

Correspondence

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Safety of rilpivirine and boceprevir coadministration in HIV-infected patients treated for acute hepatitis C virus infection

In 2012, hepatitis C virus (HCV) protease inhibitors were the first direct-acting antivirals that led to an improved treatment response when combined with peginterferon- α and ribavirin for the treatment of HCV infections. However, when used in HIV-positive patients, treatment with direct-acting antivirals is more complicated regarding possible drug–drug interactions (DDIs) with combination antiretroviral therapy. The nonnucleoside reverse transcriptase inhibitor rilpivirine is a CYP3A4 substrate and therefore potentially interacts with boceprevir, a CYP3A4 inhibitor. Based on a healthy volunteer DDI study, exposure to rilpivirine increased by 39% when given together with boceprevir [1]. This increased exposure did not lead to clinically significant corrected QT (QTc) prolongation during short-term administration in the healthy volunteers. Therefore, the product label of boceprevir states that the drug can be coadministered with rilpivirine; this also holds for other HCV protease inhibitors and CYP3A4 inhibitors, such as telaprevir and simeprevir [1–3].

We performed a subanalysis within the Dutch acute HCV in HIV study to describe the pharmacokinetic interaction between boceprevir and rilpivirine in HIV/HCV-positive patients and the possible effects on QTc-interval prolongation [4].

In the Dutch acute HCV in HIV study, 57 HIV-positive patients were treated for an acute HCV infection with 12 weeks of weight-based pegylated interferon- α , ribavirin, and boceprevir 800 mg thrice daily [5]. In this substudy, patients treated with rilpivirine 25 mg daily combined with two nucleos(t)ide reverse transcriptase inhibitors were included. Patients were instructed to take rilpivirine together with at least a 500 kcal meal. Blood samples were taken before the start of HCV therapy (T0) and at week 4 of therapy (T4) during the elimination phase of the drug ($t=4\text{--}24$ h after administration). Concurrently, with the blood draw, a single 12-lead ECG was recorded in all participants at T0 and T4. Heart rate QTc was calculated using Bazett's formula. Rilpivirine plasma concentrations were analyzed by a validated reversed-phase ultra-performance liquid chromatographic method with ultraviolet detection (linear calibration range (0.0063–3.75 mg/l). Concentration-time data were analyzed using nonlinear mixed-effect modeling (NONMEM version 7.2; ICON, Dublin, Ireland). The effect of boceprevir and alanine amino-

transferase (ALT) on rilpivirine apparent clearance (CL/F) was evaluated. Area under curve (AUC)_{0–24 h} was calculated using individual estimations for CL/F and dose. The correlation between AUC_{0–24 h} and QTc time was analyzed using linear regression.

Twelve male patients (11/12 white people) were included. Median age was 38 years [interquartile range (IQR) 33–43]. Patients had a median ALT of 126 U/l (IQR 29–198) with no signs of liver failure at T0 and their median ALT at T4 was 36 U/l (IQR 28–39). In all patients, the HIV viral load was fully suppressed at both time points. One out of 12 patients had concomitant medication potentially influencing the rilpivirine metabolism or QTc time (acetylsalicylic acid 80 mg daily, prasugrel 10 mg daily, pravastatin 40 mg daily, perindopril 2 mg daily).

Median rilpivirine concentration at T0 and T4 was 0.16 and 0.26 mg/l, respectively. In the individual patients, the absolute rilpivirine concentration increased at T4 from +0.01 mg/l (8%) to +0.10 mg/l (63%), when measured at the same time point after intake. Pharmacokinetics of rilpivirine were described using a one-compartment model with fixed values for the absorption rate ($k_a=0.7$ /h) and volume of distribution ($V_d=152$ l) based on the literature. CL/F decreased from 7.2 to 3.81/h when patients were treated with boceprevir (relative SE 14%, $P<0.005$). In the simulated pharmacokinetic profile, a clear decrease in CL/F and AUC_{0–24 h} is seen (Fig. 1).

