HIV and Malaria

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Abstract

Malaria and HIV infection are both prevalent in the areas of the world where these diseases have the largest burden. Both diseases interact with one another and this interaction is especially important in areas with non-continuous malaria transmission, in pregnant women, and in patients with more severe immunodeficiency. Malaria has been implicated in transitory higher viral load and in low CD4 counts, so it could have an influence on higher transmission rates of HIV and perhaps in the course of HIV infection. Infection with HIV has been shown to cause more clinical malaria and higher parasitemia in patients living in perennial transmission areas, and higher rates of severe malaria episodes and mortality in areas where malaria is transmitted with seasonal frequency. The HIV-infected patients have also higher rates of malaria treatment failures.

Co-trimoxazole prophylaxis has been shown to be effective in the prevention of some opportunistic infections in HIV-infected patients, but also in prevention of malaria episodes. Antiretroviral protease inhibitors demonstrate antimalarial effects that could have important clinical and therapeutic implications. For all of these reasons, HIV and malaria should be considered together as part of healthcare programs for both diseases in countries where their co-presence favors an interaction with important clinical consequences. **(AIDS Reviews 2007;9:88-98)**

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Key words

Malaria. HIV. AIDS. Africa.

Introduction

Developing countries, especially in Africa, are the distressing scenario of infection with two of the most important diseases in terms of number of deaths and morbidity. Interaction between malaria and HIV has been described. This interaction combines between the two diseases, in both cases adding a more harmful potential to each other.

It is not difficult to consider that in areas of the world where both infectious problems have a high prevalence and the economical and social situations are far from favorable for health attention and care, even a small effect on one of the illnesses can have important health consequences.

Both malaria and HIV are recognized as important epidemics in the poorest countries, as demonstrated by their inclusion in the sixth goal of the UN Millennium Development Goals: "combat HIV/AIDS, malaria, and other diseases"[1]. When we are only eight years away from the deadline of 2015, the achievement of these goals seems still far from reality. The basis of this foreseeable failure is mainly the insufficient healthcare systems in the poorest countries, but also the lack of funding, its short duration, and poor coordination of donors for global public health, which explains and maintains the occurrence and interaction of both diseases.

Even though tropical regions are the main areas of these two illnesses, the importance of population movements and immigration throughout the world should not be forgotten. In our experience in an infectious disease department in a Spanish hospital, among 78 hospitalized immigrant patients with HIV infection, 41 came from sub-Saharan

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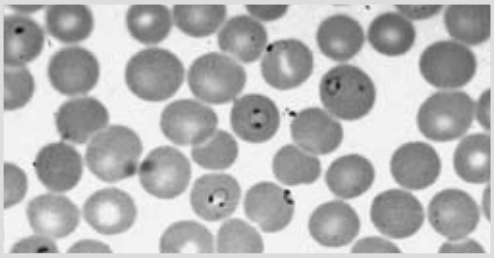

Figure 1. *Thin blood film showing parasitized erythrocytes by Plasmodium falciparum.*

Africa. Malaria was diagnosed in 22% of them, being the second most frequent infection after candidiasis[2].

Our aims in presenting this review consist of describing the interactions between the two diseases, trying to explain the possible mechanisms, and also describing the implications for treatment and prevention.

Some studies have described different and variable results related with the interactions of HIV and malaria, especially malaria produced by *Plasmodium falciparum* (Fig. 1) as it is by far the most common in Africa and the malaria parasite that causes more morbidity and mortality. It is important to distinguish between the spectrum of malaria manifestations, which can vary from asymptomatic parasitemia, uncomplicated febrile illness, and severe malaria. In general, studies have tried to distinguish malaria infection from malaria disease[3].

Most studies have been developed in Africa, the continent with the biggest burden of these two diseases, and where the overlap of them has been described in a well-known and very clear image of "two elephants colliding"[4]. This refers to the clear effect on mortality of both of them, although the evidence of these suspected interactions has not been shown until recent studies. Earlier studies failed to demonstrate them clearly, possibly due to difficulties in the design and development of the studies. While there is a geographic overlapping of these two illnesses (Fig. 2 and 3), there are some distinct characteristics: first, malaria is more common in rural areas and HIV is more frequent in urban areas, and second, malaria affects mainly pregnant women and young children, while HIV patients are mostly young adults.

It is also important to be aware of the epidemiologic and immunologic characteristics of malaria in Africa. The exposure to malaria occurs repeatedly and people acquire an incomplete immunity (semi-immune status), which means that malaria disease becomes very rare and severe malaria is almost absent in adulthood, but the malaria infection remains. This semi-immune status is reached through years of repeated exposure to the parasite, so children are non-immune and have multiple episodes of symptomatic and severe malaria. The age at which semi-immunity is reached cannot be precisely established, but it is clear that this age is earlier in areas with higher intensity of malaria. Among adults, there is a special group that is susceptible to malaria infection – pregnant women, mainly in primigravidae ones, because of the ability of the placenta to sequester parasites that express new antigens. All these considerations have to be taken into account in order to understand the different studies and the results obtained by the researchers.

