Chronic Hepatitis E in HIV Patients: Rapid Progression to Cirrhosis and Response to Oral Ribavirin

Karin Neukam,1,2 Pablo Barreiro,3 Juan Macias,1,2 Ana Avellón,1 Celia Cifuentes,1,2 Luz Martín-Carbonero,1 José M. Echevarría,4 Julio Vargas,1,2 Vicente Soriano,3 and Juan A. Pineda1,2

1Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme, Seville; 2Instituto de Biomedicina de Sevilla; 3Department of Infectious Diseases, Hospital Carlos III, Madrid; and 4National Center for Microbiology, Instituto de Salud Carlos III, Majadahonda, Spain

Chronic hepatitis E virus infection with rapid progression to cirrhosis is reported in 2 human immunodeficiency virus (HIV)–infected patients with severe immunosuppression. Monotherapy with ribavirin led to temporary viral response and marked improvement of liver damage. Chronic hepatitis E should be regarded as another opportunistic event within HIV infection.

Keywords. chronic hepatitis E; HIV; cirrhosis; ribavirin; immunosuppression

Hepatitis E virus (HEV) is a leading cause of epidemic or sporadic waterborne acute hepatitis in developing countries. For years, acute hepatitis E was considered a subclinical and self-limiting disease [1]. In Western countries, autochthonous cases of HEV genotype 3 (HEV-3) infection are increasingly reported, mostly in relation to sporadic foodborne exposure to undercooked swine products [1]. Immunosuppression has been shown to facilitate chronicity of HEV infection, HIV infection being one of the possible causes for HEV persistence [2], and there are reports of high HIV/HEV coinfecion rates for particular regions [3, 4]. In Spain, for instance, the prevalence of HEV antibodies in the general population ranges between 2.2% and 7.3% [5, 6]. Although exposure to HEV seems comparable between HIV-infected patients and the general population, chronic HEV-3 infection has been described in HIV-infected, immunosuppressed patients [2, 7–10].

There are data to suggest that HEV may enhance the progression of liver disease from other causes [11]. However, information on the natural history of chronic HEV infection, especially regarding the velocity of progression to cirrhosis, is scarce. Likewise, data on the treatment of HEV in HIV-infected patients have only been described in 2 cases, which were treated with pegylated interferon (peg-IFN) alone [2] or in combination with ribavirin (RBV) [7]. Because in some regions monoinfection with HEV or HIV represents a common health problem, HIV/HEV coinfecion may become a relevant issue. It is thus of the highest importance to clarify the natural history, as well as treatment options, for chronic hepatitis E in HIV infection.

We report 2 cases of chronic hepatitis E in HIV-infected patients with severe immunosuppression, the response to RBV monotherapy, and the course of fibrosis progression before and after therapy.

CASE REPORT 1

A 47-year-old, white homosexual man was first seen at a hospital in Seville in 2003, presenting with plasma HIV RNA of 21 000 copies/mL and a CD4 count of 17 cells/μL. In 1995 he had been classified as category C under the Centers for Disease Control and Prevention HIV classification system. Despite undetectable plasma HIV RNA after starting antiretroviral therapy (ART), CD4 counts remained <100 cells/μL during the first years on treatment. In April 2008, he presented with a peak in alanine aminotransferase (ALT) level of 482 IU/mL but was otherwise asymptomatic (Figure 1A). Serology for hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) was negative, whereas serum immunoglobulin M (IgM) antibodies against HEV were positive. In January 2009 ALT levels normalized, only to increase again 1 month later, remaining elevated with fluctuations thereafter (Figure 1A). Liver stiffness (LS) as assessed by transient elastometry increased from 4.9 kPa in April 2006 to 17.1 kPa in April 2011 (Figure 1A). In November 2011, liver biopsy confirmed macro-micronodular cirrhosis with significant steatosis. No esophageal varices were detected. HAV, HBV, and HCV serology remained negative, and CD4 counts did not exceed 200 cells/μL throughout the follow-up period. The patient reported occasional alcohol consumption (50–100 mg/day with infrequent binge drinking) in 2009. In 2011, he was abstinent.
Retrospective analysis of frozen serum samples confirmed acute HEV-3 infection in March 2008 (Figure 1A). No source of infection was recognized. In November 2011, a 24-week course of treatment with RBV 1200 mg/day was initiated. In December 2011 the patient showed normal liver enzymes and undetectable plasma HEV RNA, with detectable IgM and immunoglobulin G (IgG) against HEV. At the end of treatment and 3 months thereafter, no HEV RNA could be detected in plasma or feces (Figure 1A), liver enzymes remained normal, and LS declined to 14 kPa. In October 2012, however, HEV RNA was detectable in plasma.