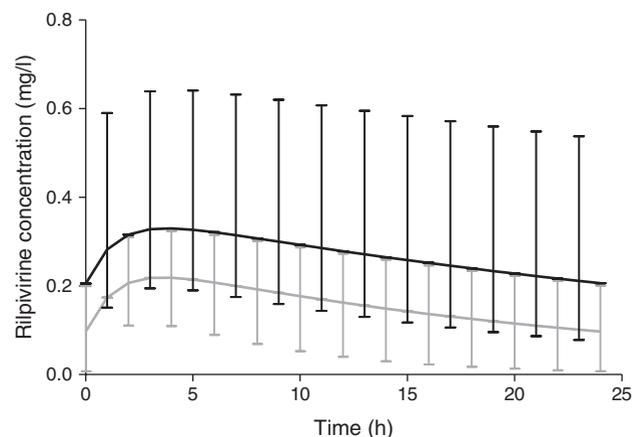


Fig. 1. Rilpivirine concentrations with and without boceprevir. Median pharmacokinetic profile and range of rilpivirine in patients treated with (black) and without (gray) boceprevir.

This DDI explained 34% of the variability in CL/F. The remaining variability of CL/F was 44% (RSE 13%). No significant correlation between ALT and CL/F was seen. Measured QTc intervals were not correlated with the calculated rilpivirine AUC_{0–24 h}. Patients without boceprevir had a median rilpivirine AUC_{0–24 h} of 3.8 mg/l/h with a corresponding QTc interval of 382 ms (range 355–425 ms) and patients treated with boceprevir had a median rilpivirine AUC_{0–24 h} of 6.5 mg/l/h and a corresponding QTc interval of 384 ms (range 349–425 ms).

The rilpivirine AUC_{0–24 h} values seen in the patients without boceprevir treatment were comparable to values previously described [6]. In contrast, the increase in rilpivirine AUC_{0–24 h} (71%) that we found in this study is higher than previously described in healthy volunteers (39%) [1]. This suggests that data from healthy volunteers cannot be translated one on one to HIV-infected patients.

This is the first analysis of rilpivirine DDI interactions with boceprevir in HIV-infected patients. More effective interferon-free treatment options have recently become available for the treatment of chronic HCV. However, given the very high costs, their availability is currently limited to a very small number of patients. Therefore, it is likely that boceprevir will continue to be used for some time. We show that it can be safely combined with rilpivirine.

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Uncontrolled hepatitis delta virus infection after initial suppression on tenofovir in a HIV/HBV-coinfected patient

Hepatitis delta virus (HDV) infection affects 10–15% of HIV/hepatitis B virus (HBV)-coinfected individuals in Europe and can lead to severe hepatic inflammation [1]. Although interferon α remains the mainstay of HDV therapy [2], the potential efficacy of tenofovir disoproxil fumarate (TDF) in reducing HDV viral replication in HIV-infected patients has been recently suggested

[3]. In a recent publication, James *et al.* described the first case of HBV and HDV clearance in a patient treated with TDF [4].

A 38-year-old man from Mali was diagnosed with HIV-1 in our clinic in October 2008. He had nine CD4⁺ cells/ μ l (1%) and an HIV viral load of 107 000 copies/ml.

He was hepatitis B surface antigen (HBsAg)-positive, hepatitis B envelope antigen-negative had an initial HBV viral load of 1 125 347 IU/ml and HBV sequencing showed a genotype E. He was also coinfecting with HDV with a baseline viral load of 300 000 copies/ml. He had elevated liver enzymes including an alanine aminotransferase (ALT) of 250 U/l and an aspartate aminotransferase of 150 U/l. The patient experienced a rapid virological suppression of HIV, HBV, and HDV within 3 months after initiation of a TDF-containing antiretroviral therapy (ART) (Fig. 1). During the following 2.5 years, the HIV, HBV, and HDV viral loads remained suppressed, his transaminases were in the normal range, and the CD4⁺ cell count increased to 406 cells/ μ l (14%). In October 2013, he travelled to Mali and interrupted his ART. As he came back 9 months later, his CD4⁺ cell count had dropped to 131 cells/ μ l (7%), he had high HIV, HBV, and HDV viral loads, and signs of active hepatitis with transaminases five times above the upper limit of the norm. He was prescribed a new TDF-containing ART regimen, according to HIV resistance testing. Although the HIV and HBV viral loads were suppressed to undetectable levels 4 months later, he maintained high-level HDV replication (Fig. 1). Transaminases remained elevated, with ALT levels mirroring changes in HDV viral load until the last measurement in June 2015. Quantitative HBsAg levels dropped from 12 252 to 6 586 IU/ml between treatment initiation in 2008 and the time of treatment interruption in 2013. At reinitiation in 2014, the level had reached 46 288 IU/ml and had only dropped to 10 122 IU/ml 10 months later.

