Interactions between ACTs for malaria and ARVs for HIV: cause for concern?

Wed 9 Oct, 13:30-15:00

Chairs: **David Schellenberg and Lasse Vestergaard**

OVERVIEW

Objective: This symposium will present findings from recent clinical and qualitative studies conducted in Tanzania and Uganda looking at the problem of concomitant treatment of malaria with artemisinin-based combination treatments (ACTs) and HIV with antiretrovirals (ARVs) in co-infected patients.

Rationale: Malaria and HIV both remains major public health problems in large parts of the world. WHO recommends artemisinin-based combination treatment (ACT) for malaria and antiretrovirals (ARVs) for treating HIV/AIDS. Although there is a potential for drug-drug interactions as these agents share common metabolic pathways, limited information is yet available regarding how such interactions might affect the efficacy and safety of these treatments when used concomitantly. Increased metabolism of artemether-lumefantrine (AL), the most commonly used ACT, could lead to decreased drug concentrations and thus reduced antimalarial efficacy and the selection of resistance. In contrast, decreased metabolism could cause increased blood concentrations leading to poorer tolerability or toxicity. Pharmacokinetic studies looking at various combinations of ACTs and ARVs have so far provided conflicting results, and most have been conducted in health volunteers in whom the impact on treatment efficacy cannot be detected. Further efficacy, safety and pharmacokinetic studies are needed in patients with HIV/AIDS andmalaria to assess the clinical significance of any interactions, inform treatment policies and guide safe and effective case management. In addition, a better understanding of how patients perceive and cope with such concomitant drug taking is needed.

Content: The ACT Consortium was formed with the goal of developing and evaluating delivery mechanisms to improve ACT access, targeting, safety and quality. The purpose of this symposium is to present some of the findings of the Consortium's studies addressing co-infection with malaria and HIV and concomitant administration of ACTs and ARVs. Two Consortium studies have addressed the question of ACT-ARV interactions: The SEACAT Study in South Africa looking at PK effects in HIV-patients without malaria, and the InterACT Study in Tanzania looking at efficacy and safety of ACT-ARV interactions in co-infected adults. The study in Tanzania also involved a qualitative study looking at perceptions of concomitant ACT-ARV drug taking. Apart from the ACT Consortium, the Makerere University in collaboration with University of California has conducted a series of studies addressing HIV and malaria co-infection and ACT-ARV interactions, also involving PK and clinical studies. Symposium panelists will present a brief summary of currently known ACT-ARV PK interactions, followed by presentations of results from recent clinical studies in Tanzania and Uganda on how potential drug interactions may affect malaria treatment efficacy and safety, discussing the potential need to revise current treatment recommendations, and how to support patients in receiving most optimal concomitant treatment for malaria and HIV.

1. Pharmacokinetic interactions between artemether-lumefantrine and drugs used in the treatment of HIV-infected patients

Presenter: Karen I Barnes (*University of Cape Town, Cape Town, South Africa*)

Background: Potential drug interactions need to be considered when treating malaria in people living with HIV/AIDS. Artemether-lumefantrine is currently the most widely used artemisinin-based combination therapy (ACT). As it is generally well tolerated with a wide-therapeutic index, it is expected that interactions that reduce exposure to artemether and or lumefantrine are more likely to be clinically significant than those that increase drug exposure. A decrease in ACT exposure is of particular concern in HIV-infected individuals as they tend to have higher baseline parasitaemias, an independent risk factor for antimalarial treatment failure.

Methods: A literature search was conducted in PUBMED using the terms “artemether” or “lumefantrine”, and “pharmacokinetics” or “concentrations”, and “HIV”. Articles were reviewed for any evidence of pharmacokinetic drug interactions with artemether-lumefantrine.

