Editorial

Balancing Individual Benefit Against Public Health Risk: The Impact of Cotrimoxazole Prophylaxis in HIV-infected Patients on Antimicrobial Resistance

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Cotrimoxazole (trimethoprim-sulfamethoxazole) is routinely provided to individuals with AIDS in the United States and Europe for prevention of opportunistic infections, especially *Pneumocystis jiroveci* pneumonia. In Africa, it has been shown to reduce human immunodeficiency virus (HIV)-associated mortality and morbidity,1,2 including reductions in the incidence of malaria, pneumonia, diarrhea, and hospital admissions.3,4 The addition of insecticide-treated bednets (ITN) and antiretroviral therapy to cotrimoxazole prophylaxis has been demonstrated to have an even more profound impact on malaria rates than cotrimoxazole alone.5 Despite the favorable outcomes associated with cotrimoxazole use in HIV-seropositive people, concerns have been raised that the widespread use of this drug for prophylaxis will contribute to antimicrobial resistance.4 Because cotrimoxazole targets the same antifolate pathway enzymes, dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), as the antimalarial sulfadoxine-pyrimethamine (SP), its widespread use could theoretically contribute to increased rates of SP resistance.

In this month’s issue of *The American Journal of Tropical Medicine & Hygiene*, Hamel and colleagues describe the effect of cotrimoxazole prophylaxis on antimicrobial resistance rates among HIV-positive and negative Kenyan adults using a prospective cohort methodology.5 They selected *Streptococcus pneumoniae* and *Escherichia coli* as their sentinel bacterial pathogens. In addition, they assessed the effect of cotrimoxazole prophylaxis on *Plasmodium falciparum* malaria by screening isolates from parasitemic patients for mutations in the DHFR and DHPS genes. The study included three arms: HIV-negative individuals not receiving cotrimoxazole, HIV-positives with high CD4 counts (≥ 350 cells/µL) who were not receiving cotrimoxazole, and HIV-positives with low CD4 counts who were taking cotrimoxazole. All patients were screened through nasopharyngeal and rectal swabs (for the pneumococcus and *E. coli* respectively) and by blood smears, at baseline, and then repeatedly out to six months of observation.

Their analyses focused on within group changes in the rates of resistance to the sentinel pathogens, as opposed to looking at differences between the three groups in the cohort. This is an important point to emphasize, and is chiefly wherein some of our questions reside in interpreting their findings. Increased resistance to cotrimoxazole occurred within two weeks in the case of the pneumococcus and *E. coli*, a finding highly concordant with our own investigations of the effect of cotrimoxazole prophylaxis on pneumococcal resistance in infants exposed to HIV at birth.6 However, the within group analysis found no effect of cotrimoxazole on the prevalence of *P. falciparum* isolates with resistance mutations. More specifically, among HIV-positive patients receiving cotrimoxazole, the proportion of those parasitemic who had triple or quintuple mutations present (these being the most important combinations in terms of resistance to DHFR or both DHFR and DHPS simultaneously, and hence of primary clinical relevance) was about the same when comparing those patients at baseline with six months later. The authors concluded that while cotrimoxazole use clearly accelerated antibiotic resistance, there was no evidence to suggest that the same problem was developing in *P. falciparum*. Moreover, parasitemia rates were reduced by almost 90% among those taking prophylaxis. Thus, this suggests a highly beneficial effect of prophylaxis, without evidence of a cost at the population level in terms of SP resistance.

But was that really the case? Our reluctance to fully embrace this conclusion rests on several points. First, in contrast with *E. coli* and *S. pneumoniae*, *P. falciparum* cannot truly be considered to “colonize” its host, where even asymptomatic patients may suffer adverse consequences such as anemia and splenomegaly. Second, the interposition of a mosquito vector adds an important and complex dimension to the host-parasite relationship in malaria. For this reason, it may be erroneous to assume that the same within host relationships seen with bacteria necessarily apply in the case of malaria drug resistance. Third, historically, the evolution of malarial resistance at the population level has been a relatively slow process occurring on a scale of months or years. Hence, failure to find an effect of cotrimoxazole on malaria resistance may simply reflect a time scale that is mismatched to the pace at which malaria resistance evolves.

At baseline, the HIV-negative subjects reported far lower rates of recent use of antimicrobials and antimalarials in general, and of sulfonamides in particular. Because sulfonamide use was so common among all the patients, the analysis could instead be constructed as comparing the effect of “lots of sulfonamide exposure” (HIV-positives, low CD4) to those with “less sulfonamide exposure” (HIV-negatives). Following this logic and using data from Table 3 in the paper by Hamel and others,7 triple mutations occurred at a rate of 25/46 (54%) in the HIV-positive group on prophylaxis and 18/45 (40%) in the HIV-negatives, for a relative risk of 1.36 (95% confidence interval [CI], 0.87, 2.1) suggesting increased risk of resistance among those who had the greatest sulfonamide exposure. Repeating this approach for the quintuple mutants, the proportions were 22/46 (48%) versus 15/45 (33%) for a relative risk

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of 1.43 (95% CI, 0.86–2.4). Although neither achieved statistical significance, the trend towards higher rates of triple and quintuple mutants among cotrimoxazole recipients was worrisome.

SP is no longer recommended for first-line treatment of malaria in Kenya with the exception of intermittent preventive treatment of pregnant women. The fact that the majority of sub-Saharan African countries have changed their national policies in favor of artesiminin-based combination therapy mitigates the potential importance of cotrimoxazole use in HIV-infected persons on SP resistance.

Furthermore, although cotrimoxazole use in HIV-infected subjects with lower CD4 cell counts provided significant protection against falciparum malaria, its use was associated with high rates of resistance to cotrimoxazole among nasopharyngeal *S. pneumoniae* and fecal *E. coli* isolates. Further evidence suggests that cotrimoxazole use may cause increased resistance of *S. pneumoniae* to other antibiotics through co-selection of linked antibiotic resistance genes. Because cotrimoxazole is one of two recommended options for the treatment of non-severe pneumonia and otitis media in children under five years of age in the World Health Organization’s Integrated Management of Childhood Illness (IMCI) guidelines, the potential impact of increased pneumococcal resistance associated with cotrimoxazole prophylaxis raises concerns. One can argue that amoxicillin is a viable alternative to cotrimoxazole for childhood pneumonia and that ciprofloxacin, as currently adopted by the Kenyan Ministry of Health, provides a viable alternative treatment of invasive diarrhea. Moreover, the clinical importance of rising resistance is admittedly difficult to measure, partly because colonization with resistant pathogens is not synonymous with disease, and because the link between drug resistance and treatment failure is hard to establish in the context of clinical studies. However, logic dictates that the more prudent approach is to assume that drug resistance matters and is to be avoided whenever possible.

All that said, given the substantial benefits of cotrimoxazole for reducing HIV-associated morbidity and mortality, the beneficial impacts of cotrimoxazole for HIV-infected individuals in sub-Saharan Africa would appear to outweigh the potential negative implications of resistance for public health programs. But from the perspective of the research question, “Does cotrimoxazole foster sulfonamide resistance among medically important bacteria and *P. falciparum* malaria?” the findings of this study were hardly reassuring.