Correspondence

A Nonviable Preparation of *Lactobacillus acidophilus* Is Not a Probiotic

To the Editor—As researchers in the field of probiotics, we are compelled to comment on the recent publication by Briand et al. [1]. Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [2, p. 5]. This is the most widespread and agreed definition in use. Briand and colleagues used a nonviable preparation of *Lactobacillus acidophilus;* it is not, therefore, a probiotic. The term "probiotic" should only be used to refer to specific, defined, live microbial preparations that have been evaluated and determined to have a positive health effect in at least 1 controlled study involving the target host. In fact, the word probiotic itself translates to "for life." Using a nonviable form rules out many of the opportunities that probiotics can afford in the prevention of traveler's diarrhea, including excretion of inhibitory metabolites and competition with pathogens for growth substrates and colonization sites.

We would suggest that the criteria delineated by a working group of the Food and Agriculture Organization [3] for characterizing a probiotic be met before the term "probiotic" is used, whether in scientific publications, research grants, or marketed products. In short, these criteria include an identification of the genus, species, and strain of the candidate probiotic using phenotypic and modern genotypic methods; the deposit of the strain in an international culture collection; functional characterization of the strain, including valid bioassays of attributes important to the health effect under investigation; safety assessments; and human studies proving the health benefit. Meeting these criteria will avoid another common mistake made in the use of the term "probiotic"—namely, applying the term to an entire species or genus, rather than to specific strains that have been tested for health benefits. It cannot be assumed that probiotic efficacy documented for 1 strain of a species automatically makes the whole species (or genus) probiotic.

Briand et al. [1] justify their choice to study a nonviable preparation of *L. acidophilus* on the basis of safety. The likelihood of adverse incidents with their healthy study population is so low as to not be of practical concern [4]. The resultant failure of their study is not unexpected, and it is important that readers of the study not draw broad conclusions about probiotics. This field is progressing well, fueled by groundbreaking research on the impact of commensal and probiotic microbes on human and animal physiology [5], elucidation of the genetic content and function of candidate probiotic strains [6], and increasing numbers of controlled, clinical studies documenting beneficial health effects of probiotics in humans [7]. It is incumbent upon authors, reviewers, and editors involved in probiotic research to seek precision in language, adherence to the formal definition of probiotics, and rejection of unsubstantiated myths that, for too long, have characterized this field.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Mary Ellen Sanders,[1] Jeremy Hamilton,[2] Gregor Reid,[4] and Glenn Gibson[3]

[1]Dairy and Food Culture Technologies, Centennial, Colorado; [2]Department of Medical Microbiology, Royal Free and University College Medical School, London, and [3]School of Food Biosciences, University of Reading, Whiteknights, Reading, United Kingdom; and [4]Canadian Research and Development Centre for Probiotics, Lawson Health Research Institute, London, Canada

References

1. Briand V, Buffet P, Genty S, et al. Absence of efficacy of nonviable *Lactobacillus acidophilus* for the prevention of traveler's diarrhea: a randomized, double-blind, controlled study. Clin Infect Dis **2006**; 43:1170–5.
2. Food and Agriculture Organization (FAO). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria: report of a joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Geneva: Food and Agriculture Organization, **2001**. Available at: http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf. Accessed 30 January 2007.
3. Food and Agriculture Organization (FAO). Guidelines for the evaluation of probiotics in food: report of a joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food. Geneva: Food and Agriculture Organization, **2002**. Available at: http://www.fermented-foods.net/wgreport2.pdf. Accessed 30 January 2007.
4. Borriello SP, Hammes WP, Holzapfel W, et al. Safety of probiotics that contain lactobacilli or bifidobacteria. Clin Infect Dis **2003**; 36:775–80.
5. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science **2005**; 307:1915–20.
6. Altermann E, Russell WM, Azcarate-Peril MA, et al. Complete genome sequence of the probiotic lactic acid bacterium *Lactobacillus acidophilus* NCFM. Proc Natl Acad Sci U S A **2005**; 102:3906–12.
7. Montrose DC, Floch MH. Probiotics used in human studies. J Clin Gastroenterol **2005**; 39:469–84.

