

Malaria and HIV: demystifying the often misunderstood relationship

Professor William Brieger on the crucial importance in obtaining proper laboratory test results for those suspected of having malaria. A recent study showed that in 75% of HIV/AIDS sufferers their first symptom was... fever

The dangers of co-infection

The part of the world where the highest HIV prevalence and the highest malaria prevalence coincide is unfortunately Africa. In general HIV as it transforms into AIDS is noted for increasing a person's susceptibility to other infections. The situation is worsened when some co-infections, like malaria, also make HIV worse. The *BMJ* noted that, 'Evidence for a biological interaction in people who are co-infected (with both diseases) has grown.'¹

A recent review of studies on co-infections in HIV found strong evidence of increased HIV viral load with acute malaria and as hoped, decreased viral load following malaria treatment.² The authors therefore concluded that 'Co-infections may increase HIV viral load in populations where they are prevalent, thereby facilitating HIV transmission.' The logic of a Global Fund that fights both HIV/AIDS and malaria thus becomes clear, though it is rare to find integrated proposals that address the negative synergies of these two diseases.

Similarly it makes sense that the Millennium Development Goals place malaria and HIV together under Goal 6. Unfortunately, the challenges of Goal 1, reduction of poverty, as well as slow achievement of gender equality (Goal 3) have resulted in less than ideal roll out of HIV and malaria treatment and prevention interventions.³

Treatment issues

Treatment of malaria in areas where it overlaps with HIV can be complicated. Clinicians may miss opportunities to identify HIV in early stages or later when HIV status is confirmed, but not undertake appropriate diagnostics to differentiate malaria from other causes of febrile illness in HIV-positive people.

Skinner-Adams and colleagues tell us that, 'Currently, there are no specific recommended treatment regimens for malaria and HIV/AIDS co-infection. Although there is little doubt that some antiretroviral and antimalarial drugs will interact if co-administered, the effects of dual treatment have been poorly studied.'⁴ Some research is being done in this direction, as seen below, but much more is needed.

People in the acute phase of HIV-1 infection may

often experience symptoms that spur them to seek treatment, while not knowing that this is the start of their battle with HIV/AIDS. A study in Kenya found that three-quarters of these may report 'fever'. Not surprisingly, many receive presumptive treatment for malaria, but few are actually tested for malaria.⁵ Unfortunately, this reflects the normal bias of health workers against diagnostic tests in favour of their less than perfect clinical judgment.⁶

The importance of testing is highlighted by the fact that normally adults in stable malaria-endemic areas have some level of acquired malaria immunity. Thus, when adults present with malaria, one should not rule out the possibility that they are co-infected with HIV. With this in mind, Bebella and co-researchers found in Uganda that, 'At multiple sites in Uganda, 1–3% of adults with suspected malaria had acute or early HIV infection.'⁷ The authors note that, 'These findings highlight a major opportunity for expanding recognition of acute and early HIV infection in Africa.'

Treatment regimens for both diseases involve a variety of different drugs, often in combination. Reithinger



Malaria, HIV, or both? The correct diagnosis and treatment regimen is crucial

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and colleagues warn readers of potential actions that have not been thoroughly researched.¹ For example, research from Uganda found a high risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria.⁸

Li and co-researchers call for an understanding of the chemotherapeutic interactions that occur during malaria and HIV co-infections, and provide evidence that such interactions may not always be negative. They found in studies of rats that chloroquine had a 100% clearance of asexual malaria parasites when used in combination with indinavir at an appropriate dose ratio and suggest further research on this novel combination.⁹ Another potentially positive finding is that, 'protease-inhibitor-containing antiretroviral regimens may demonstrate prophylactic activity against both vivax and falciparum malaria in HIV-infected patients resident in areas where multi-drug resistant *Plasmodium vivax* or *P falciparum* is found.'¹⁰

Quinine is still used for treatment of malaria in pregnancy and for severe malaria. Achan and colleagues warn that, 'In HIV and TB infected populations, concerns about potential interactions between quinine and antiretroviral and anti-tuberculosis drugs exist, and these will need further research and pharmacovigilance.'¹¹

People with HIV are prone to a number of bacterial infections that may resemble malaria at first glance – 'Meningitis, non-typhi salmonella, and pneumonia can all be misdiagnosed as malaria,' according to Reithinger and co-authors.¹ Unfortunately, they note that these possibilities are often ignored, leading to lack of testing and relevant treatments. Streptococcus pneumoniae is one common example of an undetected condition treated as malaria. In Tanzania it is closely associated with HIV infection, but researchers found that malaria was over-diagnosed clinically when in fact children had pneumonia.¹² The lack of reliance on rapid diagnostic tests for malaria puts HIV-positive children's lives at further risk.

More generally, researchers in Uganda stress the need for parasitological malaria diagnosis among people living with HIV who are receiving highly active anti-retroviral therapy (HAART) and cotrimoxazole prophylaxis.¹³ In resource-poor settings, 'there is increasing need for parasite-based malaria case management to prevent unnecessary use of anti-malarial medicines, improve patient care in parasite-positive patients, and identify parasite-negative patients in whom another diagnosis must be sought.'

