochrane Infectious Disease Group on Medline, AIDSline and Popline on internet were used, with specific

terms, 'HIV and malaria association, complications, treatment and prevention'.

#### Outcome measures.

1. Response to treatment using parasite clearance and fever clearance time.
2. Development of severe malaria.
3. Immunological response to malaria in HIV-1/AIDS people.
4. Incidence of malaria in HIV-1/AIDS people.

#### Types of intervention.

Treatment of malaria with the standard recommended treatment as stated in the Malaria Treatment guidelines from the areas where the studies were carried out.

#### Methods of review.

All studies identified were entered into a register and divided into those evaluating response to treatment, development of severe malaria. Studies that evaluated both treatment response and development of severe malaria in HIV/AIDS malaria patients were also included. The Cochrane reviewed studies were also included as per the review.

## Results

#### Immunological response to malaria antigen.

A meta-analysis of seven studies described the immunological interactions between malaria and HIV.<sup>3-4,10-14</sup> The binding of the malaria parasite merozoite to the erythrocyte membrane's glycophorin A receptor triggers a series of immunological responses against malaria. Severe forms of *Plasmodium falciparum* in children from hyper-endemic and holo-endemic areas, were found to be significantly associated with low levels of interleukin (IL)-12 and interferon alpha but high levels of IL-10 and tumour necrosis factor (TNF). Of particular interest, the CD4+ cells were low in children with cerebral malaria.<sup>11</sup> The commonest complications associated with the deregulation of IL-12 and up-regulation of IL-10, were severe malarial anaemia and cerebral malaria. The levels of IL-12, 10 and TNF normalised after treatment. The ratio of IL-10 to TNF-alpha was found to be associated with mild and high density parasitaemia without severe anaemia or cerebral malaria (OR=4.64, p<0.005).<sup>12</sup>

The effect of HIV infection and AIDS on the immune response due to malaria revealed that the HIV-1 seropositive patients had a significantly less antibody response to the synthetic *P. falciparum* ring-infected erythrocyte surface antigen (RESA), RESA-8 (p=0.001) when compared to HIV-1 sero-negative patients. The antibody levels were also low for the other ring stage peptides, RESA-4 (p=0.024) and RESA-11 (p=0.024).<sup>3</sup> This cross sectional study looked at 136 patients, 66 HIV positive and 70 HIV negative trauma patients. although the trauma may have affected this observation.

In a separate study of 37 AIDS patients and 29 HIV negative health adults, *in vitro* lymphocyte proliferative responses to a Merozoite Surface Protein-1 (MSP-1) antigen

and to a *P. falciparum* culture supernatant were lower in AIDS patients than in healthy adults (geometric mean lymphocyte proliferation 4.0 versus 10.9,  $p=0.01$  and 14.3 versus 17.7,  $p=0.03$ , respectively). The *in vitro* production of cytokines INF-gamma and IL-2 in response to MSP-1, was absent in AIDS patients.<sup>10</sup> This observation may not be true in the *in vivo* situations as there are a lot of host factors that affect immune response to any antigens.

#### **HIV and asymptomatic or uncomplicated malaria.**

Seven studies, from urban hospitals in Uganda, Zambia, Rwanda and Zaire investigated the association between HIV status and parasitaemia or non-severe malaria. Four of the studies were cross sectional, two were a review of records and two were cohort studies.<sup>6</sup> Only the cohort studies showed some significant association between HIV and malaria. The prevalence ratio (PR) of peripheral parasitaemia among the HIV sero-positive group compared to the HIV sero-negative group ranged from 0.72 to 0.94 in children less than 13 years of age and from 3.3 to 0.69 in adults, 13 years plus. The only significant difference was reported in rural Tanzania. PR = 3.3 (95% CI: 2.7 to 4.2). The incidence of fever was increased significantly among the sero-positive patients in the two cohort studies from Tanzania (RR=1.4, 95% CI: 1.1 to 1.8; RR=1.4, 95% CI: 1.2 to 1.5). A cohort study from rural Uganda demonstrated that clinical (symptomatic) malaria was significantly more common in HIV positive participants than HIV negative patients (OR 2.56; 95% CI: 1.53 to 4.29 and  $p=0.0002$ ).<sup>5</sup> The study also demonstrated that the risk of having clinical malaria increased with the advancing clinical stage of HIV-1 infection (OR=9.34; 95% C.I.: 3.07 to 28.42 and  $p<0.001$ ) and that severity of malaria measured by degree of parasitaemia increased with HIV-1 co-infection (OR=1.81; 95% CI: 1.43 to 2.29 and  $p<0.001$ ). There was however, a problem of ascertainment bias as more people with HIV-1 infection and AIDS were more prone to present with fever compared to HIV-1 negative people. The study looked at 484 participants of 13 years and above who were followed up for a period of nine years. Another cohort study of 458 children from Uganda showed no clear association between malaria and HIV-1.<sup>9</sup> There was however, a high prevalence of slide positive malaria cases in the HIV-1 positive when compared to HIV-1 negative infants (RR= 1.5; 95% CI: 1.1 to 1.9) although the level of parasitaemia was the same in both groups. There was positive association between the time to clinical AIDS ( $p=0.001$ ) and absence of malaria in HIV-1 infected children ( $p=0.02$ ). This may suggest that malaria may offer some protection against HIV-1 progression or that chloroquine used to treat malaria may have a direct effect against the HIV-1 virus. The authors of this study concluded that the development of malaria immunity in children was not affected by the presence of HIV-1 infection.