Reprints or correspondence: Mary Ellen Sanders, Dairy and Food Culture Technologies, 7119 S. Glencoe Ct., Centennial, CO 80122 (mes@mesanders.com).

Clinical Infectious Diseases 2007; 44:886

1058-4838/2007/4406-0023$15.00
DOI: 10.1086/513706

Web Resources for Antimicrobial Resistance

In recent issues of *Clinical Infectious Diseases,* 2 sets of authors have highlighted World Wide Web resources for information related to antimicrobial resistance.

Harbarth and Emonet [1] successfully compiled a large selection of general, methicillin-resistant *Staphylococcus aureus*–specific surveillance, prevention, and community-targeted resources. Falas and Karveli [2] offered data-driven surveillance Web sites, as well as several resources with extensive links to other Web sites with information about antimicrobial resistance. Both sets of authors acknowledged that their lists are unlikely to be exhaustive [1, 2].

For many users, a single Web site is often insufficient (in terms of content or scope) for providing a comprehensive answer to the user's query. Web portals are described as "Web site(s) that provides a starting point, a gateway, or portal, to other resources on the Internet or an intranet" [3]. In this sense, Web portals may be more helpful than many individual sites on the Web.

We at the Antimicrobial Resistance Education Alliance consortium realized this limitation of other Web resources in early 2006 and began, in earnest, to develop a Web portal focused on antimicrobial resistance and management strategies. The Antimicrobial Resistance Education Alliance Web portal (http://www.AREAinitiatives.org) was released in November 2006 and strives to serve health care providers as the leading Web portal for information about antimicrobial management and resistance by collating state, national, and international resources, with the goal of becoming the most comprehensive site available today. The Antimicrobial Resistance Education Alliance Web portal provides easy access to resources, such as continuing medical education opportunities, patient education materials, patient management guidelines, and the latest relevant publications.

During the 2 decades following the conceptual development of the World Wide Web, health-related information has become increasingly accessible yet increasingly fragmented. The Antimicrobial Resistance Education Alliance Web portal collates what we believe to be the best information from a wide variety of resources and presents the information on 1 easily navigated site.

Acknowledgments

Financial support. Wyeth Pharmaceuticals.

Potential conflict of interest. All authors: no conflicts.

George C. Mejicano[1] and Marc-Oliver Wright[2]

[1]Office of Continuing Professional Development in Medicine and Public Health, University of Wisconsin School of Medicine and Public Health, Madison, and [2]Marshfield Epidemiology Research Center, Marshfield Clinic Research Foundation, Marshfield, Wisconsin

References

1. Harbarth S, Emonet S. Navigating the World Wide Web in search of resources on antimicrobial resistance. Clin Infect Dis **2006**; 43:72–8.
2. Flagas ME, Karveilli EA. World Wide Web resources on antimicrobial resistance. Clin Infect Dis **2006**; 43:630–3.
3. Wikipedia. Web portal. http://en.wikipedia.org/wiki/Web_portal. Accessed 28 August 2006.

Reprints or correspondence: Marc-Oliver Wright, Marshfield Epidemiology Research Center, 1000 North Oak Ave., ML-2, Marshfield, WI 54449 (wright.marc-oliver@mcrf.mfldclin.edu).

Clinical Infectious Diseases 2007; 44:886–7

1058-4838/2007/4406-0024$15.00
DOI: 10.1086/513706

Use of Fosamprenavir, a Sulfa-Containing Protease Inhibitor, in HIV-Infected Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

