# Interactions between malaria and human immunodeficiency virus *anno* 2014

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## Abstract

Possible pathophysiological, clinical and epidemiological interactions between human immunodeficiency virus (HIV) and tropical pathogens, especially malaria parasites, constitute a concern in tropical areas. Two decades of research have shown that HIV-related immunosuppression is correlated with increased malaria infection, burden, and treatment failure, and with complicated malaria, irrespective of immune status. The recent role out of antiretroviral therapies and new antimalarials, such as artemisinin combination therapies, raise additional concerns regarding possible synergistic and antagonistic effects on efficacy and toxicity. Co-trimoxazole, which is used to prevent opportunistic infections, has been shown to have strong antimalarial prophylactic properties, despite its long-term use and increasing antifolate resistance. The administration of efavirenz, a non-nucleoside reverse transcriptase inhibitor, with amodiaquine–artesunate has been associated with increased toxicity. Recent *in vivo* observations have confirmed that protease inhibitors have strong antimalarial properties. Ritonavir-boosted lopinavir and artemether–lumefantrine have a synergistic effect in terms of improved malaria treatment outcomes, with no apparent increase in the risk of toxicity. Overall, for the prevention and treatment of malaria in HIV-infected populations, the current standard of care is similar to that in non-HIV-infected populations. The available data show that the wider use of insecticide-treated bed-nets, co-trimoxazole prophylaxis and antiretroviral therapy might substantially reduce the morbidity of malaria in HIV-infected patients. These observations show that those accessing care for HIV infection are now, paradoxically, well protected from malaria. These findings therefore highlight the need for confirmatory diagnosis of malaria in HIV-infected individuals receiving these interventions, and the provision of different artemisinin-based combination therapies to treat malaria only when the diagnosis is confirmed.

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## Introduction

Since it became obvious that resource-poor regions of the world, and in particular south-eastern Africa, carry the main burden of the human immunodeficiency virus (HIV) pandemic, there have been concerns about possible pathophysiological, clinical and epidemiological interactions between HIV and tropical pathogens. Especially *Plasmodium falciparum* malaria, one of the main tropical killers was envisaged as concomitantly malaria treatment and control were undermined by the emergence of resistance to commonly used antimalarial drugs such as chloroquine and sulphadoxine–pyrimethamine. The geographical distribution of HIV and malaria suggests that, for many sub-Saharan African countries, even a small link between the two diseases would be of extreme importance in terms of public health impact and control policies. Considering that the two diseases share similar immunological factors, such a link may be plausible, and needs to be assessed carefully. Furthermore, as malaria is not the only disease that could interact with HIV-1, information from malaria–HIV studies may be relevant for other parasitic, bacterial and viral co-infections. We present a short review of the literature, and attempt to

reiterate the reasons for the above-mentioned concerns, to assemble the available evidence, and to address outstanding or possible future questions and concerns.

## Pathophysiology

### The impact of HIV infection on malaria

Most clinical problems in HIV-1-infected individuals are related to the specific loss of pathogen-specific CD4 cell immunity of the Th1 type, and, in developing/tropical countries, tuberculosis is probably the most common consequence of Th1 depletion [1,2]. Other protozoan parasites are often contributors to mortality in individuals with AIDS: *Babesia*, *Toxoplasma*, *Giardia*, *Cryptosporidium*, *Isospora*, and *Leishmania* [3,4]. As acquired immunity to blood-stage malaria was thought to be primarily antibody-mediated, one might predict that it would be largely unaffected, particularly as cytokine patterns in HIV-infected individuals are said to be associated with a shift to Th2-type responses [5]. B-cell polyclonal expansion and total immunoglobulin concentrations, including antimalarial antibodies, in HIV-1-infected patients can be higher than or the same as those in uninfected controls, [3,6]. Today, we know that HIV-1 CD4 T-cells, the prime targets for destruction by HIV-1, have a critical role in both Th1-type and Th2-type responses to malaria [4]. Enhanced T-cell activation in co-infected patients can worsen the immune response to both diseases [7]. Phagocytosis, proliferative and Th1 cytokine responses are reduced in pregnant women with HIV infection, and pregnancy may contribute to impaired control of malaria in HIV-infected individuals [8]. However, variant surface antigen antibody levels, which seem important for the control of parasite density and treatment outcome, seem to be marginally or not affected by HIV-1 in non-pregnant adults [9]. In pregnancy, although antimalarial antibody responses are mostly unaltered, there seem to be impaired responses to some antigens, including variant surface antigens expressed on infected erythrocytes binding chondroitin sulfate A, a key receptor for placental sequestration. This impairment is greatest in women with more advanced HIV disease, and occurs across all gravidities and in women with and without current malaria infection [10].

### The impact of malaria infection on HIV

The HIV-1 life cycle is intimately related to the level of activation of the immune cells supporting viral replication, which is enhanced by increased viral cellular entry, and reverse and proviral transcription [11]. Malaria infection is associated with strong CD4 cell activation and upregulation of proinflammatory cytokines; it provides the ideal microenvironment

for the spread of the virus among the CD4 cells and for rapid HIV-1 replication [12]. In a malaria challenge trial, enhanced HIV production was related to the development of antimalaria immunity, and may have been mediated by proinflammatory cytokines [13]. HIV-1 viral load first increases in malaria-infected patients, and then decreases 4 weeks after antimalaria treatment [14]. Malaria parasitaemia also has an immediate impact on CD4 cells. Indeed, malaria in children is associated with reversible lymphopenia and an absolute lower CD4 cell count [15,16], and this has also been observed in HIV-1-infected adults [17]. Similar observations have been made in malaria-infected pregnant women. For example, the expression of CC-chemokine receptor 5, a co-receptor for HIV cell entry, is increased in the placentas of malaria-infected women, possibly contributing to intrauterine HIV transmission [18]. Malaria-infected pregnant women have an increased viral load, although lower than that observed in non-pregnant adults [19–21]. Of special concern is the risk of mother-to-child transmission (MTCT). Maternal HIV-1 viral load is currently considered to be the single most important determinant of MTCT. Studies addressing this issue produced conflicting results, and were all conducted prior to the introduction of antiretrovirals (ARVs) in Africa [18–22]. The discrepant results are probably attributable to the differences in diagnosing placental malaria, but might also reflect the complexity of maternal immune responses to malaria, which, on the one hand, may stimulate HIV viral replication in the placenta, thereby increasing the local viral load, and on the other hand may potentially control the severity of malarial infection and HIV replication [10]. The net result may be either an enhanced or a reduced risk of MTCT, depending on the specific situation. Furthermore, immunocompromised mothers with malaria–HIV co-infection have altered chemokine and cytokine profiles, less protective immune responses, and consequently higher parasite densities and viral load, leading to an increased risk of MTCT [23]. Today, schemes for the prevention of MTCT have reduced the risk to almost zero, so, in an interventional research setting, carefully designed studies, probably with huge sample sizes, will be needed to assess a modified risk of MTCT.

## Epidemiology

### Impact of malaria on HIV transmission

There is a strong correlation between viral load and the risk of heterosexual HIV-1 transmission, the predominant mode of transmission in Africa, and there is compelling evidence suggesting an epidemiological synergy between sexually transmitted infections and HIV [24,25]. Enhanced immune activation