Antimicrobial Prophylaxis in Children with HIV Infection

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(See the article by Hughes et al. on pages 136–45)

The article by Hughes et al. [1] from the Pediatric AIDS Clinical Trials Group describing a randomized comparison of daily administration of trimethoprim-sulfamethoxazole (TMP-SMZ) and atovaquone-azithromycin brings into focus a number of interesting issues related to HIV infections worldwide, as well as the daily use of prophylactic antimicrobials in general. The trial was halted early, before it was fully accrued, and perhaps as a result of this, it failed to achieve statistical significance for its central comparisons. However, in spite of this early discontinuation, the trial teaches us a few important lessons.

Hughes and colleagues’ [2] own landmark placebo-controlled, randomized, clinical trial that compared daily doses of TMP-SMZ with placebo in children with cancer and leukemia showed clearly in 1977 that not only was Pneumocystis jiroveci (formerly “carinii”) pneumonia (PCP) almost completely prevented, but the numbers of proven and presumptive bacterial infections were also reduced significantly in this population of high-risk immunocompromised patients. In HIV-infected adults, very similar results were seen in a randomized comparison between aerosolized pentamidine and daily doses of TMP-SMZ published in 1992 [3]. With the maturation and globalization of the AIDS epidemic, this important effect of prophylactic antimicrobial therapy has moved somewhat into the background in the United States and Europe, whereas it has come very much into the foreground in Africa and other parts of the developing world. In 1999, two studies involving HIV-infected adults living in Abidjan, Ivory Coast, were published in The Lancet, each of which showed a favorable effect of daily administration of TMP-SMZ not only for bacterial infections, but also for malaria and mortality [4, 5]. These studies led to a recommendation in April 2000 by the World Health Organization (WHO) that TMP-SMZ should be given daily to all adults and children with symptomatic HIV infection or AIDS in the developing world. Actual data to confirm an effect on any coinfection (other than PCP) in HIV-infected infants and children were not available until recently, with the completion of a study from Zambia showing a highly significant reduction in both mortality and hospitalization in children receiving TMP-SMZ therapy [6]. These effects were seen at all levels of CD4+ lymphocytes, and P. jiroveci, which was sought by sensitive methods, was an unusual finding. Thus, an effect on other infections, predominantly bacterial pneumonia, was postulated. In addition, and even more puzzling, Zambia is a country with widespread bacterial TMP-SMZ resistance, so the mechanism of the TMP-SMZ effect on mortality is difficult to explain.

Where does the study by Hughes et al. [1] in this issue of Clinical Infectious Diseases fit into this context?

First, the field of HIV infection in general is evolving rapidly, in large part because of the extraordinary ability of HAART to reverse much of the immunodeficiency. As a consequence, in the United States, daily antibiotic therapy has little role at present in the care of HIV-infected children. This evolution was, in fact, evident during the course of the study published here: the study was terminated prematurely because of the lack of suitable study candidates with low CD4 cell counts, and among the children already in the study, the rate of serious bacterial infections decreased strikingly during the course of the study as more enrolled children received HAART.

Second, the situation is, at least in the present day, quite different in Africa and Asia. In those settings, the WHO recommends the use of daily TMP-SMZ therapy in both children and adults with AIDS or symptomatic HIV infection. The roll-out of HAART in the developing world, particularly for children, is likely to take some time to put in place, and TMP-SMZ is available, cheap, and relatively free of side effects. The low incidence of both rash and hematologic toxicity in the study by Hughes et al. [1] is reassuring in this re-
The final point is that, although drug resistance may or may not be an important concern for prevention of respiratory infections, there is no question that it is important in a broader sense. Recipients of daily doses of antibiotics are likely to replace their resident flora with drug-resistant strains, and this, in turn, will influence the susceptibility patterns of bacteria that cause invasive disease. In addition, there is the larger risk of an increase in the prevalence of drug-resistant organisms in the environment. Finally, for TMP-SMZ, there is the issue of sulfonamide resistance in both *P. jiroveci* and *Plasmodium* species. The risks in these areas are not known.

Thus, we are left with a study that was terminated early because of the evolution of the HIV epidemic in this country and that showed marginal superiority of atovaquone-azithromycin over TMP-SMZ, but that demonstrated the equivalent safety of both regimens. The prophylactic superiority of atovaquone-azithromycin was largely based on a discrepancy in the number of cases of sinusitis, and it is tempting to speculate that resistance to TMP-SMZ might have accounted for this. On the other hand, in the larger context, atovaquone-azithromycin has one strike against it—its high cost—and this becomes the more concerning, because prophylaxis has its major relevance in the developing world, where the WHO has recently recommended routine administration of daily doses of TMP-SMZ. Recent studies confirm that daily prophylaxis has value for HIV-infected children in the developing world, but many questions arise concerning the possible consequences of such a recommendation, particularly the risks of increased antimicrobial resistance in this setting.

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**References**