To the Editor—Several protease inhibitors (PIs)—including amprenavir, fosamprenavir, tipranavir, darunavir, and brecanavir—contain sulfonamide moieties that are vital for the potency of these drugs [1]. Among glucose-6-phosphate dehydrogenase (G6PD)–deficient patients, sulfa drugs may cause hemolytic anemia [2]. G6PD is a cytoplasmic enzyme that affects production of the reduced form of the extramitochondrial nicotine-adenosine-dinucleotide phosphate coenzyme by controlling the step from glucose-6-phosphate to 6-phospho-gluconate in the pentose phosphate pathway [2]. G6PD deficiency increases the vulnerability of erythrocytes to oxidative stress and, thus, increases the risk of hemolytic anemia [2]. Hemolysis typically occurs 24–72 h after ingestion of the predisposing drug and resolves within 4–7 days after use of the drug is discontinued [3]. To our knowledge, no studies have examined the development of hemolytic anemia in G6PD-deficient patients with HIV infection who receive sulfa-containing PIs. We aimed to determine the hemolytic potential of fosamprenavir therapy.

Using the database of the Thomas Street Health Center Pharmacy (Houston, TX), we retrospectively identified all consecutive patients who were treated with fosamprenavir during September 2004 through September 2006. Patients with G6PD deficiency were identified among this patient group. The institutional review board from this institution approved the study, informed consent was waived, and patient confidentiality was protected. Fosamprenavir was selected among the sulfa-containing PIs because of its widespread use among both treatment-naive and previously treated patients [4]. Fosamprenavir-induced hemolytic anemia was defined as a new onset of pallor and anemia that occurred 24–72 h after ingestion of fosamprenavir and that resolved within 4–7 days after use of the drug was discontinued. Anemia was defined as a decrease of $\geqslant$1 g/dL from the baseline (preexposure) hemoglobin level, along with $\geqslant$1 of the following findings: increased absolute reticulocyte number or reticulocyte percentage, jaundice with increased total and indirect bilirubin concentrations, increased serum lactate dehydrogenase concentration, reduced (or absent) level of serum haptoglobin, and negative Coombs' test results. AIDS was defined according to standardized criteria [5]. To measure categorical data, we used the χ^2 test or Fisher's exact test. For continuous variables, we used Student's *t* test. Significance was assigned for P values $<.05$.

One hundred thirty-seven patients were treated with fosamprenavir during the study period. Seventy patients (51%) were

tested for G6PD, and 11 tested patients (16%) were found to have G6PD deficiency. One patient was lost to follow-up and was excluded. Among the 10 evaluable patients, most were black (9 patients [90%]), were male (6 patients [60%]), and had AIDS (6 patients [60%]). The median baseline $CD4^+$ T lymphocyte count was 158 cells/mm^3 (range, 2–710 cells/mm^3). An emtricitabine-tenofovir fixed-drug combination was the most common non-PI antiretroviral coadministered with fosamprenavir (6 patients [60%]). Fosamprenavir treatment was boosted with ritonavir treatment in all patients. Five patients (50%) received trimethoprim-sulfamethoxazole treatment concomitantly with fosamprenavir treatment.

Baseline and follow-up hemoglobin levels are presented in table 1. The median time from baseline to the first follow-up hemoglobin sample collection was 27 days (range, 4–133 days). Compared with baseline hemoglobin levels, follow-up hemoglobin levels increased in 6 patients, decreased in 3 patients, and were stable in 1 patient. The median baseline hemoglobin level was 11.90 g/dL (range, 8.8–15.1 g/dL), and the median follow-up hemoglobin level was 12.25 g/dL (range, 8.6–16.4 g/dL; $P = .79$).

The hemoglobin level decreased $\geqslant$1 g/dL from baseline in only 1 patient (patient 9). This patient experienced a decrease of 1.1 g/dL in the hemoglobin level between baseline and the first follow-up visit; however, no evidence of hemolysis (e.g., increased absolute reticulocyte number or reticulocyte percentage and increased total and indirect bilirubin concentrations) was found. The patient was receiving trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jiroveci* pneumonia. The patient maintained receipt of a fosamprenavir-based regimen and was still receiving this drug after a follow-up period of 279 days. The nonhemolytic anemia resolved spontaneously. Three subsequent hemoglobin levels were determined during the follow-up period, and all of them were higher than the baseline level (all 3 levels were $\geqslant$14.5 g/dL). One patient with chronic anemia (patient 6) had experienced severe hemolysis before the start of fosamprenavir therapy, with a 3.7-g/dL reduction in the hemoglobin level from baseline and reticulocytosis secondary to primaquine therapy against *P. jiroveci* pneumonia. Upon discontinuation of primaquine therapy and resolution of the hemolytic episode, the patient started receiving a fosamprenavir-based regimen and had no subsequent evidence of hemolysis.

