

HATiP

HIV & AIDS Treatment in Practice

Issue 64 | 01 March 2006



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HIV and malaria: when elephants collide

By Theo Smart

"HIV and malaria are diseases of massive importance with overlapping distributions, which raises the question about how these two diseases interact. Even small effects and small interactions can have a huge impact," Dr Laurence Slutsker, told an audience at the Thirteenth Conference on Retroviruses and Opportunistic Infections in Denver.

Indeed, as understanding of the interaction between the two diseases has evolved over the last 5-10 years, some of these interactions may have dramatic population-based effects and be of great public health importance. Co-management of the two conditions presents a number of medical and operational challenges - particularly when it comes to the prenatal care of HIV infected pregnant women. As just one example, the recommended treatment to prevent placental malaria, sulfadoxine-pyrimethamine (SP) should not be co-administered with cotrimoxazole prophylaxis because of the risk of serious adverse events. Nevertheless, coadministration occurs because of poor or non-existent co-ordination between malaria and HIV programmes in many countries.

Dr Slutsker has experience working in several developing countries including Malawi, Kenya, Sudan, South Africa; recently headed up the Kenyan Medical Research Institute Field Station in Western Kenya, and is currently chief of the Malaria branch of the US Centers for Disease Control (CDC). He reviewed many of the challenges in co-management of malaria and HIV at the Retrovirus Conference. Many of the same issues are also addressed in depth by a paper in February's *Lancet Infectious Diseases* (Brentlinger, Behrens and Micek).

Malaria background

Each year, there are around 500 million malaria infections, which cause between 700,000 to 2.7 million deaths, most of them in young children in Africa. Four species of malaria parasites can infect humans, but *Plasmodium falciparum* is by far the most important in terms of morbidity and mortality, and the most common in sub-Saharan Africa.

The clinical syndromes caused by malaria vary depending upon whether a patient comes from an area with stable (regular) endemic malaria transmission or unstable (irregular and/or infrequent) transmission. In areas where transmission is stable, the disease affects children and adults in different ways. Children experience chronic infections with recurrent parasitaemia resulting in severe anaemia and often death. Those who survive repeated infections acquire partial immunity by the age of 5 and carry it into their adult lives. Adults suffer from asymptomatic infections.

In unstable transmission areas, immunity is not acquired, so the overwhelming clinical manifestation is acute febrile disease which can result in cerebral malaria and death in persons of all ages.

Malaria is particularly dangerous to pregnant women. Women from an area of unstable transmission may experience acute malaria, loss of pregnancy, still birth, and abortions. Immunity acquired in areas of stable transmission may be partially lost in pregnant women, who usually experience asymptomatic infections

but can develop placental malaria that leads to birth retardation, low birth rate and the concomitant risk of increased infant birth mortality.

There are several ways that malaria and HIV could potentially interact, with effects upon transmission, clinical manifestations, and treatment outcomes of either disease. In addition, there may be drug interactions and convergent toxicity between the drugs used to treat each disease.

The impact of HIV on malaria parasitaemia and clinical severity in adults and children

HIV disease impairs the acquired immunity to malaria seen in older children and adults in endemic areas. Large cohort studies in rural Uganda and Malawi have provided evidence of increased frequency (with rates 1- to 2-fold higher) of both parasitaemia and clinical malaria in HIV-infected adults, with increasing risk and higher density parasitaemia associated with more advanced immunosuppression (Whitworth 2000, Patnaik 2005). Adults with HIV also have a higher risk of severe clinical malaria, particularly in areas of unstable transmission (Grimwade 2004).

For example, a recent prospective cohort study in South Africa evaluated whether HIV infection increased the risk of severe malaria in adults from both areas of stable and unstable transmission (Cohen 2005). The study involved 336 patients, of whom 32 (10%) had severe malaria. The HIV prevalence was 33%, and 111 patients (33%) were non-immune (from areas with unstable transmission of malaria). In a multivariate analysis, people with HIV were more likely to have severe malaria, and the risk was increased in HIV-infected patients with a CD4 cell count below 200 ($p = 0.001$).

Non-immune HIV-infected patients were significantly more likely to have severe clinical malaria (13 [36%] of 36 patients) than were non-immune patients without HIV (9 [12%] of 75 patients; odds ratio, 4.15 [95% CI 1.57-10.97]; $p = 0.003$). They were also significantly more likely to die ($p = 0.039$) or require an ICU admission ($p = 0.037$). In contrast, HIV infection did not confer an increased risk of these severity measures in semi-immune adults from areas more stable transmission.