In this HIV/HBV/HDV-coinfecting patient, rapid and sustained virological suppression of all three viruses as well as normalization of transaminases were obtained with a TDF-containing regimen. However, the same outcome was not achieved after TDF reinitiation following a 9-month treatment interruption. Despite rapid virological suppression of HIV and HBV, the HDV viral load remained very high 10 months later. Interestingly, ALT levels remained elevated and fluctuated according to HDV RNA levels.

Several hypotheses can be raised to explain the different responses to TDF in our patient. First, he started his first course of ART in a state of severe immune suppression with fewer than 10 CD4⁺ cells/ μ l, whereas his cellular immunity was less impaired at the time of ART reinitiation in 2014. Thus, it could be postulated that the recovery of cellular immunity rather than the effect of TDF on HBV replication was the main reason for control of HDV replication during the first treatment episode. It is plausible that the immune recovery effect was less pronounced after the short treatment interruption in 2013. Another possibility is that immune escape variants emerged over time and hindered the immunological control of HDV replication in the second treatment episode.

This case shows the potential benefit of long-term TDF treatment for HDV infection, but also underlines the strong link between HDV replication and liver inflammation. Treatment interruptions in HIV/HBV and HIV/HBV/HDV-coinfecting patients can lead to

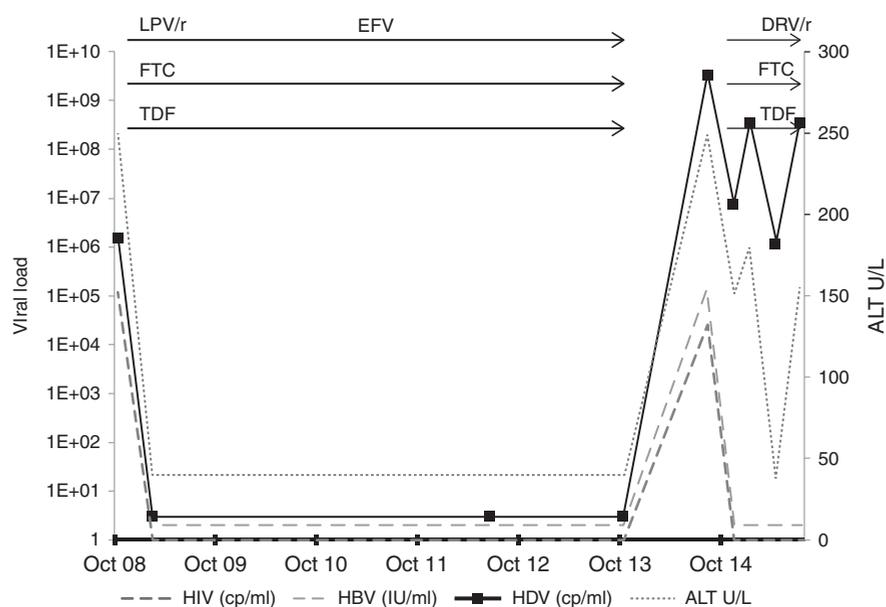


Fig. 1. Antiretroviral therapy history and laboratory measurements. ALT, alanine aminotransferase; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; HBV, hepatitis B virus; HDV, hepatitis D virus; LPV/r, ritonavir-boosted lopinavir; TDF, tenofovir disoproxil fumarate.

severe, potentially fatal hepatitis flares [5]. The mechanisms of action of TDF on HDV replication and the predictors of treatment success remain largely unknown. Thus, large, prospective studies are needed to better understand the potential role of TDF in the treatment of HDV infection.

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Favorable outcome of severe human herpes virus-6 encephalitis in an HIV-infected patient

After primary infection, the ubiquitous T-lymphotropic *Herpesviridae* human herpes virus-6 (HHV-6) establishes a life-long latent infection in most adults. In immunocompromised patients, HHV-6 reactivation may lead to various clinical syndromes including potentially life-threatening limbic encephalitis that has been mostly described in hematopoietic stem cell transplant recipients. Here, we report the successful management of severe HHV-6 encephalitis in an HIV-infected patient.