Table 1. Hemoglobin levels in patients with glucose-6-phosphate dehydrogenase deficiency who received fosamprenavir therapy.

	Hemoglobin level, g/dL	
Patient	Baseline[a]	Follow-up[b]
1	10.9	12
2	12.5	12.5
3	15.1	16.4
4	9.3	8.6
5	13.2	13.7
6	8.8	8.9
7	10.3	12.9
8	11.6	10.7
9	13	11.9
10	12.2	12.9

[a] Sample obtained before the start of fosamprenavir therapy.
[b] First sample obtained after the start of fosamprenavir therapy.

Our report is limited by its retrospective nature and small sample size. However, our preliminary data indicate that the use of fosamprenavir therapy in HIV-infected patients with G6PD deficiency seems to be safe and not associated with the development of hemolytic anemia. On the basis of these results, we speculate that the other sulfa-containing PIs may also be safe in this patient group, but this idea may need to be formally tested.

Acknowledgments

Potential conflicts of interest. H.A.T. is a member of the speakers' bureau for GlaxoSmithKline. R.C.A. received grant support and honoraria for consulting and speaker programs from GlaxoSmithKline. B.J.B.: no conflicts.

Harrys A. Torres,[1,2] Ben J. Barnett,[2] and Roberto C. Arduino[2]

[1]Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas M. D. Anderson Cancer Center, and [2]HIV/AIDS Medicine, Division of Infectious Diseases, Department of Internal Medicine, University of Texas Health Science Center at Houston Medical School, Houston, Texas

References

1. Supuran CT, Casini A, Scozzafava A. Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. Med Res Rev **2003**; 23:535–58.
2. Beutler E. G6PD deficiency. Blood **1994**; 84: 3613–36.
3. Edwards CQ. Anemia and the liver: hepatobiliary manifestations of anemia. Clin Liver Dis **2002**; 6:891–907.
4. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA **2006**; 296:827–43.
5. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep **1992**; 41:1–19.

Reprints or correspondence: Dr. Harrys A. Torres, Div. of Infectious Diseases, Dept. of Internal Medicine, University of Texas Health Science Center at Houston Medical School, 6431 Fannin MSB 6.120, Houston, TX 77030 (Harrys.A.Torres@uth.tmc.edu).

Clinical Infectious Diseases 2007; 44:887–8

1058-4838/2007/4406-0025$15.00
DOI: 10.1086/513706

The Threat of Extensively Drug-Resistant Tuberculosis

To the Editor—We read with interest the article [1] pertaining to extensively drug-resistant (XDR) tuberculosis (TB) in Iran. However, the definition of XDR TB in the article is not in accordance with the current definition. According to the new World Health Organization agreed-upon definition [2], XDR TB is defined as resistance to at least rifampicin and isoniazid, from among the first line of anti-TB drugs (which is the definition of multidrug-resistant [MDR] TB), in addition to resistance to any fluoroquinolone and to at least 1 of 3 injectable second-line anti-TB drugs used in TB treatment (capreomycin, kanamicin, and amikacin) [3]. The newer definition is likely to bring an ap-

parent increase of the numeric value of the prevalence of XDR TB, because it includes 2 second-line drugs (instead of 3 drugs, as in the older definition), which results in the addition of more patients to the XDR TB group.