Influence of malaria on HIV

Laboratory evidence

In vitro studies related to the influence of malaria on HIV infection are not conclusive. They have described an increase in HIV replication when exposed to malaria antigens related with production of tumor necrosis factor alpha (TNFα). Short stimulation with malaria antigens upregulated the expression of CCR5 but not CXCR4, but long stimulation upregulated CCR5 through the production of interferon gamma (IFNγ), which in turn blocked HIV replication. On the other hand, it has been shown that malaria antigens activate mononuclear cells, making them more susceptible to HIV infection and facilitating the replication of the virus. Another immunologic function that can be affected by malaria infection is related with the role of dendritic cells in that their presentation activity would be impaired. This could influence the presence of HIV anti-immunity. Effects described in HIV-infected pregnant women are clearer: hemozoin increases RNA viral load when in contact with blood mononuclear cells, and induces secretion of TNFα and IFNγ, and both of them are responsible for poor development during pregnancy. More confusing are the results related with CCR5 expression: it is over produced and is the main coreceptor for mother-to-child transmission. On the other hand, malaria infection induces production of some chemokines which bind CCR5 and are inhibitors of HIV invasion[5]. Consequently, more studies are necessary to clarify these findings.

Clinical aspects

Malaria produces a reversible decrease of CD4 cells. This reversibility has also been demonstrated in patients with HIV infection. Two groups of patients (HIV infected and non-HIV infected) from Zambia had been diag-

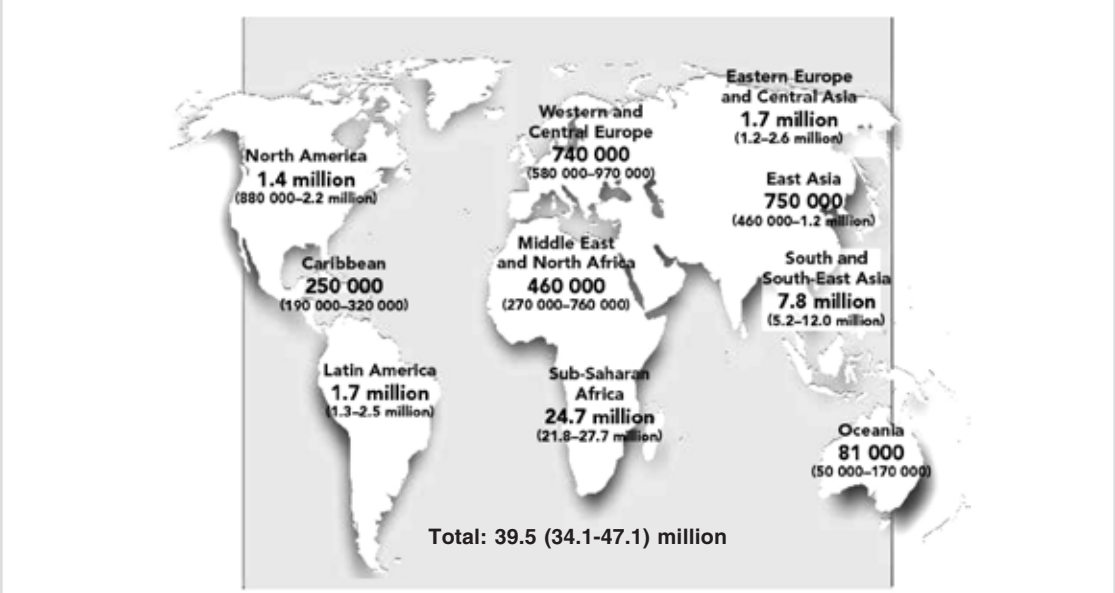

Figure 2. *Adults and children estimated to be living with HVI in 2006. World prevalence of HIV infection. Sub-Saharan Africa shows the highest rates that are especially elevated at the South region of the continent* (Adapted from UNAIDS and WHO).