Overall, these studies show that we have much to learn about treatment of either disease when both occur in the same community and same patient, and we also have a need for caution and monitoring of any treatment we provide.

Pregnant women

In a seminal review of studies, ter Kuile and colleagues found that HIV-infected women had consistently more peripheral and placental malaria, higher parasite densities, and more febrile illnesses, severe anaemia, and adverse birth outcomes than HIV-uninfected women.¹⁴ What was particularly significant from these findings was that with HIV co-infection, all HIV-positive pregnant



Good antenatal care should include HIV services to reduce the chances of inappropriate medication

women were at greater malaria risk, not just those in their first or second pregnancies. In short, pregnant women are less likely to develop a protective response to pregnancy-associated malaria when they have HIV.¹⁵

Health service implications of these findings focused on malaria prevention. Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine–pyrimethamine (SP) helps, but possibly because of faster recrudescence or re-infection, HIV-positive pregnant women are recommended to have at least three doses of IPTp. Some countries like Ghana, in order to avoid stigmatising HIV-positive women, have recommended at least three once a month doses of IPTp after quickening.

Cotrimoxazole, used prophylactically in HIV, does also have antimalarial properties.¹⁶ Since it is also a sulfonamide-like SP, the usual recommendations are to ensure that pregnant women do not take both. If HIV services are integrated into antenatal care during the time of a woman's pregnancy, the chances of inappropriate medication are reduced.

Generally infections during pregnancy expose both the mother and the foetus to risks and of the latter, stillbirth is common. A review of 25 studies on this topic was able to demonstrate clear benefits of detecting and treating syphilis during pregnancy, marginal benefits concerning malaria, and none for HIV.¹⁷ The effects of managing dual infection with HIV and malaria on stillbirth were not monitored.

HIV and malaria present a dangerous two-way street to the foetus. Research in Uganda found that 'Placental malaria increases the risk of MTCT (mother-to-child-transmission) after adjustment for viral load.' The researchers therefore recommended that, 'Programs should focus on enhanced malaria prevention during pregnancy to decrease the risk of adverse birth outcomes and MTCT.'¹⁸ HIV-positive pregnant women are also more likely to pass malaria to their unborn child as HIV increases placental parasite loads. The Kenyan researchers concluded that, 'The significantly increased burden of placental malaria increases the risk of congenital infection.'¹⁹

Health systems issues

The combined impact of HIV and malaria on health systems is substantial, especially in Africa. This is often ignored.¹ According to the *BMJ*, combined malaria and

HIV infections result in excess, or beyond normally expected cases of each, thus creating extra pressure on the health systems where both diseases co-exist. The editorial goes further to show that synergies are not yet in place...

'Worldwide, malaria and HIV/AIDS prevention and control programmes are being scaled up because of a welcome increase in support for both diseases. However, operational malaria and HIV/AIDS programmes continue to be planned separately, despite having a substantial impact on one another. One of the impacts is on human resources. In Africa, and to a lesser extent in Asia and Latin America, the shortage of experienced healthcare staff means that the same health personnel are expected to deliver the scaled-up programmes for both diseases, yet there is seldom joint planning.'

Efforts to integrate HIV and malaria prevention and management must be accompanied with good communications between providers and clients. Focused ante-natal care is one such opportunity for integration, but experiences in Uganda show that pregnant women can be discouraged from attending antenatal care (ANC) when they do not understand the services being provided. Specifically the researchers found that, 'ANC attendance was hampered by the fear of being tested for HIV at the clinic. Perceived side-effects associated with IPT-SP hindered IPT uptake and were linked to HIV-related symptoms.'²⁰

While there are often fears that provision of HIV/AIDS services may 'weaken' or 'distort' or drain resources from primary care services and malaria control, researchers in Uganda have proven that this does not have to be the case. After a well-planned introduction of HIV services in six government clinics, the researchers were not surprised to find an increase in indicators of HIV service use. There were also increases in other service indicators such as provision of malaria diagnostic tests and malaria diagnosis and treatment. The key to success in this primary care setting was collaboration among partners to strengthen existing health systems, not just to control one disease.²¹

In conclusion, each disease, malaria and HIV, put a great burden on our health systems, and even greater stress when they occur in the same environment. Treatment and prevention of malaria in HIV-positive persons is a critical element of care and support, and as we have seen, the presence of malaria in adults could



A well run clinic is vital in the primary care setting

be a sign that we need to test for HIV. Joint treatment regimens are not perfected, and while some positive synergies have been documented, negative interactions also occur. This is a new era of medical science, and all clinicians need to take part in monitoring treatment combinations. We also need to be especially vigilant for the effects of joint infection on pregnant women for the sake of their own health, and because of the negative consequences on the unborn child. To achieve these tasks we must seek an integrated approach to primary healthcare that is able to ensure adequate resources to tackle both HIV and malaria where they jointly occur.

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CPD Challenge

See page 61 to test yourself on this article