#### **HIV-1 progression and severe malaria.**

The impairment of the immunological response to malaria infection due to HIV infection should make HIV-1 positive malaria patients more prone to severe forms of malaria. In

a cohort study from rural Zimbabwe,<sup>17</sup> HIV-1 positive patients had a more than twice the risk of developing severe malaria when compared to HIV-1 negative malaria patients (RR=2.35; 95% CI: 1.85 to 2.98;  $p<0.001$ ). The commonest complications were high parasite density of 2% or more (38.5%), anaemia (29.0%) and cerebral malaria (23.1%). A total of 237 slide positive malaria patients were followed up over time. High parasite density was also reported in Ugandan adults with HIV infection (OR 1.81; 95% CI: 1.43 to 2.29;  $p<0.0001$ ) and in Zairean children with AIDS ( $p=0.068$ ), but this was not statistically significant.<sup>8,18</sup>

Children born from HIV-1 positive mothers were followed up for 13 months and all their fevers were investigated for malaria. The incidence of smear positive malaria was higher in HIV-1 positive children who did not develop AIDS but lower in the HIV-1 positive children who developed AIDS, although there was no statistical significance.<sup>15</sup> In Uganda, a study of children infected with the HIV-1 virus demonstrated that, there was a positive association between time to clinical AIDS and absence of malaria in infected children ( $p=0.02$ ). This means HIV-1 positive children who had attacks of malaria were at a lower risk of progressing from HIV infection to AIDS, compared to those HIV-1 positive children who did not suffer from malaria. This could have been due to the protective effect of malaria to HIV-1 progression to AIDS or the inhibitory effects of chloroquine to HIV-1 proliferation. However, a study in Rwandan women of childbearing age suggested that repeated malaria infection increased the progression of HIV-1 by immune stimulation, which increased the replication of the HIV-1 virus.<sup>19</sup> However, the study showed that there was no association between HIV-1 and the presence or degree of malaria parasitaemia. High case fatality ratios were reported in studies from Zambia<sup>16</sup> and Zaire<sup>15</sup> but the results were inconclusive probably due to sample sizes.

#### **HIV-1 infection and malaria in pregnancy.**

Three studies were retrieved that measured the effect of HIV-1 infection and malaria in pregnancy.<sup>17</sup> The main findings were that there was increased placental parasitaemia ( $p<0.0005$ ) especially in *multigravidae*, high peripheral malaria parasitaemia ( $p=0.003$ ), umbilical cord blood parasitaemia and high post neonatal mortality ( $p<0.001$ ). Women who presented for their first antenatal visits were enrolled and given chloroquine prophylaxis. Children born from HIV-1 positive mothers were of low birth weight although this could not be linked directly to malaria. In another study, the effect of chloroquine and mefloquine on preventing malaria transmission during pregnancy showed that mefloquine was more effective than chloroquine.<sup>18</sup> The efficacy of chloroquine in malaria prophylaxis was not measured in HIV-1 infected mothers. Snc-pyrimethamine (SP) efficacy in preventing placental malaria was affected by HIV-1 infection in a Kenyan randomised control study. SP was less efficacious in reducing placental parasitaemia and low birth weight, in

HIV-1 positive women compared to the HIV-1 negative pregnant women.<sup>20</sup> The effect of HIV-1 infection on efficaciousness of SP in pregnant women is of concern.

#### **HIV-1 infection and response to antimalarial treatment.**

The few studies that looked at the effect of HIV infection on malaria treatment did not find any statistical difference between HIV-1 positive and HIV-1 negative malaria patients.<sup>6</sup> In the randomised control study, the sample size was small (2 HIV-1 positive and 6 HIV-1 negative.<sup>21</sup>) There was a significant increase in CD4 cell count with treatment in the HIV-1 positive patients. The cohort studies from Zaire showed that the rate of treatment failure was high in AIDS patients, but the small sample sizes of 25 and 32 in each of the studies, affected the significance of the results.<sup>6</sup> An interesting observation was made in a Kenyan randomised control study, where SP was less efficacious in reducing placental parasitaemia and low birth weight, in HIV-1 positive women compared to the HIV-1 negative pregnant women.<sup>20</sup> The effect of HIV-1 infection on the efficacy of SP in pregnant women is of concern. Are there different factors then affecting malaria prophylaxis in pregnancy compared to malaria treatment in non-gravid individuals?