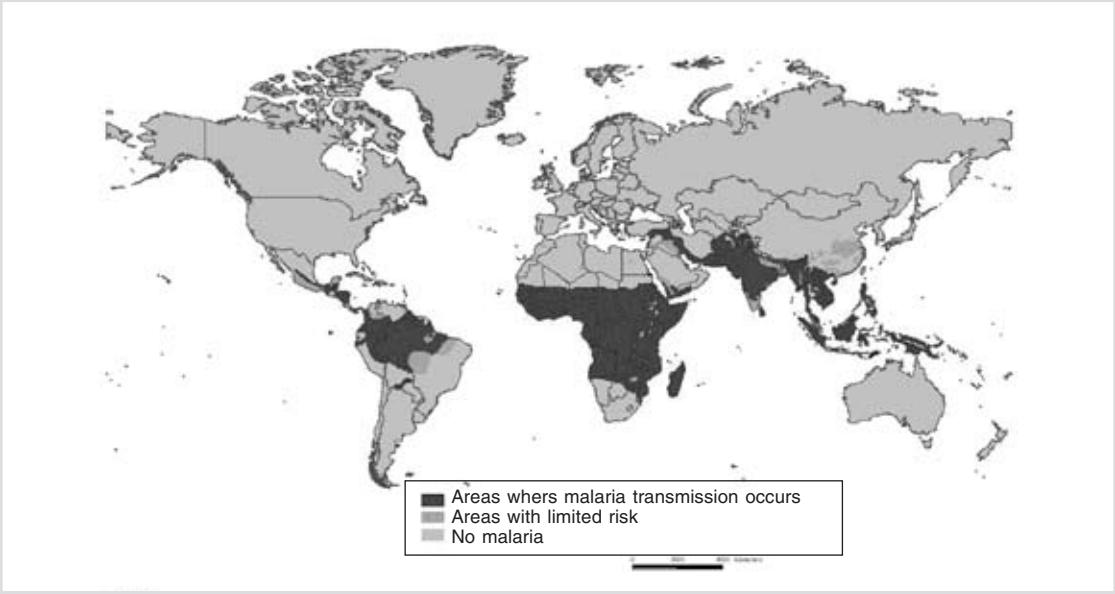

Figure 3. *Distribution of malaria worldwide. Sub-Saharan Africa shows the highest rates, except the Southern region.*

nosed and received adequate treatment for malaria. Their CD4 count increased with a significant difference at day 28 of follow-up in both groups, although the difference was significantly higher in the non-HIV-infected patients. Viral load showed a decrease after treatment, but to a non-significant degree. When parasitemia was still present 45 days after treatment, the CD4 count was similar to the one obtained at the time of diagnosis[6]. These results have

important implications for practical purposes: malaria must be discounted before taking any therapeutic decision in HIV-infected patients, and must be taken into account in the follow-up of patients with antiviral therapy in malaria areas.

Malaria, like other infectious diseases, also causes increases in HIV viral load that usually return to previous levels after finishing the episode. A study that demonstrated this interaction was carried out in Malawi[7]. It was a prospective study of HIV-infected adults who suffered any parasitemia of malaria episode and it described the changes in viral load during and after the episode. The HIV viral load increased by 0.25 log coinciding with the malaria episode, and this difference was statistically significant. After eight to nine weeks of receiving adequate antimalarial treatment, the viral load returned to previous values. When patients with baseline CD4 > 300 or < 300 were studied separately, the difference of increase in HIV viral load was only significantly higher in the first group. The growth of viral load was also greater for patients with > 2000 parasites/µl and fever. When extrapolating these results, the changes of viral load described here could reduce the survival time of untreated HIV patients by one year, and HIV transmission could be increased by 50% during the time of higher viral load[4]. These findings have important consequences on HIV transmission coinciding with malaria febrile episodes and for some weeks after them, and on the necessity for adequate malaria treatment to achieve HIV viral loads similar to previous. Whether these increases have a direct influence on HIV progression in areas of coinfection still remains unclear.

Less clear is the possible effect of malaria on long-term HIV disease evolution. Two studies, both developed in Uganda, showed different results. One of them showed no malaria effect on mortality causes of HIV-infected patients[8]. The other study described malaria episodes and changes in CD4 counts in a cohort of 449 HIV-infected patients followed during two years. A significant mean decrease of 40.5 cells/µl per year was found per each malaria episode, even when treatment was given promptly. This decrease was adjusted by baseline CD4 cell count[9].

Similar results were obtained by other studies carried out in Côte d'Ivoire, Uganda, and Kenya, in which reduced rates of malaria in relation with co-trimoxazole prophylaxis were related with better prognosis[8].

A long-term, large cohort study has investigated the effect of malaria on HIV mortality[10]. A total of 484 patients from rural Uganda were followed up during eight years (1990-1998). Almost half of them were HIV positive, and 25 patients seroconverted during the study. The study area has perennial malaria transmission, with seasonal higher endemicity coinciding with irregular rainy seasons. Patients attended routine visits each three months and interim visits if feeling sick; in these visits, blood slides were taken to assess malaria parasitemia. Mortality rates in HIV-seropositive patients were significantly associated with older age, more advanced HIV-stage, earlier enrolment year, decreasing number of routine visits, and increasing number of interim visits. No significant relation was found between any number of both kinds of visits and some level of parasitemia or clinical malaria and mortality. Mortality rates in HIV-seronegative patients were also not associated with malaria episodes. The effect of malaria on mortality was not significantly different between patients who were HIV seropositive and HIV seronegative. These results are consistent with the knowledge that malaria influence in HIV is higher in nonendemic areas. It could be considered that the influence of malaria on HIV, especially in these areas, is perhaps more subtle. Perhaps the preserved immunity in these patients could be enough to maintain some antimalarial activity, which would be effective in preventing severe malaria and the related mortality. It must also be noted that HIV viral load and CD4 counts were not available for all patients in this study. For these reasons perhaps, mortality has too many confounding factors to be a sensitive outcome for discovering the influence of these two diseases.

Diagnosis

With regard to diagnosis, malaria has been identified as a confounding factor when an HIV-diagnostic EIA test has been applied[11]. A higher prevalence of false-positive tests has been described among patients with acute, uncomplicated malaria when comparing the results of two EIA tests with a Western Blot confirmatory test. Younger age was also associated with a higher rate of false-positive EIA tests, so the authors propose that younger patients with a less-developed immune response against malaria are more likely to present B-cell activation and production of antibodies that cross-react with HIV antigens without being infected by HIV.

