Is there an interaction between human immunodeficiency virus and *Plasmodium falciparum*?

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**Background** There is a potential for interaction between malaria and human immunodeficiency virus (HIV) infection. HIV infection might reduce immunity to malaria resulting in more frequent and severe infections; conversely malaria might enhance the progression of HIV infection to AIDS. In this paper we have reviewed some of the studies that have addressed this topic.

**Methods** Studies identified by a MEDLINE search were systematically reviewed and the measures of association between the two infections were either abstracted or recalculated from the reported data. Inferences drawn from these studies and the biological plausibility of an interaction are discussed.

**Results** The prevalence ratio (PR) of peripheral parasitaemia among HIV seropositive (HIVSP) individuals compared to HIV seronegative (HIVSN) individuals ranged from 0.72 to 0.94 in children and from 3.3 to 0.69 in adults. However, only one study showed a statistically significant difference between HIVSP and HIVSN groups (PR 3.3, 95% CI: 2.7–4.2). The rate ratio of non-severe malaria among HIVSP children compared to HIVSN children was 1.4 (95% CI: 0.99–2.0). Data from a trial of chemoprophylaxis during pregnancy suggested that placental malaria may predispose to perinatal transmission of HIV. Studies that have investigated the immune response to *P. falciparum* among HIVSP subjects have given variable results.

**Conclusion** There is no convincing evidence for an interaction between malaria and HIV with the possible exception of an interaction between placental malaria and HIV infection. Several studies, however, had potentials for bias and/or an inadequate sample size. There is a need for carefully designed studies to resolve whether mortality from severe malaria, in particular cerebral malaria, is increased in HIVSP subjects, whether malaria infection of the placenta increases the risk of vertical transmission of HIV, and whether malaria infection increases the progression of HIV infection to AIDS.

**Keywords** HIV, malaria, interaction

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Two of the greatest medical challenges facing Africa today are human immunodeficiency virus (HIV) infection and malaria, and yet the interaction between these two infections has been little studied. An interaction between HIV infection and malaria could work in either direction. HIV infection might reduce immunity to clinical malaria resulting in more frequent infections among the semi-immune and more severe disease among the semi-immune and non-immune; conversely malaria might enhance the progression of HIV infection to clinical AIDS.

The consequences of inoculation with malaria sporozoites range from an aborted infection to a fulminating illness that kills within the first 24 hours of the appearance of symptoms. The course that any individual infection takes depends upon a large number of parasite and host variables. Immunological mechanisms can prevent the development of infection. This is probably achieved most frequently by the destruction of pre-erythrocytic stages of the parasite in the liver by cytotoxic T cells and related mechanisms. If these protective mechanisms fail, and parasites gain access to the blood, parasite density, and hence the severity of clinical infection, may be controlled by antibodies directed against blood stage antigens. Finally, immune
responses directed at parasite components involved in the pathogenesis of the clinical features of malaria, such as those involved in the production of fever or in cyto-adherence to endothelial cells, may help to modify the clinical consequences of malaria when clinical infection occurs. CD4 cells are thought to play an important role at all levels of the immune response to malaria. CD4 cells provide help in the production of antimalarial antibodies and they may help to control parasitaemia through the production of cytokines. The critical role of CD4 cells in the development of immunity to malaria has been demonstrated in some rodent models using depletion and cell transfer experiments. Thus, it might be anticipated that HIV, by depleting CD4 cells, would have a major effect on the ability of the host to mount an effective immune response to malaria. In endemic areas it would be anticipated that this effect would be most marked in children during the period in which they are establishing immunity. The effect of HIV infection on the pattern of malaria might take the form of an increased incidence of successful as opposed to aborted infections, an increased incidence of clinical as opposed to asymptomatic infections, or an increased incidence of severe rather than mild malaria.