The patients with prior exposure to any quinolones are likely to develop cross-resistance to other quinolones. High-level phenotypic resistance to fluoroquinolones among *Mycobacterium tuberculosis* clinical isolates appears to be predominantly due to *gyrA* mutations, and the isolates exhibit cross-resistance to all of the 6 important fluoroquinolones [4]. Because quinolones are broad-spectrum antibacterial agents, their widespread and indiscriminate use (often in subtherapeutic doses) is likely to enhance the quinolone-resistant organism (including mycobacteria). Cases of quinolone-resistant TB are constantly being reported [5], and we are rapidly losing a very effective group of drugs for the management of such cases. Presently, we do not have very effective second-line drugs. Some restrictions on the use of fluoroquinolones are needed.

Global plans to stop TB during 2006–2015 include the treatment of 800,000 MDR TB cases during the next 10 years [6]. The control of TB may be complicated by XDR TB, a difficult variety of MDR TB. There is an urgent need to reinforce the TB-control program with regard to detection of XDR TB. Diagnosis of MDR TB has been difficult because of the paucity of laboratories for mycobacteria culturing and drug-susceptibility testing in India. Resources are needed to establish such laboratories to facilitate early diagnoses in resource-limited settings. If we do not make every effort to contain MDR TB, we may eventually reach a point at which DOTS-plus will be of limited effectiveness [7], and the threat posed by XDR TB may have devastating consequences.

Acknowledgments

Potential conflicts of interest. P.R.M.: no conflicts.

Prasanta Raghab Mohapatra

Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh, India

References

1. Masjedi MR, Farnia P, Sorooch S, et al. Extensively drug-resistant tuberculosis: 2 years of surveillance in Iran. Clin Infect Dis **2006**; 43:841–7.
2. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. Wkly Epidemiol Rec **2006**; 45:430–2.
3. Centers for Disease Control and Prevention. Revised definition of extensively drug-resistant tuberculosis. 3 November **2006**. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5543a4.htm. Accessed 16 November 2006.
4. Cheng AF, Yew WW, Chan EW, Chin ML, Hui MM, Chan RC. Multiple PCR amplimer conformation analysis for rapid detection of *gyrA* mutations in fluoroquinolone-resistant *Mycobacterium tuberculosis* clinical isolates. Antimicrob Agents Chemother **2004**; 48:596–601.
5. Sullivan EA, Kreiswirth BN, Palumbo L, et al. Emergence of fluoroquinolone-resistant tuberculosis in New York City. Lancet **1995**; 345: 1148–50.
6. Stop TB Partnership Working Groups. Stop TB working group on MDR-TB. Available at: http://www.stoptb.org/wg/dots_plus. Accessed 17 November 2006.
7. Mohapatra PR, Janmeja AK, Saini V, Das SK, Deb A. Second-line treatment for chronic tuberculosis. Lancet **2002**; 360:1430.

Reprints or correspondence: Dr. Prasanta Raghab Mohapatra, PGI Campus, House no. 4, Teachers Flat, Chandigarh, 160012 India (prmohapatra@hotmail.com).

Clinical Infectious Diseases 2007; 44:888–9

1058-4838/2007/4406-0026$15.00
DOI: 10.1086/513706

Hepatotoxicity Due to a Drug Interaction between Amodiaquine plus Artesunate and Efavirenz

To the Editor—Limited data exist on pharmacokinetic interactions between antiretroviral and antimalarial drugs, with both classes of drugs being metabolized through cytochrome P450 pathways. To evaluate interactions between the widely adopted antimalarial drug combination of amodiaquine plus artesunate (AQ/AS) and the commonly used antiretroviral drug efavirenz (EFV), we administered AQ/AS alone (days 1–3) and then AQ/AS (days 18–20) combined with EFV (days 7–23) to healthy volunteers.

Five healthy volunteers were enrolled, but the study was prematurely discontinued after the first 2 subjects developed significant increases in hepatic transaminase levels (figure 1). Subject 1, a 51-year-old African American man, was noted to have increased transaminase levels 34 days after study completion; the levels peaked 3 days later, with an alanine aminotransferase (ALT) level of 206 U/L and an aspartate aminotransferase (AST) level of 78 U/L. The patient was found to be asymptomatic, with a normal physical examination. Other laboratory values were normal, including the serological test results for hepatitis virus A, B, and C; Epstein-Barr virus; and cytomegalovirus. The subject denied ingestion of potentially hepatotoxic substances. His transaminase levels slowly decreased and returned to normal 102 days after study completion.