HIV transmission

Blood transfusions for anemia secondary to malaria in areas of high endemicity have been described as a transmitter of HIV infection. This is important in young children in these areas. Abu-Raddad, et al.[12] have designed a mathematical model that considers some biological values, previously defined in different studies as being related with HIV and malaria transmission.

The main values are:
- Rate ratio increase in HIV coital transmission probability per one-log rise in viral load.
- Logarithmic increase in HIV viral load level during malaria infection in different HIV infection stages.
- Susceptibility enhancement to malaria infection in HIV-infected persons.
- Duration of heightened viral load during malaria episodes.
- Fractional reduction in sexual activity during malaria infection.
- Fraction of malaria-infected patients developing clinical malaria.
- Enhanced HIV mortality in dually infected patients.

When using this model to examine the impact of both infections in Kisumu (Kenya), the excess prevalence was 2.1% for HIV and 5.1% for malaria. Taking into account that the adult population in the area is approximately 200,000, malaria can account for a cumulative 8500 excess HIV infections, and HIV would be responsible for 980,000 excess malaria episodes since 1980. Applying this model, they have described different possible situations related with different HIV and malaria prevalence. They conclude that the influence of one disease on the other is higher when the independent prevalence of one of them is very high and the other is very low, but when both prevalences are very high the interaction does not affect them significantly. This means that areas with high HIV endemicity and low or unstable malaria prevalence, and areas with high malaria transmission and low HIV prevalence are the most at risk for the interaction. These results are of important epidemiologic relevance as the treatment of malaria in HIV infected patients, following this mathematical model, proved to be effective not only in reducing malaria prevalence, but also in reducing HIV prevalence. They also obtained diminished rates of HIV infection when they tested the influence of some behavioral changes directed to lessen sexual activity during malaria episodes.

HIV influence on malaria

Laboratory evidence

As described above, the impact of HIV on malaria immunity differs depending on the degree of acquired immunity against the parasite and the timing of the coinfection. It has been proposed that if coinfection occurs simultaneously, there could be a nonspecific effect on parasite development or against immune-mediated malaria pathology, and later on, if malaria is not treated, the development of malaria immunity would be affected. This perturbation could be explained by defects in antigen presentation and predominantly Th2 responses. Infection with HIV acquired prior to malaria could also affect malaria infection through the induction of regulatory T-cells, which secrete suppressive cytokines, and in that way could lead to an increase in parasite density. When HIV infection occurs in people already infected by malaria, some animal models have described less-effective responses to treatment, but mainly in situations of advanced immunosuppression. This could be because clearance of malaria parasites depends on B-cell-mediated mechanisms.

The influence of HIV infection can also affect the acquired antimalarial immunity. The proposed mechanisms are the decreased number of CD4 cells considered as essential for the development of this immunity, but also the loss of memory T-cells induced by viral infection[5]. Other *in vitro* findings consist of the decrease of antibodies and IFNγ responses to *P. falciparum*[13].

Infection with HIV has also been related with malaria treatment failure, secondarily to new malaria infections. The explanation of these findings can be found in a weaker cell-mediated response that would be responsible for eliminating parasites from liver cells, hindering their developing in this liver stage. It has also been suggested that the more frequent febrile episodes that HIV-infected patients suffer could be attractive for thermophilic *Anopheles* mosquitoes. This would explain the higher rates of inoculation in HIV-infected patients[14].

Special characteristics of malaria and HIV in children make it possible that an interaction between the two diseases is less evident, as these children have not acquired any immunity against malaria that can be lost because of HIV infection. Thus, they are as exposed as HIV-negative patients to malaria, but not more so. Studies have not yet proved any effect of HIV in malaria, and some authors have even considered a protective effect of HIV against malaria[15,16].

Clinical aspects

In spite of these immunologic explanations for the HIV influence on malaria, initial clinical studies failed to demonstrate any relationship. It must be said that studies carried out at the beginning of the 1990s were usually descriptive cross-sectional or case-control studies, and that CD4 counts or immunologic status were not reported[8].

After that date, different studies, mainly prospective, have clarified this interaction and the factors that can influence in it. As has been remarked before, the influence is

different if areas with unstable or stable malaria transmission are considered. Immunosuppression associated with HIV infection established more symptomatic malaria and higher parasitemia in adults considered to be immunized against malaria in regions with stable transmission. But the highest effect of HIV on malaria infection has been described in regions with unstable transmission (South Africa, Zimbabwe, India, Burkina Faso). In these areas, HIV infection is associated with significantly higher rates of complicated and severe malaria and death.