It has been shown in vitro that stimulation of CD4 cells infected with HIV increases viral turnover and it has recently been demonstrated in vivo that tetanus and pneumococcal vaccination leads to a marked but transient increase in plasma viral load. However, this effect has not been observed with all vaccines. Several opportunistic infections have been shown to increase HIV replication in vivo, including Mycobacterium tuberculosis, Mycobacterium avium complex, Pneumocystis carinii, and Herpes simplex. It is likely that cellular activation is a common mechanism by means of which infection with pathogenic microorganisms leads to increased HIV replication. Malaria is a powerful stimulator of the immune system. Subjects exposed frequently to malaria have enhanced serum levels of immunoglobulins and an accelerated rate of IgG turnover. This chronic B cell over-activation is probably a consequence of a cumulative series of specific immune responses to variant malaria antigens and to non-specific stimulation of B cells by malaria derived toxins or mitogens which may act directly on B cells or via activation of T cells. Evidence for over-activation of T cells in subjects exposed repeatedly to malaria is less strong than that for B cells but induction of a series of specific immune responses is likely to involve repeated activation of T helper cells.

There is evidence that T cell function is impaired during acute episodes of malaria. Proliferative responses to a variety of antigens are depressed during acute episodes of malaria when assessed by tests carried out on peripheral blood mononuclear cells but it is possible that this anergy is due in part to sequestration rather than depletion of competent cells. Of particular importance to discussions of the interaction between malaria and HIV is the observation that T cell control over Epstein-Barr virus infection is lost transiently in children with acute falciparum malaria. Thus, one might expect malaria infection to have an adverse effect on HIV infection both by stimulating T cell turnover and by impairing T cell cytotoxic function. Finally, malaria infection may damage the placenta in such a way as to facilitate transmission of HIV in utero.

What evidence is there that HIV infection increases the incidence or the severity of malaria or that malaria exacerbates the course of HIV infection? In this paper we review some of the studies that have addressed this question.

Methods

Studies that have investigated the association between HIV and malaria were identified by a MEDLINE search for the period 1983–1996. These reports were reviewed systematically in relation to the period, setting, type, population and sample size of each study. The measures of association between the two infections were either abstracted or recalculated from the reported data in order to allow comparison between studies. In this review, HIV refers to HIV-1 and malaria/parasitaemia refers to P. falciparum unless stated otherwise. Many studies did not define the species of malaria parasites involved.

Results

HIV and asymptomatic or uncomplicated malaria infections

The key features of the studies that have investigated the association between HIV status and parasitaemia or non-severe malaria are summarized in Table 1. Between 1986 and 1991, seven studies were reported from urban hospitals in Uganda, Rwanda, Zambia and Zaire, and from a rural dispensary in Tanzania. The age range of the study populations varied widely between studies and one study was restricted to 18–35-year-old women. The prevalence ratio (PR) of peripheral parasitaemia among the HIV seropositive group (HIVSP) compared to the HIV seronegative group (HIVSN) ranged from 0.72 to 0.94 in children (<13 years) and from 3.3 to 0.69 in adults (>11 years). However, only one difference, a PR of 3.3 (95% CI: 2.7–4.2) reported from a study of adults in rural Tanzania, was statistically significant. The rate ratio (RR) of non-severe malaria (fever + parasitaemia) among HIVSP was higher compared to HIVSN in two cohort studies (RR 1.4, 95% CI: 1.0–1.96; RR 1.4, 95% CI: 0.99–2.03), but differences between groups were only of borderline significance.

The PR for fever in HIVSP compared to HIVSN subjects ranged from 0.6 (95% CI: 0.36–0.98) to 1.2 (95% CI: 0.97–1.6) in children and from 14.2 (95% CI: 7.29) to 2.1 (95% CI: 1.3–3.4) in adults. The incidence of fever was increased significantly among HIVSP compared to HIVSN in both cohort studies (RR = 1.4, 95% CI: 1.1–1.8; RR = 1.4, 95% CI: 1.2–1.5). There were no significant differences in the proportion of slides positive for malaria among fever cases or in the parasite density between HIVSP and HIVSN groups.