Subject 2, a 26-year-old white woman, experienced a similar course, with a peak ALT level of 868 U/L and a peak AST level of 559 U/L 42 days after study completion; normalization occurred 154 days after study completion. Of note, subject 2 had ingested ~9 alcoholic beverages per week after completing the study and was taking an oral contraceptive containing ethinyl estradiol and drospirenone during the study.

Subject 3 withdrew from the study after day 3 because of nausea. Subjects 4 and 5 were removed from the study prior to receiving the second course of AQ/AS therapy and had no laboratory abnormalities.

Plasma levels of AQ, desethylamodiaquine (DEAQ)–active metabolite, and EFV were analyzed by high-performance liquid chromatography, using previously published methods [1, 2]. The addition of EFV therapy resulted in increases in AQ area under the plasma concentration–versus-time curve ($AUC_{0-96\,h}$) of 114.7% and 302.3% in subjects 1 and 2, respectively, and increases in the maximum concentration (C_{max}) and half-life for AQ. For DEAQ, a 23.7% decrease in $AUC_{0-96\,h}$ and

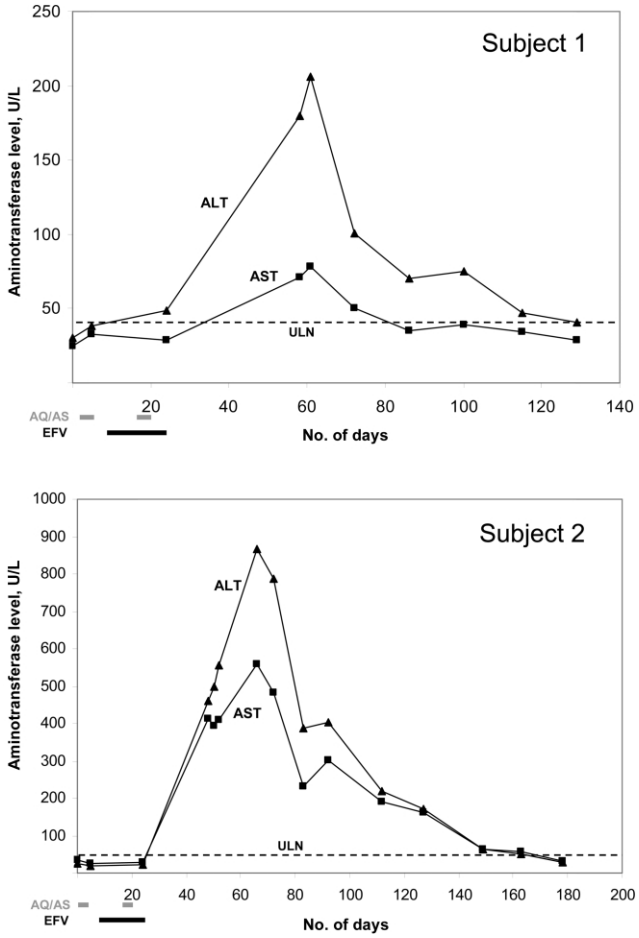

Figure 1. Time course for abnormalities in liver-associated enzyme levels. *Bars,* duration of study drug administration. ALT, alanine aminotransferase; AQ/AS, amodiaquine plus artesunate; AST, aspartate aminotransferase; EFV, efavirenz; ULN, upper limit of normal for ALT and AST level.

increases in C_{max} and half-life were observed in subject 1; an 8.5% decrease in $AUC_{0-96\ h}$, a decrease in $C_{max,}$ and a minimal increase in half-life were noted in subject 2. EFV $AUC_{0-24\ h}$ was noted to be within the reported range for healthy volunteers in subject 1 and higher than the reported values in subject 2 [3].