One of the first large cohort studies that proved some relationship between HIV and malaria was developed in a rural area of Uganda where malaria transmission is perennial[17]. The researchers followed almost 500 patients who were HIV seropositive and non-HIV-infected during eight years. The participants attended routine visits and self-demanded visits (interim visits) when they felt sick. Fever, HIV serology, CD4 count, and parasitemia were checked during these visits. The study found a significantly higher risk of having parasitemia when patients were HIV positive (OR 1.81; $p < 0.0001$), and a more than double risk of having clinical malaria in the same group compared with HIV-negative patients. The risk of clinical malaria increased significantly with lower CD4 counts and with more advanced HIV clinical stage. Also, the parasite density was significantly inversely related with CD4 count in HIV-positive patients, but not in HIV-negative ones. When patients attended interim visits, the rate of clinical malaria was more than three-times higher than in HIV-negative patients, and the risk of suffering clinical malaria in each one of the visits was double for HIV-positive than HIV-negative patients. The study had some weaknesses, especially related with the absence of CD4 counts in all the visits, but it is large enough to reveal important interactions. The authors conclude that if we take into account areas with an HIV prevalence of 8%, this illness will be responsible for about 4% of parasitemia and for 5% of clinical malaria. These proportions will be higher where the HIV prevalence is greater than 8%, as is frequently the situation in sub-Saharan Africa.

Another study that showed similar results was a longitudinal observational study in Malawi (holoendemic malaria transmission area with seasonal peaks)[18]. It was found that clinical malaria (defined as clinical malaria in general, clinical malaria with significant parasitemia, and febrile malaria) was associated with lower CD4 counts. Parasitemia density was inversely related to CD4 levels, and both associations appeared to be statistically significant. Growing immunodeficiency was also associated with other infections (tuberculosis, pneumonia, sepsis) more strongly than with malaria. This has important clinical consequences, as malaria parasitemia in HIV-infected patients does not rule out other severe opportunistic infections.

In order to assess the effect of HIV on malaria in sub-Saharan Africa, some authors have estimated the increases in malaria incidence and in malaria deaths due to HIV infection in different countries[19]. They used approximations of malaria incidence (without HIV infection), taking into account indexes of transmission relative to climate, studies that had described the effects of HIV on malaria incidence, published data of malaria mortality and the effect of HIV infection on it, estimations of HIV prevalence for different countries and different areas, and also the CD4 count distribution in these different areas. With these data, they estimated an increase of malaria incidence for 41 African countries. It varied between 0.2% in Mauritania and Niger, and 28% in Botswana, and on average it was 1.3% (range: 0.6-7.9%). The rate of increase was higher in countries with unstable malaria transmission. They also assessed the increase on mortality due to malaria caused by HIV coinfection, and this was calculated to vary between 0.65% for countries such as Gambia and 114% for Botswana. For the whole continent, the HIV infection increased malaria deaths by 4.9% (range: 3.1-17.1%); rates were higher in southern Africa. These figures imply that coinfection is responsible for 65,000 of the total malaria deaths, and approximately of the 3% of the total HIV/AIDS deaths. Even recognizing the limitations of these approximations, the study shows an important impact of HIV on malaria, mainly in areas of low transmission. This should be the rationale for making HIV-infected patients the objective of preventive measures and quick and effective treatment against malaria.

In areas with a seasonal transmission and where adults do not reach a semi-immune status, HIV infection has been related with a higher frequency of severe malaria and with atypical presentation of the illness[20]. These regions (e.g. India, South Africa, Zimbabwe, Brazil, Vietnam, Burkina Faso) have unstable malaria transmission and increased rates of severe, complicated malaria and death. Also, patients from these areas with severe malaria are more frequently infected by HIV[8].

One of the studies carried out in this region, compared the prevalence of severe malaria in HIV-infected and non-infected patients in South Africa[21]. They also distinguished between semi-immune and nonimmune malaria patients, as they included some immigrants coming from stable malaria transmission areas. They included more than 300 patients, 33% of them HIV infected, and 33% in each group (infected and noninfected) were defined as nonimmune for malaria. Severe malaria was significantly more

frequent in the HIV-infected group. When studying the different malaria features that define severe malaria, the following were presented with significantly higher frequency: severe anemia, acidosis, and renal impairment. It was also more frequent for patients in the HIV-infected group to be admitted to ICU or to be dialyzed. When they analyzed the risk factors associated with severe malaria in comparison with nonsevere malaria, applying multivariate techniques, they found a significant association with HIV-infection, with those nonimmune for malaria having higher parasitemia and higher WBC counts. As has been described in other studies, they found severe malaria more frequently associated with a nonimmune situation. Interestingly, they could compare in two groups: immune and nonimmune patients, and the risk of severe malaria between HIV-infected and noninfected patients. These results are very informative; when they compared, in the nonimmune group, patients with and without HIV-infection, they found that severe malaria, death, or admission to ICU were significantly more frequent in the HIV-infected patients. These differences were not found in the semi-immune group of patients. These results confirm the described different HIV effect in malaria, depending on the immune status of the patients.

It is also important to note that when CD4 cell counts were available in HIV-infected patients, severe malaria was significantly associated with having less than 200 CD4 cell counts. Other interesting findings come from studies among injecting drug users: coinfection with HIV and malaria and outbreaks of malaria have been demonstrated in areas of Brazil and Vietnam previously free from this parasitic disease[8].

Diagnostic implications

The usual practice of diagnosing malaria only based on clinical symptoms, especially fever, in some underdeveloped areas can have very important consequences when HIV infection is also present. Worse outcomes for other infectious febrile illnesses different for malaria have been described among patients with HIV infection when other diagnoses were not taken into account[8].