During a 13-month period follow up of 5–9-month-old children with HIV-1 infection, Greenberg et al. did not find any statistically significant difference in the incidence of malaria in 36 children who developed AIDS (0.33/child-years) and in 37 children who did not develop AIDS (0.54/child-years; P = 0.6). HIV and severe malaria

The key features and results of studies of the interaction between HIV status and severe malaria are shown in Table 2. The sample sizes of these studies are too small to draw any statistically significant conclusions. However, in both studies of severe malaria among adults, the case-fatality ratio (CFR) was more than twice as high in the HIVSP compared to the HIVSN group.
and HIVSN primigravidae (60.0% versus 66.1%; PR = 0.91, CI : 0.71 — 1.16). but that it was higher among HIVSP multigravidae than HIVSN primigravidae (43.9% versus 12.4%; P < 0.0001).

A secondary analysis of data from a cohort study of mothers enrolled in a trial of chemoprophylaxis during pregnancy undertaken in rural Malawi from 1987 to 1989, Steketee et al. observed that the prevalence of parasitaemia at the time of enrolment (mean 5.6 months gestation) was similar among HIVSP and HIVSN primigravidae (60.0% versus 66.1%; PR = 0.91, CI : 0.71 — 1.16), but that it was higher among HIVSP multigravidae (≥3rd pregnancy) compared to HIVSN multigravidae (52.9% versus 28.5%; PR = 1.85, CI : 1.46 — 2.35). The geometric mean density of parasitaemia (GMPD) was higher in HIVSP primigravidae than in HIVSN primigravidae (4390/μl versus 1375/μl; P = 0.0003). While the GMPD decreased with gravidity it was consistently higher in HIVSP than in HIVSN pregnant women (38.2% versus 22.5%; P < 0.0005), and this difference was more marked among multigravidae (34.8% versus 12.4%; P < 0.0001).

### Table 1 Summary of key features and results of the studies that investigated the interaction between HIV and malaria

<table>
<thead>
<tr>
<th>Study period</th>
<th>Study area</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Prevalence/Incidence of fever</th>
<th>Prevalence/Incidence of PP</th>
<th>SPR among fever cases</th>
<th>Parasite density</th>
</tr>
</thead>
<tbody>
<tr>
<td>87–89</td>
<td>urban Uganda</td>
<td>review of records</td>
<td>13+ year-old patients tested for HIV</td>
<td>737</td>
<td>372</td>
<td>19.3%</td>
<td>15.6%</td>
</tr>
<tr>
<td>1991</td>
<td>rural Tanzania</td>
<td>cross sectional</td>
<td>18–41-year-old, attending clinic for diarrhoea &gt;2 weeks</td>
<td>62</td>
<td>238</td>
<td>90%</td>
<td>27%*</td>
</tr>
<tr>
<td>1987</td>
<td>urban Rwanda</td>
<td>cross sectional</td>
<td>18–35-year-old women attending prenatal or paediatric clinic</td>
<td>955</td>
<td>2371</td>
<td>9.1%</td>
<td>9.3%</td>
</tr>
<tr>
<td>1987</td>
<td>urban Zambia</td>
<td>cross sectional</td>
<td>&gt;11-year-old having symptoms suggestive of malaria</td>
<td>28</td>
<td>142</td>
<td>29%</td>
<td>42%</td>
</tr>
<tr>
<td>87–89</td>
<td>urban Uganda</td>
<td>review of records</td>
<td>&lt;8-year-old patients tested for HIV</td>
<td>202</td>
<td>216</td>
<td>17.3%</td>
<td>18.5%</td>
</tr>
<tr>
<td>1986</td>
<td>urban Zaire</td>
<td>cross sectional</td>
<td>0–13-month-old seen at a hospital</td>
<td>40</td>
<td>1006</td>
<td>37.5%</td>
<td>52.2%</td>
</tr>
<tr>
<td>86–87</td>
<td>urban Zaire</td>
<td>cohort</td>
<td>HIV +ve or –ve blood transfused patients (all ages)</td>
<td>438 (pm)</td>
<td>702 (pm)</td>
<td>14.8/100pm</td>
<td>10.5/100pm</td>
</tr>
<tr>
<td>87–88</td>
<td>urban Zaire</td>
<td>cohort</td>
<td>5–21-month-old HIV +ve or –ve children</td>
<td>838 (pm)</td>
<td>4134 (pm)</td>
<td>4.7/100pm</td>
<td>3.3/100pm</td>
</tr>
</tbody>
</table>

* P < 0.05 for the comparison between HIV+ve vs HIV –ve

- a fever >1 month.
- b parasite density >5000/μl of blood
- c % of infected red blood cells.
- d parasites/μl.
- e log mean difference.