The situation is somewhat more complicated in children. In a recent cohort evaluation in Uganda, rates of parasitaemia among older HIV infected children under the age of 5 were 1.7 fold higher than in those without HIV, and they had greater parasite density as well (Mermin 2004). However, in infants, cohort studies have failed to demonstrate an increase in frequency or density of parasitaemia (Greenberg 1991, Kayesubula 1997). "This seems to suggest that, in terms of interactions, older children with HIV may be more like adults and be affected because of HIV-induced impairment of acquired immunity to malaria," said Dr Slutsker.

However, a study from western Kenya, suggested that severe anaemia and hospitalisation due to malaria was more common in HIV infected infants (van Eijk 2002). Limited data also suggest HIV is associated with more severe malaria in older children (Grimwade 2003).

The effect of HIV on malaria treatment outcomes

"There have been some recent studies that have shown HIV infected adults may have poorer response to anti-malarial therapy, though the data are a bit mixed on the reasons," said Dr Slutsker.

For example, a retrospective analysis in Uganda showed that adults with HIV infection had a poorer response to anti-malarial therapy than HIV negative patients during the 28 days following treatment, but that treatment failure was due to higher frequency of

new infections rather than recrudescence (Kamya 2006). In contrast, in a large but as yet unpublished prospective clinical trial among adults in Western Kenya, there was a 3.6-fold increase in risk failure with sulfadoxine-pyrimethamine (SP) in HIV-infected persons with low CD4 counts and anaemia (HB < 11 g/dl) compared to HIV-negative individuals — except, in this case, the failures were due to recrudescence and not new infections.

The effect of HIV on malaria treatment outcomes in pregnancy

There are currently no data on how HIV may affect response to treatment of clinical malaria in pregnancy. However, older studies in Malawi have compared different chloroquine prophylaxis or intermittent preventive treatment (IPT) regimens (Steketee 1996). In these studies, HIV infected women had higher rates of persistent and breakthrough parasitaemia, and peripheral and placental parasitaemia at delivery, indicating a poorer response to both prophylaxis and treatment.

IPT involves the administration of a full treatment dose of an effective antimalarial drug at predefined gestational intervals. At least two doses of SP are currently recommended to be given at routine ANC visits in non-HIV-infected women after quickening. However, a clinical trial in Western Kenya found that HIV-infected primigravidae and secundagravidae required at least three doses to achieve similar reduction of placenta parasitaemia (Parise 1998). Subsequent studies have shown that three or more doses of SP are more cost effective than the two-dose regimen when ANC HIV prevalence is greater than 10%. “WHO has recently changed the recommendations for intermittent preventive treatment to take this into account,” said Dr Slutsker.

Overall impact of HIV on malaria

Using conservative estimates of these interactions, Korenromp et al recently evaluated the overall impact of HIV on malaria. Their modelling suggests that 1) overall there were three million excess cases and a 5% increase in malaria deaths due to HIV, translating to 65,000 excess deaths annually; and 2) that these interactions would be most compelling in regions with very high rates of HIV and unstable malaria transmission — areas such as Botswana, Zimbabwe, Swaziland, northern South Africa and Namibia, with malaria incidence increased as much as 28% and the number of deaths as much as doubled.

The impact of malaria on HIV

Like major opportunistic infections and TB, malarial episodes can transiently increase viral load, and thus could theoretically have an impact on HIV disease progression and HIV transmission. According to a report by Kublin et al in *The Lancet* last year, people with an asymptomatic malaria infection experience about 0.25 log increase in viral load, and up to about 0.89 log if they have a fever and parasite density > 2000, with a return to baseline about 8-9 weeks following effective treatment.

“However, the clinical relevance and long term impact of these short term changes is not clear, particularly in individuals,” said Dr Slutsker. Mermin et al recently reported an association between malaria infection and decline in CD4 cell count, but a causal relationship was not established.

In pregnant women, recent studies also confirmed that malaria is associated with increased HIV concentrations with a magnitude similar to that seen in asymptotically infected non-pregnant adults. One study also assessed the relationship between placental

malaria and placental viral load and found a similar twofold increase in placental HIV concentrations with the greatest increase of women with higher placental densities.

