
Safely of Artemisinin Antimalarials

To the Editor—Franco-Paredes et al. [1, 2] are thanked for adding to the literature on artemisinin neurotoxicity, and Newton et al. [3] are thanked for contributing to the debate. The reply from Newton and colleagues [3] is similar to a previous response by White [4], which followed a case report in Clinical Infectious Diseases that associated artemisinin with neurological abnormalities [5].

Newton et al. [3] assert that there is no evidence supporting neurotoxicity of artemisinins in humans. Unfortunately, there is published evidence documenting irreversible ototoxicity in adults treated with arteether-lumefantrine for uncomplicated malaria [6, 7], and in a healthy volunteer treated with arteether [8]. Additionally, ototoxicity findings of amodiaquine and arteether-lumefantrine, compared with findings of amodiaquine alone, were recently reported in children [9]; the latter study also documented reversible nystagmus in 4 artemisinin recipients, 2 of whom had preexisting neurological disorders. All 3 audiogram studies [6, 8, 9] included baseline audiograms performed before artemisinin exposure and measured threshold changes in individuals; the audiometric studies quoted by Newton and colleagues did not conduct preexposure audiograms and were thus not able to assess individual subjects’ threshold changes [10, 11].

The large prospective series study of artemisinin-treated patients referred to by Newton and colleagues included “a brief neurologic examination” only [12, p. 548]; therefore, it is possible that subtle neurological signs may have been overlooked, explaining the discrepancy with the more recent prospective study referred to above [9].

The neuropathological study referred to by Newton and colleagues in defense of artemisinin is called into question by earlier in vitro studies. Schmuck et al. [13] demonstrated that neural networks exposed to artemisinin for 24 h showed no pathological changes before 7 days, with changes becoming fully evident only after 14 days; the median artemisinin exposure to death time in the neuropathological study was 76.5 h (interquartile range, 8–331 h); the “no effect concentration” for brainstem neuron cytotoxicity reported by Schmuck et al. [13] was 0.1 μg/mL.

Delayed manifestation of neurotoxicity also calls into question conclusions from 1 recent prospective study referred to above [9].

The planned widespread deployment of artemisinins calls for a re-examination of the safety of artemisinins in current clinical use, rather than the uncritical attribution of clinically observed abnormalities to the disease itself.

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Is Clostridium difficile the Leading Pathogen in Bacterial Diarrhea in HIV Type 1–Infected Patients?

To the Editor—I read with interest the article by Sanchez et al. [1] that was recently published in Clinical Infectious Diseases. In their article, Sanchez and colleagues [1] recognized that Clostridium difficile is the most common cause of bacterial diarrhea in patients infected with HIV-1, and that patients whose illness is at a more advanced stage are at significantly greater risk of developing C. difficile–associated diarrhea. However, Sanchez and colleagues [1] raise several issues about the pathogenic role of C. difficile infection in patients with clinical and/or immunological AIDS.

First, a close correlation between colonization with C. difficile and episodes of acute diarrhea in an immunocompromised patient is often tricky to evaluate and establish. It has been reported that >25% of patients admitted to the hospital are colonized with C. difficile and that these patients were less likely to develop C. difficile–associated disease while hospitalized [2]. In addition, there was no correlation between the propensity for having C. difficile–associated disease and being colonized with a particular strain (i.e., toxigenic [toxin A–or toxin B–producing] vs. nontoxigenic strains). In the study by Sanchez et al. [1], laboratory protocols were not standardized, and thus, there is no clear correlation between isolation of and the detection of C. difficile toxins A and B in cultures of stool samples from HIV-1–infected patients with diarrhea. In fact, C. difficile toxins A and B play a key role in damaging intestinal cells through neutrophil accumulation, chemokine activation, disruption of tight junctions of epithelial intestinal barrier, and apoptosis of intestinal cells [3].

Because a significant portion of individuals are colonized with C. difficile, infection associated with clinical disease is a combination of several concomitant conditions, including hospitalization, past antibiotic therapy (e.g., antimicrobial chemotherapy), and primary exposure to C. difficile. It should be noted that, in a study by Anastasi and colleagues [4], the rate of hospitalization of HIV-1–infected patients who have a diarrheal illness was very low (2.8%), despite a high rate of isolation of C. difficile in stool sample culture (51.3%).

In a recent review article, my colleagues and I analyzed the impact of HAART on organ-specific manifestations; in particular, we focused attention on bacterial gastrointestinal manifestations [5]. HAART can restore immunity to opportunistic pathogens, such as Cryptosporidium and Microsporidium species, among patients infected with HIV-1, resulting in complete clinical, microbiological, and histological resolution of infection [6, 7]. In contrast, it seems that, in the HAART era, diarrheal illness caused by enteric bacterial pathogens, such as Salmonella species, Shigella species, Campylobacter species, and Yersinia species other than C. difficile, continue to occur, especially among HIV-1–infected patients with advanced disease. However, other investigators have demonstrated that the incidence of C. difficile–associated diarrhea among HIV-1–infected patients has decreased during the HAART era [8].

Unfortunately, studies addressing the incidence of bacterial diarrheal illness among HIV-1–infected patients before and during the HAART era are lacking. Sanchez et al. [1] did not address this crucial issue, and they did not attempt to analyze and stratify their data on the incidence of diarrheal illness into pre-HAART era and HAART era groups.

Our understanding of C. difficile–associated disease in both the immunocompetent host and in the immunocompromised host must improve through better appreciation of the mechanisms of action of C. difficile toxins A and B. In fact, C. difficile strains that produce toxin B but not A have been found in a variety of different patients, ranging in age from infants to older persons [9].

In conclusion, a prospective, controlled study is needed to better understand and clarify the incidence of C. difficile–associated diarrhea in patients infected with HIV-1 with respect to several defined patient and illness characteristics, including colonization compared with infection, the presence of toxins A and B in stool and/or blood samples, past antibiotic therapy, hospitalization compared with outpatient care, influence of antiretroviral therapy, and how different stages of C. difficile–associated disease correlate with viral load and CD4 cell count.

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