PP: peripheral parasitaemia.

SPR: slide positive rate.

NR: not reported

pm: person-months of observation.

### Table 2 Summary of studies that investigated the interaction between severe malaria and HIV

<table>
<thead>
<tr>
<th>Study period</th>
<th>Study area</th>
<th>Type of study</th>
<th>Study population</th>
<th>Prevalence of HIV antibody among non-survivors</th>
<th>Case-fatality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>91–92</td>
<td>urban Burundi</td>
<td>case series</td>
<td>adults admitted with severe malaria</td>
<td>4/7 (57%)</td>
<td>15/24 (33%)</td>
</tr>
<tr>
<td>86–88</td>
<td>urban Zambia</td>
<td>case series</td>
<td>adults admitted with severe malaria</td>
<td>2/4 (50%)</td>
<td>6/23 (26%)</td>
</tr>
<tr>
<td>1986</td>
<td>urban Zaire</td>
<td>cross sectional</td>
<td>9 month to 12-year-old hospitalized for malaria</td>
<td>1/59 (1.7%)</td>
<td>1/105 (0.95%)</td>
</tr>
</tbody>
</table>

**HIV and malaria in pregnancy**

In a secondary analysis of data from a cohort study of mothers enrolled in a trial of chemoprophylaxis during pregnancy undertaken in rural Malawi from 1987 to 1989, Steketee et al. observed that the prevalence of parasitaemia at the time of enrolment (mean 5.6 months gestation) was similar among HIVSP and HIVSN primigravidae (60.0% versus 66.1%; PR = 0.91, CI : 0.71–1.16), but that it was higher among HIVSP multigravidae (≥3rd pregnancy) compared to HIVSN multigravidae (52.9% versus 28.5%; PR = 1.85, CI : 1.46–2.35). The geometric mean density of parasitaemia (GMPD) was higher in HIVSP primigravidae than in HIVSN primigravidae (4390/μl versus 1375/μl; P = 0.0003). While the GMPD decreased with gravidity it was consistently higher in HIVSP than in HIVSN pregnant women at all parities (at enrolment: 1558/μl versus 670/μl, P < 0.0001; and at delivery: 1589/μl versus 373/μl, P < 0.0005). The incidence of placental malaria was also higher among HIVSP than HIVSN women (38.2% versus 22.5%; P < 0.0005), and this difference was more marked among multigravidae (34.8% versus 12.4%; P < 0.0001).
**HIV and immune response to malaria**

In a cross-sectional study, Wabwire-Mangen et al. observed that the proportion of HIVSP patients with clinical AIDS (n = 49) who had antibodies to synthetic peptides of the *P. falciparum* blood stage antigen (RESA) below a cutoff point was significantly higher than in a comparable group of 17 HIVSN patients (RESA-8 61% versus 12%, P = 0.001; RESA-4 61% versus 29%, P = 0.02; and RESA-11 61% versus 29%, P = 0.02). They also reported that the proportion of HIVSP patients without clinical AIDS (n = 22) who had antibodies below the cutoff point was lower, although not significantly so, than the proportion found in a comparable group of 48 HIVSN patients (RESA-8 36% versus 58%, P = 0.09; RESA-4 36% versus 52%, P = 0.22; and RESA-11 36% versus 52%, P = 0.22).

In a study which involved 37 African AIDS patients and 29 HIVSN healthy 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). However, there was no statistically significant difference in lymphocyte proliferation in response to a schizont extract between the two groups (geometric mean 10.9 versus 7.4, P = 0.35). In vitro production of cytokines IFN-γ and IL-2 in response to MSP-1 was absent in AIDS patients while the geometric mean IFN-γ was 3.1 U/ml and IL-2 16.1 in the healthy adults. Similarly, the production of these two cytokines in response to a *P. falciparum* culture supernatant was lower in AIDS patients than in the controls (geometric mean IFN-γ 2.3 versus 6.1, P = 0.005; IL-2 72.4 versus 133.5, P < 0.001). However, there were no significant differences in production of these cytokines in response to the schizont extract. Thus it was suggested that AIDS may not modify some important components of the human immune response to *P. falciparum*, although others are affected.

