

factors, including exposure to fecally contaminated food or water, direct contact with swine and potentially other animals, and consumption of undercooked mammalian meats, especially organ meats [13], may also be good candidates for HEV testing. Finally, because the evidence to date suggests that only individuals who are immunocompromised develop chronic HEV viremia [4–7], testing could be limited to these patients.

In the absence of HEV data, it is not possible to determine the frequency of chronic alanine aminotransferase elevations in the Swiss HIV Cohort Study attributable to HEV infection. However, both HIV and HEV are ubiquitous global pathogens, and a current research priority is to better understand the frequency and clinical consequences of coinfection with these 2 viruses.

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References

- Kovari H, Ledergerber B, Battegay M, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis B or C virus co-infection. *Clin Infect Dis* **2010**; 50:502–511.
- Khuroo MS. Study of an epidemic of non-A, non-B hepatitis. Possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am J Med* **1980**; 68:818–824.
- Wong DC, Purcell RH, Sreenivasan MA, Prasad SR, Pavri KM. Epidemic and endemic hepatitis in India: evidence for a non-A, non-B hepatitis virus aetiology. *Lancet* **1980**; 2: 876–879.
- Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* **2008**; 358: 811–817.
- Gerolami R, Moal V, Colson P. Chronic hepatitis E with cirrhosis in a kidney-transplant recipient. *N Engl J Med* **2008**; 358:859–860.
- Dalton HR, Bendall RP, Keane FE, Tedder RS,

- Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. *N Engl J Med* **2009**; 361:1025–1027.
- Colson P, Kaba M, Moreau J, Brouqui P. Hepatitis E in an HIV-infected patient. *J Clin Virol* **2009**; 45:269–71.
- Kuniholm MH, Purcell RH, McQuillan GM, Engle RE, Wasley A, Nelson KE. Epidemiology of hepatitis E virus in the United States: results from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Infect Dis* **2009**; 200:48–56.
- Thomas DL, Yarbough PO, Vlahov D, et al. Seroreactivity to hepatitis E virus in areas where the disease is not endemic. *J Clin Microbiol* **1997**; 35:1244–1247.
- Madejon A, Vispo E, Bottechia M, Sanchez-Carrillo M, Garcia-Samaniego J, Soriano V. Lack of hepatitis E virus infection in HIV patients with advanced immunodeficiency or idiopathic liver enzyme elevations. *J Viral Hepat* **2009**; 16:895–896.
- Lewis HC, Boisson S, Ijaz S, et al. Hepatitis E in England and Wales. *Emerg Infect Dis* **2008**; 14:165–167.
- Renou C, Moreau X, Pariente A, et al. A national survey of acute hepatitis E in France. *Aliment Pharmacol Ther* **2008**; 27:1086–1093.
- Wichmann O, Schimanski S, Koch J, et al. Phylogenetic and case-control study on hepatitis E virus infection in Germany. *J Infect Dis* **2008**; 198:1732–1741.

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Reply to Kuniholm et al

TO THE EDITOR—We thank Kuniholm et al [1] for their interest in our study on the incidence and risk factors for chronic elevation of alanine aminotransferase (ALT) levels in human immunodeficiency virus (HIV)–infected persons without hepatitis B or C virus coinfection [2]. They suggest that chronic hepatitis virus E (HEV) infection should be considered in the differential diagnosis in this patient group. We indeed did not look for HEV as a cause for chronic ALT elevation. However, the prevalence of HEV infection is very low in our study population, as reported at the Conference on Retroviruses and Opportunistic Infections by investigators of the Swiss HIV Cohort Study [3]. In this study,

Swiss HIV Cohort Study participants with chronic elevated ALT values and no hepatitis B and C infection were screened for positive anti-HEV immunoglobulin G in the latest stored plasma sample. In HEV-seropositive subjects, HEV polymerase chain reaction was performed on a plasma sample stored 3 months prior to, at the time of, and 3 months after the first elevated ALT value. Among 735 patients with chronic ALT elevation, 19 (2.6%) were HEV seropositive. At the time of ALT elevation, HEV polymerase chain reaction results were positive in only 1 of these 19 patients.

Whether tests to detect HEV are indicated among HIV-infected persons with chronic ALT elevation in the absence of hepatitis B or C virus coinfection or other causes of chronic hepatitis must depend on the local epidemiology of HEV infection and the travel history of individual patients. Because of its low prevalence in our study population, we do not expect that the omission of HEV serology or molecular tests had a relevant influence on the results of our study.

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References

- Kuniholm MH, Labrique AB, Nelson KE. Should HIV-infected patients with unexplained chronic liver enzyme level elevations be tested for hepatitis E virus? *Clin Infect Dis* **2010**; 50(11):1545–1546 (in this issue).
- Kovari H, Ledergerber B, Battegay M, et al. Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis B or C virus co-infection. *Clin Infect Dis* **2010**; 50:502–511.
- Kenfak Foguena A, Schöni-Affolter F, Bürgisser P, et al; The Swiss HIV Cohort Study. Hepatitis E virus sero-prevalence and chronic infection in HIV patients with unexplained ALT elevation: The Swiss HIV Cohort Study. In Program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA. **2010**. Poster 697.