Treatment implications

Related with the response to treatment, it seems logical to consider that malaria treatment would be less effective to eliminate malaria parasites in those patients coinfected with HIV, as the immune system is necessary to attain this elimination. In a study developed in Kenya in a high-transmission area, it was found that patients infected with HIV and with CD4 counts < 200 had a significantly higher parasite density than patients with > 200 CD4 and patients non-HIV-infected. They also had a significantly higher prevalence of documented fever and anemia. The study demonstrated that treatment failure (recrudescence and reinfection) was higher in the group of HIV-infected patients with CD4 < 200. In the multivariate analysis, anemia was also a significant predictor of treatment failure: HIV-infected patients with a low CD4 cell count and anemia had a more than threefold risk of treatment failure. This study was developed using sulfadoxine-pyrimethamine, which was the recommended first-line treatment at that time[22].

In a retrospective study in Uganda, more than 2000 children and adults with malaria (fever and parasitemia) were given treatment with three different regimens: sulfadoxine-pyrimethamine plus chloroquine, sulfadoxine-pyrimethamine plus amodiaquine, or amodiaquine plus artesunate. Patients older than 18 months were also tested for HIV. Response to treatment and clinical treatment failure was checked during 28 days of follow-up through thick-blood smears. For adults (older than 18 years) the global risk of clinical treatment failure was more than threefold higher in those HIV-infected. This difference did not exist for children. When analyzing separately recrudescence risk or new infections risk, the difference in recrudescence was not significant between the two groups, but the risk of new infection was more than six-times higher in the HIV-infected adults, especially after 21 days of follow-up. There were no differences among the three different arms of treatment[13]. These results strongly suggest that the mechanism by which HIV affects malaria must be the reversion of acquired antimalarial immunity. Therefore, in children in whom immunity has not been completely developed, HIV infection does not alter the incidence of malaria. Another interesting result obtained by these authors is that the rate of HIV infection was higher in the patients of the study (diagnosed with clinical malaria) than projected for the adult population in Uganda, so they concluded that adults presenting with clinical malaria should be offered voluntary counseling and treatment for HIV infection.

Another study carried out in Zambia (an area with perennial transmission, but with a peak of incidence from November to April) focused on patients treated with sulfadoxine-pyrimethamine or with arthemeter-lumefantrine. They found a higher risk of treatment failure when patients had a CD4 count < 300, and for early failure and for failure after 45 days of follow-up. The higher rate of recrudescence was also significant for the group of patients with CD4 < 300, but not for reinfection. It must be said that the treatment which more

frequently failed was sulfadoxine-pyrimethamine. Another important result of this study was that some symptoms like fever, weakness, headache, dizziness, diarrhea, abdominal pain, and backache lasted longer in HIV-infected than in noninfected patients[23].

Other studies have been developed obtaining similar results: prolongation in time for parasite clearance in HIV-infected patients when using artemisinin in Ethiopia; significantly higher hazard ratios for recurrent parasitemia in coinfected patients with sulfadoxine-pyrimethamine in Malawi; and also significantly higher hazard ratios for treatment failure due to reinfection in HIV infected patients treated with chloroquine, sulfadoxine-pyrimethamine, amodiaquine, or artesunate in Uganda[8].

Interactions between antimalarial agents and antiretroviral therapy

First *in vitro* studies of antiretroviral drugs and malaria, developed prior to the introduction of the treatment in Africa, described interactions between them and some receptors related with pathophysiology of *P. falciparum*. Nevirapine, ritonavir, and saquinavir were studied in relation with their capability of decreasing the expression of CD36 receptor in the surface of macrophages and C32 cells. This receptor is implicated in phenomena of cytoadherence and phagocytosis of the parasitized erythrocytes, and it has been described that antiretrovirals decrease CD36 surface concentrations. The two protease inhibitors reduced the CD36 expression and thus the cytoadherence and the phagocytosis of parasitized erythrocytes; this change was not induced by nevirapine. The authors concluded that protease inhibitors could alter the plasmodium-host interactions, decreasing the pathophysiology of the parasite or altering the host defense against it[24]. *In vivo* studies are awaited. A commentary study published in the same issue remarked on the importance that the immune reconstitution could have on the malaria disease, even if the antiretrovirals had a negative influence on the severity of malaria[25].

Subsequently, some beneficial effects were described related with protease inhibitors. Proteases are similar to plasmepsins localized in a vacuole of *P. falciparum*[26]. It will be important to know the possibility of these drugs to control malaria in HIV-infected patients, the research in new antimalarial drugs related with them, and to know if changes in blood concentrations can have some importance in creating resistances. The latest knowledge about this effect has been published in a recent study that has demonstrated an anti-parasitic effect, inhibiting the growth of malaria parasites, of sera from patients taking protease inhibitors (saquinavir/ritonavir or lopinavir/ritonavir)[27]. However, studies in these regions are awaited to confirm these findings.