**HIV and response to antimalarial treatment**

Two studies have examined the prevalence of treatment failure on day 7 following treatment with quinine given in a dose of 20 mg/kg daily for 5 days in HIVSP and HIVSN children in urban Zaire; there was no significant difference in the level of treatment failure in the two groups. In one study the level of treatment failure was 8% (2/25) in HIVSP compared to 16% (6/34) in HIVSN children, and in the other it was 3% (1/32) versus 4% (7/166).

**Malaria and progression of HIV infection**

In a community-based study in Guinea-Bissau, no significant difference in provirus load of HIV-2 was found between subjects who had peripheral parasitaemia and those who did not; the geometric mean provirus loads in the two groups were 103 (95% CI: 37-287) and 146 (95% CI: 96-220) respectively.

**Discussion**

The inconsistency in the observed relationship between the prevalence of parasitaemia (PP) and the HIV sero-status observed in the various studies that have been done could be due to (i) the fact that the PP included both symptomatic and asymptomatic parasitaemias; (ii) the fact that the proportion of AIDS cases in the HIVSP group may have differed between studies; (iii) the wide range in age groups of the study populations; (iv) variations in the endemicity of malaria in the different study settings. The negative relationship between the prevalence of PP and HIVSP status observed in several studies could have been due to the fact that HIVSP individuals resident in malaria endemic areas are more likely than HIVSN individuals to have febrile illnesses of many kinds and thus to receive chloroquine prior to attending a health facility and hence to have a lower prevalence of PP compared to HIVSN individuals. The fact that the study that showed a strong negative association is an urban hospital-based study supports this view. In the only study done in a rural area where the effect of antimalarial drug treatment prior to entry into study is likely to be low, the prevalence of PP was 90% among HIVSP compared to 27% in HIVSN. Since the majority of the HIVSP individuals in this study had symptoms suggestive of AIDS (50% had weight loss >10%, 65% had diarrhoea >1 month, 47% had fever >1 month), it could be argued that AIDS can suppress the 'anti-parasite immunity' and thereby lead to asymptomatic or symptomatic parasitaemia. Unfortunately, measurements of parasite density which would allow further examination of this hypothesis were not reported in this study.

Although the incidence of non-severe malaria was significantly higher among HIVSP compared to HIVSN, the investigators suggest that this is probably due to ascertainment bias because there was a higher incidence of fever among the HIVSP subjects and there was no difference in the proportion of slides positive for MP among HIVSP and HIVSN individuals presenting with fever. A strong argument against there being any interaction between the two infections is the absence of a significant increase in the parasite density in the HIVSP group. However, this observation needs to be treated with caution because, with the exception of the cohort study from Zaire, all studies that investigated this phenomenon had potentials for bias since they were either a review of hospital records or had only a small sample of HIVSP individuals. Since the density of parasitaemia at any one time may not be an indicator of clinical disease, it could be argued that HIV can suppress immune responses that control symptoms but not parasitaemia (antitoxic immunity) leading to severe clinical malaria in children rather than to an increase in the level of parasitaemia.

