Background: Cotrimoxazole (CTX) prophylaxis is recommended by the WHO for all HIV-infected individuals in settings with high prevalence of HIV and infectious disease. These guidelines were developed prior to scale-up of antiretroviral therapy (ART). Following ART, the threshold for CTX discontinuation after ART initiation remains undefined in resource-limited settings. We conducted a randomized clinical trial among adults on ART to determine whether discontinuation of CTX was non-inferior to continued CTX prophylaxis in decreasing morbidity.

Methodology: From February 2012 to September 2013, we conducted a non-blinded non-inferiority randomized clinical trial of CTX prophylaxis cessation versus continuation among HIV-infected adults who had been on ART for >18 months and had CD4 >350cells/mm³ (Clinical trials registration NCT01425073). The study was conducted in a large HIV Treatment Program in Homa Bay, Western Kenya, a region with endemic malaria. Participants were randomized to continue or discontinue CTX using block randomization and followed 3-monthly for 12 months with systematic ascertainment of malaria, diarrhea and pneumonia morbidity. Malaria was defined as rapid diagnostic test (RDT) or smear positive with fever. Primary endpoint was a composite of morbidity (malaria, pneumonia, and diarrhea) and mortality. A secondary endpoint was severe adverse events (SAEs) grade 3 or higher. Incidence rate ratios (IRRs) were estimated using Poisson regression with robust error variance. Analyses were intent-to-treat.

Results: Of 538 adults screened, 500 were eligible, enrolled and randomized; 250 to each arm. Median age was 40 years, 361 (72%) were women, and 442 (88%) of participants reported bednet use. Median enrollment CD4 count was 595 cells/mm³ and median ART duration was 4.5 years. These baseline characteristics did not significantly differ between arms. Retention was high with 245 (98%) participants completing 12-month follow-up in each group. Combined morbidity/mortality was significantly higher in the CTX discontinuation arm (IRR=2.27, 95% CI: 1.52-3.38; p<0.001), driven by malaria morbidity. There were 34 cases of malaria, 33 in the CTX discontinuation arm (IRR=33.02, 95% CI: 4.52-241.02; p=0.001). Diarrhea and pneumonia rates did not differ significantly between arms (IRR=1.36, 95% CI: 0.82-2.27, and IRR=1.43, 95% CI: 0.54-3.75, respectively). Rates of SAEs ≥ Grade 3 did not differ significantly between arms (IRR=2.00, 95% CI: 0.90-4.44), with limited power to detect a difference.

Conclusions: CTX discontinuation among ART-treated adults in a region with endemic malaria results in increased incidence of clinical malaria but not pneumonia, diarrhea or combined severe SAEs compared to those who continue CTX.