Placental malaria is also associated with increased expression of placental macrophages with CCR5 receptors raising the possibility of placental malaria leading to increased mother to child transmission (MTCT) of HIV (Tkachuk 2001).

“However, whether malaria during pregnancy enhances the risk of MTCT, remains a bit elusive,” said Dr Slutsker. Early studies from Malawi reported an increased risk of post-neonatal mortality in infants born to coinfecting mothers, beyond the independent risk associated with either exposure to maternal HIV or placental malaria, which might suggest that placental malaria could be leading to increased MTCT. However, studies in the DRC, Uganda and Kenya have reported contradictory results.

Nevertheless according to Dr Slutsker, “malaria may have “an important indirect effect on the risk of HIV transmission,” because anaemia caused by *P. falciparum* remains a frequent cause of blood transfusions. This relationship was documented in DRC in the 1980s where 70% of children hospitalised for malaria were transfused and there was a strong dose response between transfusions and HIV risk.

Unsafe blood transfusions are estimated still to be responsible for 10,000 new infections annually. Few countries in Africa are yet practising universal screening of blood, but efforts to improve the safety of the blood supply are having some impact. In Kenya, for example, selection of low risk donors has led to a reduction in the rates of HIV infection among donated units from 6% to 2% over a ten-year period.

“Obviously there are several responses to this risk,” said Dr Slutsker, “including reducing the risk of malaria and malaria-related anaemia, efforts to prevent unnecessary transfusions, and efforts to improve the safety of the blood supply.”

The quandary of cotrimoxazole

However, some of the biggest challenges in the co-management of HIV and malaria concern the drugs used in their care — in particular, cotrimoxazole.

Cotrimoxazole prophylaxis has been recommended for all HIV-infected people in sub-Saharan Africa. However, cotrimoxazole, an anti-folate drug like SP, shares a mechanism of action and an adverse event profile with SP. In some countries, the use of cotrimoxazole prophylaxis was even delayed because of concerns that it might increase malarial resistance to SP, which until recently was the first-line recommended treatment for malaria in many African countries.

Some of the reduced response in people with HIV to malaria treatment with SP, at least, may be the result of the use of cotrimoxazole prophylaxis. In fact, a study presented at the Retrovirus Conference found that the use of cotrimoxazole prophylaxis was associated with higher risks of treatment failure in children (RR 1.77, 95% CI 1.04 to 3.05) and adults (RR 2.05 95% CI 0.8 to 5.0) (Byakika 2006).

However, a number of studies have demonstrated that daily cotrimoxazole prophylaxis also leads to a reduction in malaria incidence (Anglaret 1999, Mermin 2004, Chintu 2004, Thera 2005). This effect “may still occur in settings even where resistance to SP is high,” said Dr Slutsker. “Obviously, the resistance can be a concern in individuals who develop malaria while taking cotrimoxazole and non-sulfa based drugs need to be used for treatment in these individuals. The current shift in first-line malaria

treatment toward artemisinin-based combination therapies (ACT) for malaria may help to address some of these concerns.”

But the question of what to use in pregnant women becomes more complicated. Cotrimoxazole has been shown to be beneficial in HIV-infected pregnant women. In fact, a study presented at the Retrovirus Conference demonstrated that cotrimoxazole prophylaxis significantly improves birth outcomes in women with HIV (see <http://www.aidsmap.com/en/news/5FC7F0F9-3158-4BDA-B677-875B82B3C1D9.asp>).

However, concurrent administration of ITP with SP and co-trimoxazole has been associated with a substantially increased incidence of severe adverse reactions in HIV-infected patients and therefore is not recommended. While cotrimoxazole does have anti-malarial activity, according to the recent LID paper by Brentlinger, Behrens, and Micek, “no published data yet describe the effectiveness of daily cotrimoxazole for the prevention of malaria and its consequences (specifically maternal anaemia, placental parasitaemia, and low birth weight) during pregnancy.” And according to Dr. Slutsker, studies are needed to determine whether “cotrimoxazole prophylaxis is sufficient to prevent placental malaria and obviates the need for other preventive interventions.”