The observed increased CFR in HIVSP subjects reported in two studies may well be due to chance as the sample size was small and difference between groups was not statistically significant. Nevertheless it is plausible that the fatality from severe malaria should be high among HIVSP individuals. Recently in a referral hospital in Zimbabwe, it was observed that the CFR from malaria was higher among 20–49-year-old adults (n = 895) compared to 5–14-year-old children (n = 192) admitted for severe malaria (CFR 13.6% versus 5.7%; P < 0.001) (personal communication: Mpilo Hospital malaria report, August 1996. Presented by Dr Mark Dixon at the malaria conference, Victoria Falls, September 1996). The reasons for this apparent difference in the CFR among different age groups cannot be deduced from this routine health statistic. Nevertheless, this observation highlights the need to investigate the possible role of HIV in increasing CFR among adults with malaria. Surprisingly, no large studies have yet been done to compare the incidence and outcome of severe malaria among HIVSP and HIVSN individuals.
The consistently higher GMPD in HIVSP pregnant women compared to HIVSN women, which was more marked among multigravidae, reported from Malawi, suggests that the HIV infection can interfere with the maintenance of immunity to malaria during pregnancy. From further analysis of this data, Bloland et al. reported that the odds of dying during the post-neonatal period for an infant born to a mother with both HIV and placental malaria was between 2.7 and 7.7 higher than that of an infant born to a mother with HIV infection only depending on birthweight. Although neither the incidence of infant HIV infection nor the cause of death was evaluated in this study, these results suggest that malaria increases the risk of vertical transmission of HIV and malaria chemoprophylaxis might be effective in reducing HIV transmission rates. Several factors such as maternal p24 antigenemia, low CD4+ lymphocyte count (<29% of total lymphocytes or <700/µl), intravenous drug use during pregnancy, duration of rupture of membranes >4 hours, vaginal delivery, episiotomy, application of scalp electrodes, vacuum or forceps delivery, premature delivery (=34 weeks gestation), and breastfeeding have been reported to be associated with an increased risk of vertical transmission of HIV. Studies have reported specific histologic changes in malaria infected placentas. Thus it is plausible that the altered integrity of the placenta caused by malaria infection could facilitate in utero infection of HIV. Although a cause-effect relationship between placental malaria and increased risk of vertical transmission of HIV has not yet been established, there appears to be some evidence for an interaction between Plasmodium falciparum and HIV in pregnant women. How might immunity to malaria be sustained in the face of loss of CD4 cells? It is easier to imagine how this might happen in adults rather than in children who have yet to establish effective protection. It would be anticipated that established antibody responses would be sustained for several years in the absence of helper T cells and the protective immunity in immune adults wanes only slowly on leaving an endemic area. However, it would be anticipated that CD4 cells would play a vital role in young children developing their immunity. Could other cells take over their role? Macrophages may contribute to malaria immunity through production of cytokines and phagocytosis, but they function most effectively when stimulated with T cell derived cytokines. In addition, macrophages are infected by HIV. CD8 cells may play a part in cytotoxic immunity directed against liver stages and γ cells which are usually CD4 negative may be involved in the acute response to malaria infection. However, there is no obvious immunological explanation of how immunity to malaria could develop effectively without CD4 cell involvement.

The absence of a reduced response to quinine in the HIVSP group has been cited in support of the argument that there is no interaction between HIV and malaria. Since the response to quinine is unlikely to depend on the cellular or humoral immunity of the host it is not surprising that there was no difference in the HIVSP and HIVSN individuals. However, it would be of interest to know whether a difference would be seen if a less effective drug was used for treatment as, in the circumstances, the immune response may contribute to the therapeutic effect.

In a prospective study, it has been shown that isoniazid prophylaxis can delay the progression of HIV to AIDS and death in HIV-infected PPD positive individuals. Although it is plausible that malaria can facilitate progression of HIV to AIDS, no study has demonstrated this phenomenon. There is a need to investigate the effect of malaria infection on replication of HIV and the progression of HIV infection to AIDS.

The majority of the studies that investigated the interaction between HIV and malaria were done in urban settings in the late 1980s and these did not demonstrate any convincing evidence for an interaction between malaria and HIV. Several studies, however, were health facility based cross-sectional studies and their results have to be interpreted cautiously. There is a need for further carefully designed studies before it can be finally concluded that no interaction occurs. Important issues that need to be resolved are whether mortality from severe malaria, in particular cerebral malaria, is increased in HIVSP subjects, whether malaria infection of the placenta predisposes to perinatal HIV infection and can be prevented by chemoprophylaxis, and whether malaria infection facilitates progression of HIV infection to AIDS.

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References
INTERACTION BETWEEN HIV AND MALARIA