The administration of EFV therapy in the context of AQ/AS therapy increased AQ exposure and decreased DEAQ exposure in both subjects. Both subjects had normal transaminase levels throughout the period of study drug administration but developed substantial asymptomatic increases in their transaminase levels several weeks following study completion. Changes in AQ/DEAQ exposure and hepatotoxicity were surprising and could not be explained by available data on AQ/DEAQ metabolism [4]. Hepatitis induced by EFV therapy is uncommon and has not been associated with AS therapy [5]. AQ therapy has resulted in hepatitis when used for chronic malaria chemoprophylaxis [6–8], but 3-day treatment courses of AQ/AS therapy have not been linked to hepatotoxicity.

Optimal malaria treatment regimens for HIV-infected persons receiving antiretroviral therapy are not clear. The dramatic, delayed onset of hepatitis we observed in 2 subjects suggests that patients treated with a regimen containing AQ or AS while receiving EFV-based antiretroviral regimens should be monitored for liver toxicity. Continued research is needed to establish the safety and efficacy of antimalarial regimens in patients receiving antiretroviral therapy.

Acknowledgments

Financial support. National Institutes of Health, University of California San Francisco-Gladstone Institute of Virology & Immunology Center for AIDS Research (P30 AI27763) and the General Clinical Research Center at San Francisco General Hospital, funded by the National Center for Research Resources, National Institutes of Health (MO1-RR00083-43). N.L. is supported by The Wellcome Trust of Great Britain as part of the Wellcome Trust Mahidol University Oxford Tropical Medicine Research Programme.

Potential conflicts of interest. All authors: no conflicts.

Polina German,[1] Bryan Greenhouse,[2] Carrie Coates,[1] Grant Dorsey,[2] Philip J. Rosenthal,[2] Edwin Charlebois,[2] Niklas Lindegardh,[3,4] Diane Havlir,[2] and Francesca T. Aweeka[1]

[1]Drug Research Unit and [2]Department of Medicine, San Francisco General Hospital, University of California, San Francisco, California; [3]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; and [4]Nuffield Department of Clinical Medicine, Centre for Tropical Medicine, University of Oxford, United Kingdom

References

1. Blessborn D, Neamin G, Bergqvist Y, Lindegardth N. A new approach to evaluate stability of amodiaquine and its metabolite in blood and plasma. J Pharm Biomed Anal **2006**; 41:207–12.
2. Rezk NL, Tidwell RR, Kashuba ADM. High-performance liquid chromatography assay for the quantification of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci **2004**; 805:241–7.
3. Aarnoutse RE, Grintjes KJ, Telgt DS, et al. The influence of efavirenz on the pharmacokinetics of a twice-daily combination of indinavir and low-dose ritonavir in healthy volunteers. Clin Pharmacol Ther **2002**; 71:57–67.
4. Li XQ, Bjorkman A, Anderrson TB, Ridderstrom M, Masimirembwa CM. Amodiaquine clearance and its metabolism to n-desethylamodiaquine is mediated by CYP2C8: a new high affinity and turnover enzyme- specific probe substrate. J Pharmacol Exp Ther **2002**; 300:399–407.
5. Martin-Carbonero L, Nunez M, Gonzalez-Lahoz J, Soriano V. Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine. HIV Clin Trials **2003**; 4:115–20.
6. Larrey D, Castot A, Pessayre D, et al. Amodiaquine-induced hepatitis: a report of seven cases. Ann Intern Med **1986**; 104:801–3.

7. Bernuau J, Larrey D, Campillo B, et al. Amodiaquine-induced fulminant hepatitis. J Hepatol **1988**; 6:109–12.
8. Raymond JM, Dumas F, Baldit C, Couzigou P, Beraud C, Amouretti M. Fatal acute hepatitis due to amodiaquine. J Clin Gastroenterol **1989**; 11:602–3.

Reprints or correspondence: Dr. Francesca T. Aweeka, Drug Research Unit, University of California, 521 Parnassus Ave., San Francisco, CA 94143 (faweeka@sfghsom.ucsf.edu).

Clinical Infectious Diseases 2007; 44:889–91
 1058-4838/2007/4406-0027$15.00
DOI: 10.1086/513706