A 41-year-old HIV-1-infected male presented to our department on 12 February 2014 for an acute confusional state. On 20 January 2014, he was asymptomatic with a CD4⁺ T-cell count of 44 cells/ μ l (4%) and a plasma HIV-1 viral load of 5 log₁₀ copies/ml. An antiretroviral therapy (ART) based on ritonavir-boosted atazanavir, tenofovir and emtricitabine together with cotrimoxazole chemoprophylaxis was started. On admission, clinical examination revealed confusion, periods of loss of contact, and a bilateral Babinski sign without neurological focalization. Brain MRI showed on fluid-attenuated inversion recovery (FLAIR)-weighted images confluent signal hyperintensities in the corpus callosum and the adjacent white matter (Fig. 1a and b). Electroencephalography was suggestive of seizures. Cerebrospinal fluid (CSF) cytological and biochemical analysis were normal. PCR on CSF were positive for HIV-1 (4.1 log₁₀ copies/ml) and HHV-6 (5 log₁₀ copies/ml), and negative for herpes simplex virus varicella-zoster virus Epstein–Barr virus

(EBV), cytomegalovirus (CMV) enterovirus and John Cunningham virus. Direct staining, antigen titer, cultures and PCR for mycobacteria, *Toxoplasma* and *Cryptococcus* on CSF were negative. Blood CD4⁺ T-cell count was 137 cells/ μ l (13%), whereas plasma HIV-1 viral load had dropped to 3.8 log₁₀ copies/ml. PCR on whole blood were positive for CMV (3.1 log₁₀ copies/ml), EBV (4.8 log₁₀ copies/ml) and HHV-6 (4.2 log₁₀ copies/ml). Serology for syphilis was negative. A diagnosis of HHV-6 encephalitis was made. ART was continued and a therapy based on i.v. ganciclovir 5 mg/kg bid associated with oral leviteracetam 500 mg bid and lacosamide 100 mg bid was started. The patient gradually improved. At 3 weeks, HHV-6 viral load in the CSF decreased below the detection threshold, and ganciclovir was switched to oral valganciclovir 900 mg bid before the patient was discharged home with a complete clinical recovery (Fig. 1e). On May 2014 brain MRI showed only subtle residual hyperintensity of the corpus callosum (Fig. 1c and d), which disappeared in September 2014. HHV-6 viremia remained stably detectable in blood from February 2014 to January 2015 (mean 3.5 \pm 0.4 log₁₀ copies/ml) and then decreased below the detection threshold (3 log₁₀ copies/ml). PCR for HHV-6 performed on hair follicles in November 2014 was negative. Blood PCR for CMV remained undetectable from March 2014. Antiepileptic drugs were stopped in August 2014. Valganciclovir was tapered to 900 mg/day in December 2014 and stopped in July 2015. By September