Co-trimoxazole prophylaxis has been described as having accounted for a significant reduction in malaria incidence in the families of HIV-infected people taking this prophylactic regimen. In a cohort study in Uganda, they found that HIV-uninfected people living with HIV-infected patients taking co-trimoxazole prophylaxis had an incidence rate ratio (IRR) of malaria significantly lower than those living with HIV-uninfected persons. Interestingly, the IRR of having malaria resistant to sulfadoxine-pyrimethamine was also lower in the household group of HIV-infected patients taking co-trimoxazole[28].

A complete sequential study developed in Uganda has demonstrated the benefits of three different interventions in HIV-infected patients in a high-transmission area. These sequential interventions were: co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bed nets. First-line antiretroviral treatment consisted of stavudine, lamivudine and nevirapine or efavirenz. Second-line for treatment failure or toxic effects consisted of didanosine, zidovudine, tenofovir, and lopinavir/ritonavir. Each one of the interventions showed to be beneficial for decreasing the incidence of *P. falciparum* parasitemia in HIV. The incidence rate ratio of episodes of fever and parasitemia were significantly decreased with each one of these interventions when compared with no intervention and when comparing with previous intervention in the sequential analysis. The reduction of malaria episodes in this group of patients has important health consequences, as reducing malaria episodes will improve morbidity and will lessen the effects of malaria on HIV evolution[29].

Interactions with significant clinical relevance can result from the use of antiretroviral drugs and malaria treatment. Some of them are of clinical importance. Halofantrine or lumefantine when coadministered with protease inhibitors or nonnucleoside reverse transcriptase inhibitors (NNRTI) can increase their potential cardiotoxicity. Quinine coadministered with protease inhibitors or NNRTI can also enhance the potential cardiotoxicity and other adverse effects of quinine such that the levels of this drug are elevated. Sulfadoxine-pyrimethamine, if coadministered with co-trimoxazole or nevirapine, increases the risk of hepatic or cutaneous reactions. If sulfadoxine-pyrimethamine is administered simultaneously with zidovudine, bone marrow toxicity would be expected more frequently[30]. People involved in the care of these patients must be aware of such interactions. A sumary of these drug interactions is shown in Table 1.

Table 1. Interactions between antiretroviral and antimalarial drugs

Antimalarial Drug	HIV Treatment	Mechanisms	Management
Quinine	PI NNRTI	Inhibition of cytochrome P450. High levels of quinine. More cardiologic and other side effects.	Do not coadminister. Reduce quinine doses. Cardiologic monitoring.
Artemether	PI	Decreasing the levels of dihydroartemisinin, an active metabolite. But increasing the levels of, also active, parent drugs.	?
Atovaquone	AZT	Lower AZT clearance.	?
" "	Ritonavir, Lopinavir	Probable decreases in atovaquone AUC.	?
Proguanil	Ritonavir	Decreasing the metabolism of proguanil and its effectiveness.	?
Mefloquine	Ritonavir	Decreasing levels of ritonavir.	?
Chloroquine	Indinavir, Ritonavir, Saquinavir	Increasing the effect of PI against viral replication. Decreasing indinavir concentration.	?
Sulfadoxine-pyrimethamine	Co-trimoxazole	Increasing risk of severe adverse cutaneous or hepatic reactions.	Avoid coadministration.
" "	Nevirapine	Possibility of additive risk of severe adverse cutaneous or hepatic reactions.	Do not initiate both drugs simultaneously.
" "	AZT	Higher risk of bone marrow toxicity (anemia).	Carefully coadministration, hematologic controls.
Co-trimoxazole	Lamivudine	Decreasing clearance of lamivudine.	No clinical relevance.
" "	Nevirapine	Possibility of adverse cutaneous reactions.	Do not initiate simultaneously both drugs.
" "	AZT	More risk of anemia due to bone marrow toxicity.	Hematologic controls.
Halofantrine/Lumefantrine	PI NNRTI	Potential risk of cardiotoxicity.	Avoid coadministration.

PI: protease inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; AZT: zidovudine; AUC: area under the curve.

HIV and malaria – interactions in pregnancy

A special case is related with pregnant women infected by HIV. It has been demonstrated that coinfected women have impaired humoral responses to variant antigens expressed by parasitized red blood cells sequestered in the placenta, explaining increased malaria illness and diminished parity-related immunity in pregnant women with HIV[5].

It is calculated that one million pregnancies occur in women affected by HIV and malaria each year in sub-Saharan Africa. As it has been explained before, the first pregnancy is the situation where semi-immunity against malaria is lost, but successive pregnancies are related with less parasitemia. Maternal malaria is associated with maternal anemia, low birth weight, and maternal and infant mortality. On the other hand, maternal HIV is associated with maternal anemia, low birth weight, and increased risk of maternal malaria, irrespective of the number of pregnancies. So, in coinfected women, maternal anemia and low birth weight could be expected to be even more frequent[30,31].

In a study developed in Tanzania among HIV-infected women, the risk of low birth weight was calculated as to be 2.66 (p = 0.01) for maternal parasitemia at the first antenatal visit. Parasitemia at the first antenatal visit was related with parasitemia at delivery, and this was also related with cord parasitemia. Maternal parasitemia at delivery was significantly associated with higher risks of preterm delivery, intrauterine growth retardation, and neonatal death. Also, cord parasitemia was significantly associated with an increase in the risk of neonatal death (RR 8.75; p = 0.03)[32].