Results: Artemether / dihydroartemisinin exposure was decreased by rifampicin, nevirapine, efavirenz, lopinavir/ritonavir, darunavir/ritonavir and etravirine. Lumefantrine exposure was decreased by rifampicin and efavirenz, but was increased by nevirapine, lopinavir/ritonavir and darunavir/ritonavir. However, some inconsistency between studies was found for the effect of nevirapine on lumefantrine exposure, with 2 studies finding increased lumefantrine exposure and another finding similar lumefantrine exposure with nevirapine co-administration. In one study, artemether/lumefantrine reduced nevirapine exposure. Among the few studies conducted in malaria-HIV co-infected patients, the co-administration of lopinavir/ritonavir decreased the risk of recurrent malaria following artemether-lumefantrine treatment of uncomplicated malaria in Ugandan children, but also increased the number of serious adverse events. Limitations of some studies included small sample sizes, administration of a single artemether-lumefantrine dose, the co-administered drug not reaching steady state during the study, and conduct in healthy volunteers precluding assessment of the effect of the observed drug interaction on therapeutic efficacy.

Conclusions: Further clinical data from carefully designed population pharmacokinetic and pharmacodynamic field trials are urgently needed for evaluating the clinical significance of these drug interactions, particularly for guiding the management of uncomplicated malaria in patients on efavirenz-based antiretrovirals or rifampicin-based tuberculosis treatment. As resistance emerges and spreads, other drug interactions that increase the risk of artemether-lumefantrine treatment failures may become detectable.

2. Efficacy and safety of artemether-lumefantrine for the treatment of uncomplicated malaria in HIV-positive adults receiving first-line antiretrovirals in Tanzania

Presenter: **Lasse Vestergaard** *(University of Copenhagen)*

Team: Lasse S. Vestergaard, Nyagonde Nyagonde, Bonnie Cundill, Trinh Duong, William Sebe Sebe, Filbert Francis, Ola Persson, Marie Helleberg, Jens Asbjoern, Ben Amos, Lubbe Wiesner, Karen Barnes, Michael Alifrangis, Martha M. Lemnge, Ib C. Bygbjerg

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BACKGROUND: Although there is concern of drug-drug interactions between artemisinin-based combination treatment (ACTs) for malaria and antiretrovirals (ARVs) for treating HIV/AIDS, very limited information is available about the clinical importance of such interactions. The aim of this study was to examine the efficacy and safety of artemethemter-lumefantrine (AL), the most commonly used ACT, for the treatment of uncomplicated falciparum-malaria in HIV-positive adults recieving first-line ARVs in Tanzania.

METHODS: The InterACT Study was conducted from July 2009 to September 2012 at Muheza District Hospital in northern Tanzania. HIV-positive adults (>15 years) receiving either nevirapine- or efavirenz-based ARVs were enrolled and followed-up for 42 days using WHO standard protocols. Three additional groups of patients were included for comparison: 1) HIV-positive malaria patients not receiving ARVs but treated with AL, 2) HIV-negative malaria patients treated with AL, and 3) HIV-positive patients receiving ARVs but without malaria.

RESULTS: A total of 17,269 patients were screened for malaria, amongst whom 385 HIV-positive patients with confirmed malaria were enrolled into the study and followed-up successfully for 42 days. Analysis of AL therapeutic efficacy and safety and day-7 lumefantrine drug levels is ongoing.

CONCLUSIONS: The clinical significance of possible drug interactions between AL and nevirapine- and efavirenz-based ARVs will be discussed.

3. Efficacy and safety of artemisinin-based combination therapy in HIV-infected children in Uganda

Presenter: Jane Achan

Team: Abel Kakuru, Jane Achan, Gloria Ikilezi, Mary K. Muhindo, Florence Mwangwa, Emmanuel Arinaitwe, Theodore Ruel, Tamara D. Clark, Edwin Charlebois, Philip J. Rosenthal, Diane Havlir, Moses R. Kamya, Jordan W. Tappero, Grant Dorsey

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Background: Artemisinin-based combination therapies (ACTs) are now widely recommended as first line drugs for the treatment of uncomplicated malaria in nearly all African countries. However data on the safety and efficacy of ACTs in HIV-infected populations are still limited.