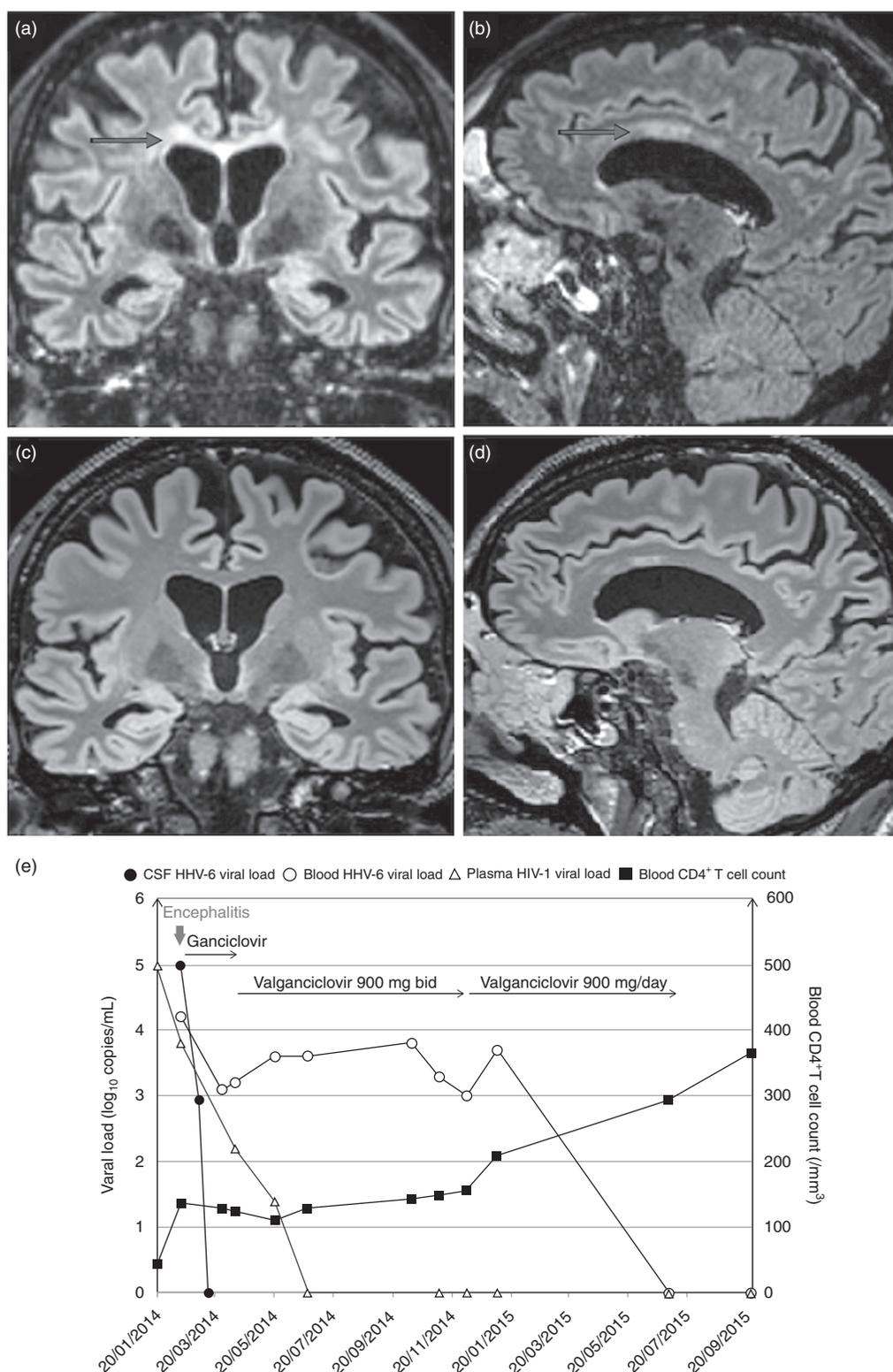


Fig. 1. (a–d) Brain MRI: coronal (a, c) and sagittal (b, d) reformatted FLAIR images. Initial images (a) and (b) demonstrate confluent signal hyperintensities in the corpus callosum and the adjacent white matter that significantly decrease after 3 months (c and d). At that time, only subtle residual hyperintensity can be depicted on the sagittal view at the anterior aspect of the corpus callosum. No enhancement of the lesions was observed on postgadolinium T1-weighted images (not shown). (e) Course of whole blood HHV-6 viral load, plasma HIV-1 viral load, and CD4⁺ T-cell count and therapy. Of note, undetectable viral load for HHV-6 means below the detection threshold.

2015, the patient was fully independent without any neurological abnormalities and had an undetectable HIV-1 viral load and a CD4⁺ T cell count of 365 cells/ μ l (18%) on ART.

The central nervous system (CNS) is considered as one site of persistence of HHV-6 following primary infection [1–3]. Immunosuppression may allow HHV-6 reactivation and the emergence of manifestations that include encephalitis, hepatitis, pneumonitis, and bone marrow suppression. Encephalitic syndromes related to HHV-6 in transplanted patients are mostly represented by limbic encephalitis with confusion, memory dysfunction, consciousness disturbance and seizures, together with hippocampus and amygdala lesions on brain MRI. However, involvement of limbic structures outside of the medial temporal lobe has been described [4]. Three cases of HHV-6 encephalitis in HIV-infected patients have been reported, all with a fatal issue [5–7]. HHV-6 DNA was only rarely detected in the CSF of immunocompromised HIV-infected patients, and relationship between HHV-6 replication and encephalitis is debated [8,9]. Because of the ubiquitous presence of latent HHV-6 infection in adults, separating latent from active HHV-6 infection is indeed crucial. In immunocompromised patients with suggestive neurological and brain MRI manifestations, as in our patient, the detection of HHV-6 DNA in CSF is however key to consider the diagnosis of active CNS infection. Moreover, in our patient, the negativity of the PCR for HHV-6 performed on hair follicles argued against a chromosomal integration of HHV-6 [10]. No consensus on therapeutic management of HHV-6 encephalitis has been formulated, and ganciclovir, foscarnet or cidofovir has been used alone or in combination. In our patient, 3 weeks of ganciclovir until drastic reduction of CSF HHV-6 viral load followed by prolonged valganciclovir were well tolerated and associated with a long-term favorable outcome. The ART-induced immune recovery associated with a possible unmasking immune reconstitution inflammatory syndrome in this patient might have also favored the control of HHV-6 reactivation [11–14].

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