It has been proposed that coinfection could be associated with a higher rate of mother-to-child HIV transmission, since malaria infection has been related with a higher viral load. Some preventative measures and treatment for coinfected pregnant women have been proposed. Insecticide-treated bed nets have been effective for the prevention of anemia in primigravidae of unknown HIV status. This efficacy was calculated as 41.6 %. It has not been studied in HIV-infected women, but it seems reasonable to suppose that their use will reduce the burden of malaria during pregnancy in HIV-infected women. Co-trimoxazole given daily has demonstrated a significant reduction in febrile malaria (> 70%) in HIV-infected adults. Although the effect during pregnancy has not been described, current WHO recommendations are daily co-trimoxazole prophylaxis in pregnant women. But there are concerns about toxicity, especially if sulfadoxine-pyrimethamine is also administered, and also about the possibility of developing malaria resistance to this treatment. In HIV-negative pregnant women, intermittent antimalarial treatment with sulfadoxine-pyrimethamine is being indicated for the prevention of malaria-induced morbidity during pregnancy. In HIV-positive women, more frequent doses of sulfadoxine-pyrimethamine have been proposed in order to reach a similar antimalarial effect as among uninfected pregnant women. There is no defined frequency of administration. Some worries are beginning to appear, especially the ones related with the frequency of doses, the possibility of malaria resistance to this drug combination, and also toxicity with antiretroviral drugs[30].

Conclusions

Even taking account of the important difficulties of researching in the geographic areas involved, the recent studies have demonstrated evident interactions between HIV and malaria, as it was supposed at the beginning of the epidemics.

Important factors of these interactions must be taken into account for a better understanding that can help

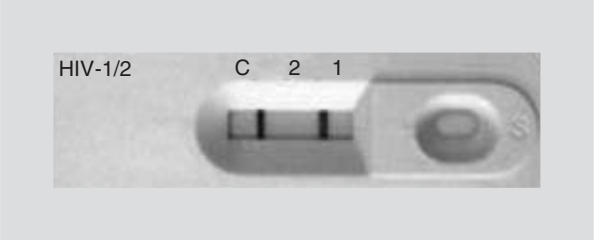

Figure 4. *One of the several rapid HIV tests that can be used in developing countries.*

preventive measures and programs. The knowledge about the semi-immune status reached by people living in areas with perennial malaria transmissions, and that it is not completely abolished by HIV infection, is important for elucidating different interactions in different areas. It explains that immunity altered by HIV infection seems to be enough for precluding severe malaria and death, but not for avoiding more malaria parasitemia and more clinical malaria than would be present if there were no HIV coinfection. This has significant consequences not only in quality of life of HIV-infected patients, but also in the economic burden at a family level and a society level, given the high numbers of young productive people affected.

The interaction is even more dramatic when it is studied in areas with seasonal malaria transmission, especially if HIV rates are high, as is the case of southern African countries. Malaria and HIV coinfection is implicated as a severe illness or cause of mortality in these areas. Similar results are described when pregnant women are affected by these two diseases.

When antiretrovirals are beginning to be used in developing countries, some measures must be considered if the results of these studies are taken into account. Voluntary counseling and testing for HIV should be proposed for adults diagnosed with clinical malaria, or with high parasitemia, or with treatment failure in areas with non-seasonal malaria transmission (Fig. 4). As malaria has been shown to increase HIV viral load and to diminish CD4 counts, treatment of malaria episodes in HIV-infected patients with effective drugs should be strongly considered when HIV programs are being developed. If possible, patients should be warned about the higher risk of HIV transmission during and after malaria episodes, and given advice on changes in lifestyles. On the other hand, doctors and health workers must be aware that even when malaria parasitemia is found, HIV-related infection could also be present.

With regard to prophylaxis, co-trimoxazole has shown a beneficial effect, and its use together with antiretroviral

treatment and the use of insecticide-treated bed nets has been proposed as a successful measure for controlling malaria in HIV-infected patients[33]. These measures should be even more important for coinfected pregnant women, not only in primigravidae but also in all parities.

The introduction of antiretroviral treatment should be made taking into account their implications related with antimalarial effects, with special attention being paid to protease inhibitors as they have demonstrated antimalarial effects. Programs for HIV and malaria are currently separated, but they share some important aspects. For instance, pregnant women, newborns, and young children are important populations for both infections; fever is an important manifestation for malaria and other HIV infectious diseases and malaria must be precisely diagnosed or ruled out in HIV-infected patients for accurate treatment; and co-trimoxazole has important benefits as prophylaxis for malaria and for other opportunistic infections. So, although malaria is not considered as an opportunistic infection related with HIV, its surveillance should be included in monitoring these patients in such areas and both programs should be coordinated[33].

The difficulties in the fight against malaria and HIV are well known when health programs are implemented in disadvantaged areas, but a better knowledge of the diseases and their implications are perhaps a good starting point in the search for a better outcome.

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