Disease and Drug Interactions: Treating Malaria with Artesunate plus Amodiaquine in Patients also Receiving Treatment for Concomitant HIV Infection

Piero Olliaro
UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases, Geneva, Switzerland

In this issue, Gasasira et al. [1] report the effects of treating malaria in people with concomitant HIV infection with artesunate plus amodiaquine, one of the World Health Organization–recommended artemisinin-containing combination therapies. Although prospects of controlling malaria are much more promising now than ever because of the availability of effective curative and preventive measures and because of mechanisms to finance country-based programs, this article adds one more issue to an already alarming list of concerns regarding the interaction between malaria and HIV infection.

Both malaria and HIV infection are preventable and treatable conditions, provided that effective measures are set in place and made available. However, although all elements of the interaction between these 2 diseases are not yet clear, there is mounting evidence that coinfection adversely affects either disease and causes excess morbidity and mortality, particularly among vulnerable groups, such as young children and pregnant women. Drugs may also behave differently in the context of coinfection or when concomitant treatment is given. Paradoxically, the expanded access to antimalarial and antiviral drugs may create a significant public health issue, if the combination of disease and drug interactions makes treatments less effective or more toxic.

The article by Gasasira et al. [1] highlights several such elements of concern. Antimalarial treatment with artesunate plus amodiaquine was highly effective for patients with malaria who did not have HIV infection, although HIV-infected patients tended to experience more episodes of malaria during the study period. Although the difference was not statistically significant, repeated treatments may generate toxicity and, in the longer term, render a drug ineffective through selective pressure on the parasites, particularly if the host immune response is weak.

Of the 2 components of this artemisinin-containing combination therapy, artesunate is very well tolerated and has a broad therapeutic window, and amodiaquine has caused rare but serious (and even fatal) toxicity when it has been used for prophylaxis of malaria for prolonged periods but not when it has been used for treatment of malaria. The most feared adverse events associated with amodiaquine are hepatotoxicity (1 of 15,500 exposures lasting from 3 weeks to 10 months) and WBC dyscrasia (1 in 2200 exposures lasting 5–14 weeks; fatality rate, 1 in 31,300 persons). No such event has been described in association with this drug when it is has been used for malaria treatment. The reason for the difference in the effects of amodiaquine prophylaxis and treatment is accumulation (the drug dose in cases of serious toxicity following prophylaxis was 2.3 times the dose taken for treatment) and resides in the mechanism of amodiaquine toxicity. Amodiaquine is transformed in the body by liver microsomes and peroxidases to a quinonimine (or iminoquinine), an electrophilic metabolite that is chemically reactive and cytotoxic; it undergoes nucleophilic attack and forms highly immunogenic drug-protein complexes. This bioactivation process is related to the presence of a p-amino-phenol moiety in the molecule; thus, this process is not related to direct toxicity of the parent compound, and it is not unique to amodiaquine but is shared with other related molecules, such as pyronaridine,
another antimalarial Mannich base being developed as an artemisinin-containing combination therapy. What determines individual susceptibility is unclear; the patients treated in this study had various predisposing factors.

In the patients in the study by Gasasira et al. [1], no liver toxicity was seen, and it is difficult to ascribe neutropenia to a single cause. Hematological changes at large are not well characterized in malaria after treatment. However, a review of neutrophil kinetics suggests that neutropenia seen in the context of *Plasmodium falciparum* infection may be associated with early release of neutrophils (immature), with consequent sequestration in the spleen. Furthermore, neutropenia has been found to be associated with various antimalarial treatments, but the comparative incidence has not been assessed systematically. Neutropenia is also a common feature of HIV infection and is possibly the result of modulation of IL-12, which is down-regulated in HIV infection, with associated monocyte and neutrophil sequestration. Neutropenia is also a known result of toxicity of other drugs that the patients were taking in this study, notably trimethoprim-sulfamethoxazole and antiviral azidothymidine.

Because of the complexity of presentations and interactions, do the results presented here mean that drugs such as amodiaquine are simply too difficult to handle in the context of concomitant HIV infection and treatment? Before reaching this conclusion, we need to understand what determines the toxicity and which other antimalarial options are safe in the same circumstances.

A 2004 World Health Organization report [2] identified the key implications for public health and the research priorities for the interaction between malaria and HIV infection. The article by Gasasira et al. [1] investigated some of these aspects and highlighted the complexity of case management when malaria and HIV infection occur and are treated concurrently. The World Health Organization report [2] asks for more research in this area to understand how diseases and drugs interact. This research will help with understanding of how concomitant diseases and drug interactions affect the deployment of current interventions, as well as provide guidance for the design of future interventions.

**Acknowledgments**

Potential conflicts of interest. P.O.: no conflicts.

**References**