Nevertheless, WHO recommends daily cotrimoxazole as an alternative to intermittent preventive treatment with SP for immunocompromised HIV-infected women. But even if it is as effective as ITP with SP, the LID paper points out that “operational constraints resulting from late diagnosis may limit the use of daily cotrimoxazole for malaria prophylaxis. Women who are not diagnosed with HIV until after the first antenatal visit may not present for HIV care until late pregnancy, especially where HIV care is not offered at the antenatal clinic itself. In many settings, prescription of cotrimoxazole may also be contingent on clinical and/or laboratory staging, which may introduce further delays in initiation of cotrimoxazole prophylaxis. If cotrimoxazole is not begun until the third trimester, malaria-related maternal anaemia and foetal growth retardation may already have developed.”

Another issue is whether the pregnant woman has already been received SP – in which case, cotrimoxazole should not be administered for at least one month. But this presumes that ANC and HIV care clinics are in close communication, and that healthcare workers at each site know what the patient has been prescribed.

Other drug issues

The expanding use of antiretroviral drugs could have implications for malaria control if the drugs have anti-malarial activity. Indeed most of the HIV protease inhibitors (PIs) have anti-malarial activity, possibly at clinical relevant concentrations (Parikh 2005). However, they have yet to show any demonstrable clinical impact on malaria – and, as expensive second-line drugs, are still not commonly used in malaria-endemic areas.

Conversely, some anti-malarial drugs may have direct anti-HIV activity. For example, chloroquine has demonstrated modest anti-HIV efficacy – however, because of widespread malaria resistance, this drug is no longer commonly used for treatment.

There are a number of potential drug interactions between antimalarial drugs and HIV drugs. For example, ritonavir (*Norvir*) or lopinavir/ritonavir (*Kaletra*) may boost levels of quinine or lumefantrine, perhaps to dangerous levels, while non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine may lower concentrations and effectiveness of these drugs. The balance between artemether and its metabolites might also be impacted by

PIs or NNRTIs, but the data there are still limited and the clinical implications are unclear.

Drug toxicity also complicates the clinical co-management of HIV and malaria. For example, a common side effect of AZT is anaemia, which is an obvious concern in patients who are anaemic due to malaria. Another issue is the convergent toxicity of nevirapine-based ART and SP, particularly in pregnant women who are taking or have taken ITP. Hypersensitivity reactions to nevirapine, including potentially fatal liver and skin reactions, are fairly common and clinically indistinguishable from reactions to SP.

The authors of the LID report suggest that “staggering the introduction of SP and nevirapine... would reduce the potential for diagnostic confusion should an adverse event occur. However, because both drugs have long half-lives, their introduction may need to be separated in time by a month or more.”

Implications for individual patients and programmes

Dr Slutsker concluded his talk by reviewing some of the implications of the interaction between HIV and malaria both for individual patients and disease control programmes.

“HIV infected individuals should be targeted for malaria prevention interventions such as insecticide-treated nets for those living in endemic areas and chemoprophylaxis for [non-immune] HIV-infected persons travelling to malarial areas,” he said. Given the high efficacy of cotrimoxazole to prevent malaria infection, cotrimoxazole-treated patients present with fever may be much less likely to have malaria and may warrant a more detailed diagnostic evaluation; while for those on cotrimoxazole prophylaxis who do develop malaria, treatment needs to be with non sulfa-based/anti-folate drugs. Similarly pregnant women on cotrimoxazole should not receive sulfa-based intermittent preventive treatment for placental malaria.

Studies are needed to determine “what the optimal approach is to fever diagnosis and management in people with HIV on cotrimoxazole in resource limited settings,” said Dr Slutsker.

Drug interactions for patients on ARV's and anti-malarials need to be considered; and patients with advanced HIV need prompt and effective malarial treatment. He stressed that studies have yet to determine whether artemisinin-based combination therapies are efficacious in people with advanced HIV or who are on antiretroviral therapy.

Finally, there needs to be better coordination between HIV and malaria control programmes. “In terms of programme implications, an important target group for malarial prevention in control programmes should be HIV-infected individuals and conversely HIV prevention and treatment programmes offer the opportunity to deliver malarial prevention interventions. Sites that provide opportunities for integration, include the laboratory where we can enhance laboratory diagnostic capacity for both diseases, ANC delivery units where ITNs and IPT can be given along with VCT and PMTCT; and delivery of ITN's, anti-malarials and anaemic prevention interventions through HIV treatment and care clinics,” Dr Slutsker concluded.

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A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

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