**CASE REPORT 2**

A 53-year-old homosexual man, born in Cuba and resident in Spain since 1979, was seen for the first time in 2005 at an HIV...
outpatient clinic in Madrid. The diagnosis of HIV infection had been made in 1999, when he presented with a CD4 count of 18 cells/μL and plasma HIV RNA of 361 116 copies/mL. He initiated ART shortly after diagnosis but discontinued several regimens due to side effects and/or his own decision. In April 2006, his ALT level flared to 261 IU/L. By then, the CD4 count was 88 cells/μL. ALT persisted elevated in subsequent visits (Figure 1B). Throughout the follow-up, no significant CD4 cell count recovery occurred despite the use of ART. He had negative serology for HAV, HBV, and HCV. Likewise, plasma HCV RNA and HBV DNA were negative. He denied alcohol abuse or intake of drugs other than antiretroviral agents.

Liver stiffness increased from 6.7 kPa to 38.5 kPa within 3 years (Figure 1B). Upper gastrointestinal endoscopy in 2009 showed grade II esophageal varices, and β-blocker prophylaxis was instituted. No liver decompensations have occurred to date. HEV serology was ordered in 2009, which showed positive IgG and negative IgM results. Retrospective analyses of stored samples showed negative HEV serology before the first acute ALT elevation and positive anti-HEV IgM afterward (Figure 1B). HEV RNA was intermittently positive in blood but persistently positive in feces. Sequencing confirmed infection by HEV-3. On direct interview, the patient admitted as the most likely source of infection the consumption of homemade pork liver pâté manufactured by relatives owning a farm in northwestern Spain.

In September 2011, monotherapy with oral RBV 1000 mg/day was initiated and given for 24 weeks. In January 2012, both his plasma and feces were negative for HEV RNA. Concomitantly, ALT levels subsided to normal values and LS declined (Figure 1B), and the CD4 count increased to 289 cells/μL. However, 10 weeks after the end of treatment, the patient presented with detectable plasma HEV RNA, which disappeared again in October 2012 (Figure 1B).

**DISCUSSION**

The 2 cases reported herein show that in HIV-infected patients with severe immunosuppression, chronic HEV-3 infection can lead to cirrhosis within <3 years. Of note, neither patient showed symptoms of HEV exposure, a flare in liver enzymes being the only relevant finding. The lack of clinical expression, but the fast progression to cirrhosis, requires clinicians with a high level of suspicion to diagnose chronic hepatitis E in immunodepressed individuals.

HEV exposure could be a risk factor for progression of liver disease related to other causes [11]. Furthermore, an association between exposure to HEV and cirrhosis has been described [12], and chronic HEV infection as a cause of cirrhosis in an HIV-coinfected patient has been recently reported [2]. Likewise, 2 other cases of severe liver damage in HIV-infected patients have been described at the time of HEV diagnosis [7, 10]. In the cases described herein, we observed LS increases from normal values before HEV infection to values indicative of cirrhosis after infection and persistence of HEV. Furthermore, etiologies other than HEV could be excluded as a cause of cirrhosis development. Importantly, the period of time in which fibrosis progression took place was alarmingly short. Thus, in the setting of immunosuppressed HIV-infected patients with chronic hepatitis E, progression to cirrhosis may be even faster than that observed in HBV or HCV/HIV coinfection.

A delay in the diagnosis of HEV infection and, as a result, in starting antiviral therapy, can lead to clinical complications and hazardous consequences for the patient. However, clinicians managing HIV infection are often not aware of the possibility of chronic HEV infection and its potential adverse outcome. Therefore, a small number of cases have been diagnosed to date, and very few data on the treatment of chronic HEV infection in the HIV-coinfected population are available. Dalton et al described a patient in whom negativization of HEV RNA was not achieved after 6 months of monotherapy with peg-IFN [7]. Subsequent treatment with peg-IFN plus RBV for 12 weeks led to a rapid negativization of HEV RNA, and reduction of inflammation and fibrosis was observed with therapy [7]. Jagit Singh et al report sustained response 27 weeks after monotherapy with administration peg-IFN for 24 weeks [2]. Viral clearance was accompanied by aminotransferase normalization. Our cases demonstrate that successful control of HEV replication with RBV leads to a marked improvement in LS. Importantly, and in contrast to peg-IFN, RBV can be used even in cases of decompensated cirrhosis. Both patients showed good tolerance to therapy. Furthermore, to our knowledge, this is the first report to show that monotherapy with RBV may be transiently efficacious against chronic hepatitis E in HIV-infected patients. However, intermittently detectable HEV RNA in plasma after treatment discontinuation underlines the need for research to define the optimum treatment regimen and duration for this population.

Our findings confirm the scarce data available from isolated cases of chronic hepatitis E in HIV-coinfected individuals with a CD4 cell count of <200 cells/μL, where infection was caused by HEV-3 [2, 7–10]. In the setting of HIV carriers, HEV-3 infection should be regarded as an opportunistic infection, as it appears to evolve differently in HIV infection. Special attention regarding possible HEV-3 coinfection should be given to this subset of patients.

In conclusion, HEV infection may cause rapidly progressing chronic hepatitis in severely immunosuppressed HIV-coinfected patients, with development of cirrhosis in the short term. Screening for HEV in HIV-infected individuals presenting unexplained aminotransferase elevations or with hepatic fibrosis of unknown origin is warranted. A short course of RBV may temporarily control viral replication; however, optimal treatment regimens need to be defined.
Notes

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References