

ABSTRACT

Strategies to reduce HIV-related morbidity and mortality include scale up of Antiretroviral Therapy (ART) and provision of broad spectrum antibiotics. Cotrimoxazole (CTX) is a widely available low cost antibiotic recommended by WHO in settings with high infectious disease prevalence for treatment and prevention of opportunistic infections and malaria in all HIV-infected individuals. With immune reconstitution following ART, the risk of opportunistic infections greatly diminishes. Continuing CTX indefinitely raises concern about persistent antibiotic exposure, resistance and pill burden. The effect of CTX discontinuation on malaria remains undefined. This blinded Randomized Controlled Trial (RCT) investigated the effect of CTX discontinuation on malaria parasite prevalence, incidence, parasite density and Multiplicity of Infection (MOI) on HIV-infected adults with evidence of immune reconstitution. Five hundred participants were enrolled from Homabay County hospital and randomized into two study arms: discontinue CTX vs continue CTX. They were followed quarterly for 12 months and whenever they reported sick between February 2012 and September 2013. Blood was drawn from study participants at each visit and spotted on paper blots with subsequent DNA extraction. Malaria parasites were detected by qRT-PCR and MOI evaluated by nested PCR targeting MSP-1 (K1, MAD20 and RO33) and MSP-2 (FC27 and IC3D7) alleles. Chi-square was used to test differences in parasitemia prevalence over time between study arms. Where parasites were detected, parasite density values were log-transformed, and the difference between arms tested using generalized estimating equations. The frequency of mixed infections (MOI >1) was compared between the two study arms. Rates of parasitemia in the two study cohorts were calculated on the basis of person-time at risk. Among the 500 participants in the RCT, median CD4⁺ count was 595 cells/mm³ and the median ART duration was 4.5 years. Parasite prevalence at enrolment was: 4% for discontinue CTX arm and 6% for continue CTX arm. Within 3 months of CTX discontinuation, parasitemia prevalence increased steadily in the discontinue CTX arm during the year to >5-fold: 4% (11/248) at M3, 8% (21/249) at M6, 14% (33/244) at M9 and 22% (54/245) at M12. In comparison, the continue CTX arm had parasitemia prevalence of <1% (1/248) at M3, 2% (5/247) at M6, 2% (4/245) at M9 and 4% (10/245) at M12 (P < 0.0034). Post enrollment, discontinue CTX arm had 90 new infections compared to 23 in the continue CTX arm. Parasitemia incidence was 42.0 in discontinue CTX arm versus 9.9 per 100 person years in continue CTX arm; with an incident rate ratio of 4.3 (95% CI: 0.14-0.37; p<0.001). Among follow-up visits where parasites were detected, the discontinue CTX arm had a significantly higher mean parasite density (log₁₀) than the continue CTX arm (4.42 parasites/mL vs. 3.13 parasites/mL, p < 0.001). Post enrolment, mixed infections (MOI >1) were only present in the STOP-CTX arm. Results from this study indicate despite immune reconstitution following ART provision and use of ITNs. Discontinuation of CTX prophylaxis in individuals with HIV results in increased parasite prevalence, incidence, parasite density and MOI overtime, in malaria endemic regions. The increased malaria incidence seen in those who discontinue prophylaxis, is not due to a short-lived rebound effect following withdrawal of CTX but continues for a longer period. Therefore stopping CTX prophylaxis may not be recommended in the context of malaria in resource-limited settings.