### **Discussion**

#### **The evidence.**

The results discussed above demonstrate that there is some association between malaria and HIV-1 infection but the direction of the association is not conclusive. It is clear from the studies that there is a high incidence of fever and *P. falciparum* parasitaemia in HIV-1 positive people. Fever is a common symptom in both malaria and HIV positive individuals. People living in malaria endemic areas and are HIV-1 positive tend to be investigated for malaria more often than HIV-1 negative people. This may explain the high smear positive rate in HIV-1 positive individuals than HIV-1 negative people (performance bias). Future studies should be community based rather than hospital based, where selection of participants is random and not based on presence of symptomatic malaria infection.

The studies so far have indicated that high *P. falciparum* parasitaemia, anaemia and death may be the commonest complications associated with people with HIV-1 and malaria co-infection. Malarial anaemia was not reported in the other studies except in Zimbabwe. Renal failure was also reported in a hospital-based study (unpublished thesis) from Zimbabwe, as one of the commonest complications, although it was not statistically significant.<sup>22</sup> Although the evidence may suggest the high malaria case fatality rate in HIV-1 positive patients, the figures from Zimbabwe's inpatient malaria deaths show a steady decrease in case fatality from 5.09% in 1995 to 3.90% in 2000.<sup>23</sup> Since malaria and HIV infections are highly prevalent in Zimbabwe, the expectation is that the malaria case fatality should be high assuming that the hospital based health data is reliable and that HIV-1 infection is normally distributed in the population. Although these complications occur in malaria patients who delay seeking treatment, the evidence

from the available literature seems to suggest that these complications occur more often in the presence of HIV-1 infection.

In all the studies that were reviewed in this literature, the overall risk ratio of developing severe malaria in HIV positive malaria patients ranged from 0.6 to 7.0. Although most of the studies did not show statistical significance due to small sample sizes and selection bias from hospital based studies, the results offer a general idea of the direction of the interaction between malaria and HIV. The available literature is enough to suggest implementation of some practical malaria interventions whilst further research is going on.

#### **The gaps.**

The assessment of malaria response to treatment in HIV-1 positive individuals, was not appropriately evaluated as there was one study with eight participants. No other study was found that evaluated the response to treatment as the results presented were coincidental findings. The results on response to treatment contradict the report from Zimbabwe and southern Africa, of high malaria deaths in the 15 to 49 year age group.<sup>6</sup> This age group is the most affected with HIV-1 infection in Zimbabwe and Southern Africa. Why do we have more cases of *P. falciparum* in HIV-1 positive people who also complicate more than HIV-1 negative individuals, if there was no difference in response to treatment?

The participants in all the studies were patients who had presented with either symptoms of malaria or other diseases. One study tried to evaluate the effect of HIV-1 infection to the immunological response to malaria. There were no other studies identified that evaluated the effect of HIV-1 infection in participants who had malaria infection rather than malaria disease. It would therefore be interesting to know the general prevalence of malaria in the general population and at the same time measure the prevalence of HIV-1 infection in those people who were *P. falciparum* malaria positive but are not suffering from the malaria. This would estimate the risk of malaria infection in the presence of HIV-1 infection. The effect of other debilitating diseases like tuberculosis and malnutrition on the malaria infection is also not known. Is it the effect of HIV-1 infection only that is important or the combination of other poverty related diseases like malnutrition?

How does the HIV-1 virus affect the efficacy of SP in pregnant women? What other physiological factors, similar to those in pregnancy might affect the efficacy of anti-malarial drugs in HIV-1 positive individuals? What is the level of efficacy of chloroquine and SP in HIV-1 positive people who are not pregnant? There might be need to test all those patients who fail to respond to chloroquine and SP for HIV-1 infection in future. What effect does HIV-1 infection have on the efficacy of quinine?

### **Conclusion and recommendations**

This review concluded that there is increased risk of clinical malaria and development of severe malaria in the

presence of HIV-1/AIDS. The efficacy of anti-malarial drugs in the presence of HIV-AIDS has not been adequately looked at. Also not clear is the relationship of asymptomatic malaria infection and HIV/AIDS.

From the available evidence it may be suggested that people who are HIV-1 positive and are staying in malaria epidemic and endemic prone areas may require specific and appropriate interventions. People from malaria epidemic areas and are HIV-1 positive would benefit from malaria prevention methods such as the use of insecticide treated bed nets and appropriate malaria case management following the current Zimbabwe malaria treatment guidelines. Vulnerable groups of people living in malaria endemic areas, pregnant women and children under five, would also benefit from the religious use of malaria prevention methods.

Voluntary counselling and testing for HIV-1 in malaria endemic and epidemic prone areas to identify more people who are HIV-1 positive, for purposes of targeting them, would be an ideal intervention method but prohibitively expensive and logistically impossible. The current efforts of health education and promotion should continue targeting the women of child bearing age emphasizing the importance of seeking malaria treatment early and use of prophylaxis during pregnancy. A multi-centred study using the existing malaria sentinel sites and areas where both malaria and HIV-1 infections are highly prevalent, is recommended to evaluate the response to malaria treatment in HIV-1 positive and AIDS patients.

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