

### ANTIMALARIAL DRUG-RESISTANCE: WHAT DO HIV AND IMMUNITY HAVE TO DO WITH IT?

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The rise and spread of drug resistant malaria parasites is one of the major challenges for malaria control, and indeed will be a huge obstacle for malaria eradication. Successful drug treatment is dependent on both the killing effect of the drug and the killing effect of the immune system. In addition, the immune system is known to play an important role in within-host competition between parasites, which in turn has been shown to be a key part of resistance evolution. Moreover, there are the historical observations that resistance initially occurs in area of low transmission intensity and hence low level of antimalarial immunity. It is thus hypothesized that the immune system is a critical factor in the emergence and spread of drug resistant mutants. If immunity indeed plays a role, this has significant implications for malaria elimination where reduced immunity is a natural consequence yet this is achieved by using a high amount of drug pressure. Using data of clinical trial on IPTp use in pregnant women in Benin, Gabon, Kenya and Mozambique, we present the occurrence of resistant mutants in a variety of immune contexts: (i) HIV-co-infections, (ii) women with different levels of antibody titers, (iii) placental and peripheral infections, and (iv) primigravidae and multigravidae women.

### EFFICACY OF ARTEMETHER-LUMEFANTRINE FOR TREATMENT OF UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA IN CRUZEIRO DO SUL, ACRE, BRAZIL

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*Plasmodium falciparum* malaria has high morbidity and mortality; there were 143,551 cases in the Brazilian Amazon Region in 2014, of which 15.9% were *P. falciparum* mono-infection. Artemether-lumefantrine (AL) is the first-line treatment. Following the World Health Organization recommendation to routinely evaluate antimalarial treatment policies, we are conducting a therapeutic efficacy *in vivo* trial of AL for treatment of uncomplicated *P. falciparum* malaria in Cruzeiro do Sul, Acre, Brazil from December 2015 to May 2016. The objectives of this study are to evaluate the efficacy of the first-line antimalarial regimen for treatment of uncomplicated *P. falciparum* malaria and ensure effective case management practices are maintained in Brazil. Febrile participants  $\geq 5$  years old with microscopically confirmed *P. falciparum* mono-infection with parasitemia between 250 and 200,000 asexual parasites/microliter were enrolled and treated with a supervised 3-day course of AL, dosed according to Brazilian guidelines for malaria control. Clinical and parasitological parameters are monitored for 28 days. Recrudescence is differentiated from reinfection by comparing parasite genotypes from Day 0 and the day of failure. Genetic markers associated with artemisinin resistance, including the K13 gene mutation will be assessed. A total of 127 patients have been screened, and all 85 participants have been

enrolled. Four participants were excluded after enrollment; two due to parasitemia below inclusion range, one due to *P. vivax* infection upon slide review, and one due to absence of fever in the previous 48 hours. Among enrolled patients, 61 have completed follow-up, 17 are still being followed and three have been lost to follow-up. No patient has met criteria for treatment failure, although one participant was diagnosed with *P. vivax* on day 28. Patient follow-up will be completed by May, 2016. Final results will be presented. Preliminary results suggest that AL remains highly efficacious for treatment of uncomplicated *P. falciparum* in the Brazilian Amazon Region. These results will be corroborated by molecular testing for the K13 resistance gene.

### SHOULD WE STILL USE QUININE IV FOR SEVERE MALARIA?

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Malaria represents a significant health problem in patients coming back from endemic areas. Severe malaria is life threatening and the acute respiratory distress syndrome (ARDS) is among the more serious complications that invariably leads to death. We have noted the occurrence of ARDS in a few patients with severe malaria being treated with quinine IV, the only available recommended drug at the time. The question of whether quinine IV is a triggering or contributing factor of ARDS in those cases was raised. A retrospective analysis of several cases of malaria was initiated and a literature search was done. Both outcomes were not definitive in corroborating evidence against quinine IV, but the suspicion remains. In the USA, quinine IV has not been available or used in severe malaria for over 20 years! Quinidine is available in the USA. In the era of better antimalarial therapy, especially with the recommended relatively recent and effective artemisinin derivatives, or the fairly safer quinidine, should quinine IV still be listed among the treatments or used for severe malaria?

### SAFETY AND TOLERABILITY OF DIHYDROARTEMISININ-PIPERAQUINE AS INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA IN A REFUGEE CAMP, ADJUMANI, UGANDA

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The use of dihydroartemisinin-piperazine (DP) is increasing in sub-Saharan Africa, though safety data in Africa is sparse. DP was used by Médecins Sans Frontières in an Intermittent Preventive Treatment (IPT) program in a refugee camp in northern Uganda in 2015. All children aged 6 months to 14 years resident in the camp were eligible for participation in the program, which consisted of three mass distributions of DP at 8 week intervals. Weight-based dosing following 2014 guidelines was used and a total of 40 611 doses of DP were administered during 3 distributions. A health-center based pharmacovigilance system was implemented during the program, and an existing community-based mortality surveillance system was continued. Signs and symptoms of both common and severe side effects due to DP were part of key sensitization messages during the campaign. Participants experiencing any symptoms were encouraged to present to the health centers in the camp, where free health care was provided. A total of 56 adverse events (AE) were reported during the 24 week follow-up period. All AEs were reported in the 10 days following DP administration. Of the 56 AEs, 28 were judged to be probably or definitely related to DP; the most common symptoms were rash or itching (12) and vomiting (6). One case of urticaria was notified. Symptom severity was noted for all AEs regardless of causality: 75% were mild and 25% were moderate. One SAE was reported: an unexplained death in the community which occurred in a 12-year old girl who was diagnosed with varicella 12 days after taking the first distribution of DP. On the 8<sup>th</sup> day of her