Pharmacokinetics of the Treatment Switch from Efavirenz to Nevirapine

TO THE EDITOR—Because of its potency, easy dosing (1 tablet per day), and relatively favorable adverse-effect profile, efavirenz (EFV) is one of the most widely studied antiretroviral agents for the treatment of human immunodeficiency virus infection. The most common symptoms after initiating EFV include neuropsychiatric adverse effects. Other adverse effects include rash, gynecomastia, teratogenicity, fat redistribution, and dyslipidemia. EFV toxicity may require a switch to nevirapine (NVP), a safe and effective alternative [1–4], but whether NVP should be started at 200 or 400 mg per day remains unclear [5]. EFV increases the metabolism of other

coadministered drugs that are metabolized by the cytochrome P450, such as methadone, voriconazole, and NVP. Consequently, the NVP dose escalation may not be justified in the presence of EFV. The dose-effect relationship between steady-state plasma EFV levels and subsequent enzyme induction has not been studied. The study by Parienti et al [3] was a prospective randomized controlled trial evaluating the impact on low-density lipoprotein cholesterol of switching from EFV to NVP in case of EFV-associated dyslipidemia. This post hoc analysis aimed to describe the pharmacokinetics of the steady-state plasma NVP level during the switch from EFV and identify factors associated with suboptimal NVP plasma levels.

EFV was randomly switched to NVP in 18 of 37 white patients. NVP was introduced at 200 mg per day for 14 days, followed by 400 mg twice per day with intensive pharmacokinetic sampling. The drugs' steady-state plasma levels were determined in a central laboratory at the end

of the study. The steady-state plasma EFV level at week 0 and the steady-state plasma NVP levels at weeks 2, 4, 6, 8, and 12 were plotted by use of box plots. First, we used linear regression to assess the correlation between the steady-state plasma EFV level at week 0 and the steady-state plasma NVP level at week 2. Second, we modeled the steady-state plasma NVP level using a mixed model, including age, sex, weight, baseline steady-state plasma EFV level, NVP dosage (200 mg per day vs 400 mg per day), and time as potential predictors.

A higher steady-state plasma NVP level at week 2 was significantly and positively correlated with a higher steady-state plasma EFV level at week 0 ($r = 0.54$; $P < .03$). As shown in Figure 1, there were 7 of 18 patients who had a steady-state plasma NVP level below 3000 ng/mL at week 2 (lower than the recommended limit for antiviral activity), and 5 of these 7 patients subsequently regained a therapeutic steady-state plasma NVP level when treated with an NVP dosage of 400 mg per day. Only baseline steady-state plasma

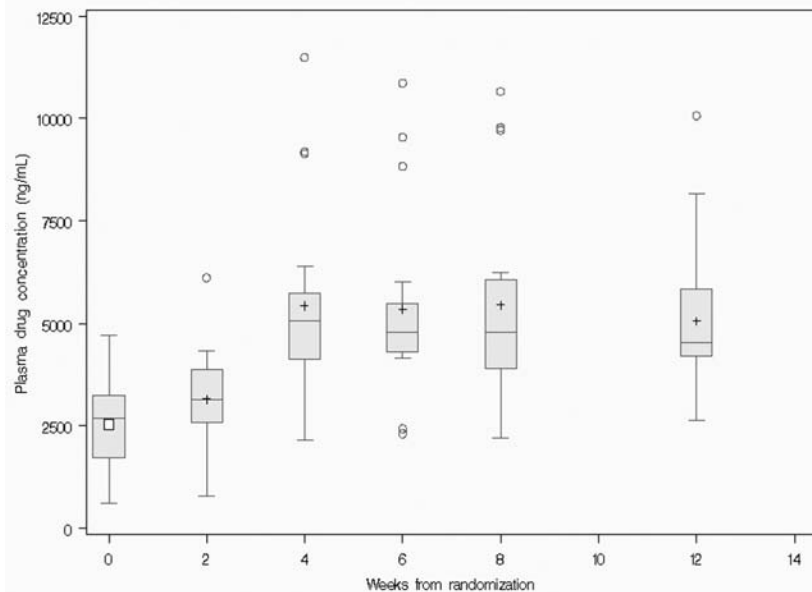


Figure 1. Efavirenz (week 0) and nevirapine (weeks 2–12) plasma concentrations during the switch from efavirenz to nevirapine (for 18 patients). The box plot shows a comparison of the plasma concentrations, with the upper and lower edges of the boxes representing upper and lower quartiles, respectively. Lines extending above and below the boxes represent the highest and lowest values, respectively. Circles represent outliers. Plus signs represent the mean values of the nevirapine plasma levels, and the small white square inside the first interquartile range (IQR) box represents the mean value of the efavirenz plasma level. The horizontal line within each IQR box represents the median value of the nevirapine or efavirenz plasma level.