Methods: We evaluated malaria treatment outcomes in the setting of two cohort studies of in HIV infected children - Promote and the TCC studies. All children received insecticide treated bed nets, trimethoprim-sulphamethoxazole prophylaxis and antiretroviral therapy when indicated. Children were followed up for their medical care at a dedicated study clinic that was open daily. Children with uncomplicated malaria were treated with artemether-lumefantrine (AL) in the Promote study, AL or dihydroartemisinin- piperaquine (DP) in the TCC study. All children were followed up for 28 days and thick blood smears were done on day 2, 3, 7, 14, 21 and 28 of malaria follow-up. Treatment outcomes and adverse events were assessed over the 28 day follow-up.

Results: There were 184 and 57 HIV-infected children in the Promote and the TCC studies respectively. One hundred twenty three and 43 children in the Promote and TCC studies respectively had at least one episode of malaria. In the Promote study, 527 episodes of uncomplicated malaria were treated with AL while 201 episodes and 165 episodes in the TCC study were treated with AL and DP respectively. During follow-up, all children in the Promote cohort were on ARVs while 52 (91%) children in the TCC were on ARVs. By day 3 of malaria follow-up, only 5 (0.9%) of AL treatments in the Promote study, 2 (1%) of AL and 2(1.2%) of DP treatments in the TCC study still had parasitemia. After 28 days of follow-up, 399 (69.8%) AL treatments in the Promote study, 127(63.2%) AL and 149(90.3%) DP in the TCC study had adequate clinical and parasitological response (ACPR). The rate of late parasitological failure (LPF) with AL treatment was 21.5% in the Promote study and 26.4% in the TCC study. DP had a lower rate of LPF (6.7%). The risk of recurrent parasitemia was significantly lower with DP compared to AL in the TCC study (8.6% Vs 36.2%, $P<0.001$). The rates of grade 3 or 4 adverse events were low in both studies.

Conclusion: AL and DP were efficacious and safe in treatment of uncomplicated malaria in both studies but DP had a less risk of recurrent parasitemia compared to AL in the TCC study.

4. Perceptions and experiences of taking ACTs concomitantly with ARVs among patients with malaria and HIV in Tanzania

Presenter: Peter Mangesho

Team: Peter Mangesho, Joanna Reynolds, Martha Lemnge, Lasse S. Vestergaard, Clare Chandler

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Background: Co-infection of HIV and malaria is common in Sub Saharan Africa. The InterACT clinical trial in Muheza in northern Tanzania sought to understand how drugs for the two diseases may interact. However, little is known about how those with HIV perceive malaria or its treatment. It is important to understand whether risks of co-infection or risks of drug interactions are perceived and whether this affects prevention or treatment practices.

Methods: This qualitative study explored how HIV-positive people conceptualize malaria and antimalarial medication, in comparison with HIV-negative people. We conducted the study using focus group discussions with people receiving treatment for HIV and/or malaria, and in-depth interviews with health workers responsible for HIV care.

Results: Results suggest that people living with HIV saw malaria as unavoidable, and perceived the disease to be more harmful due to their compromised immune status. However, this did not seem to translate into extra efforts to prevent malaria infection. For those enrolled in a clinical research study, taking antimalarials together with ARVs was largely seen as unproblematic, with health workers' advice and endorsement of concomitant drug taking influential in reported adherence. However, perceptions of drug strength compelled some people, mainly those not enrolled in clinical research, to take the drugs at separate times to avoid anticipated harm to the body. Many reported self-medication with antimalarials, in spite of being aware that clinicians advise assessment prior to any additional treatment. This self-medication practice was in part due to lack of funds but also appeared to relate to the perception that there was no problem with mixing ARVs with antimalarials.

Conclusion: The social and material dynamics of clinical research may have influenced attitudes towards concomitant medication. Interventions are required to increase awareness of malaria risks, access to prevention strategies and to support diagnosis and treatment of malaria for people living with HIV.