V75I, K103N, V108I, Y115F, F116Y, Q151M, M184V and G109A in the reverse transcriptase region, and I117V, L3I, L63P and V77I in the protease region. The last HAART regimen before transplantation, discontinued pre-operatively, was lamivudine 150 mg twice a day, tenofovir 300 mg once daily and fosamprenavir 1400 mg twice a day. Immunosuppression was initially achieved with cyclosporin (300 mg twice a day) and steroids, and then maintained with cyclosporin only. On the third post-operative day, HAART was resumed with emtricitabine 200 mg, tenofovir 300 mg once daily and a subcutaneous (sc) injection of enfuvirtide 90 mg twice a day. At 3 months after transplantation, the CD4+ T cell count and HIV RNA level were 263 cells/mm³ (20%) and <50 copies/mL, respectively, while HCV RNA was 4.09 log₁₀ copies/mL (Cobas Ampliprep/Cobas TaqMan HCV Test Roche Diagnostics). After 9 months, because of a further increase in HCV RNA levels (6.09 log₁₀ copies/mL) and of macro- and micronodular cirrhosis revealed by transjugular liver biopsy, the patient started anti-HCV treatment with pegylated interferon (PEG-IFN) alfa 2b (180 μg sc once a week) and ribavirin (1200 mg twice a day). Cyclosporin was administered twice daily and its dosage was adjusted individually to match target trough levels of 75–125 μg/L. Four weeks later, because he had ongoing injection site reactions and complained of injection fatigue due to enfuvirtide and PEG-IFN, the patient switched from enfuvirtide to raltegravir (400 mg twice a day). Four weeks later, HIV RNA was still <50 copies/mL, while the CD4+ T cell count had increased from 162 (18%) to 336 (23%). Self-reported therapeutic adherence was apparently optimal. No other potentially interacting drugs were administered. Cyclosporin levels were monitored at regular intervals during outpatient visits (Figure 1). Moreover, at week 4 and week 8 raltegravir concentrations were also measured by a validated HPLC method before the morning dose and 3 h later and showed drug levels to be 60 and 5165 ng/mL at week 4, and 119 and 3386 ng/mL at week 8, respectively. No specific toxicity related to antiretroviral and immunosuppressive therapies was recorded. No administration of factor VIII for treatment of haemophilia A was requested. After 18 months of follow-up post-transplantation, the patient is alive and HIV RNA levels are undetectable.

In our patient, a raltegravir-based regimen was chosen in order to avoid the potential deleterious effect of PIs on cyclosporin. A new NNRTI-based regimen was excluded because etravirine is a substrate for, and inhibitor of, several CYP enzymes. Because of the concomitant administration of ribavirin, zidovudine, didanosine and stavudine were not feasible, in order to avoid risks of toxicities.

In clinical trials raltegravir was shown to be well tolerated with no risk of additive haematological toxicities. Raltegravir might be considered as a suitable option in HIV-infected patients undergoing liver transplantation. The switch from an injectable to an oral medication is highly acceptable to patients and may facilitate long-term adherence. Plasma concentrations of raltegravir were shown to be comparable with published data, suggesting no significant impact on its plasma exposure by concomitant use of cyclosporin. Raltegravir and cyclosporin may be co-administered without dose adjustments.

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References

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Early hepatitis B virological rebound on entecavir through selection of lamivudine-associated mutations

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antiviral
Sir,

There have been significant recent advancements in the antiviral therapy of chronic hepatitis B. In addition to L-nucleosides, such as lamivudine and telbivudine, the deoxyguanosine analogue entecavir and the acyclic nucleoside phosphonates adefovir and tenofovir are also available as treatment choices. Entecavir, a potent inhibitor of hepatitis B polymerase, has shown excellent results in studies with hepatitis B e antigen (HBeAg)-positive as well as HBeAg-negative chronic hepatitis B patients. Further studies have shown that entecavir has a high genetic barrier to resistance and that development of resistance to entecavir in nucleoside-naive patients is rare after 5 years of therapy. Most virological failures with entecavir occurred in patients with lamivudine-refractory resistance and occurred late into the treatment course. Here, we report a treatment-naive patient who unexpectedly developed early-onset treatment failure with entecavir.

A 34-year-old man, whose risk factor for blood-borne viruses was sexual contact with other men, was referred with HBeAg-positive chronic hepatitis B and was treatment naive. At baseline, his hepatitis B viral load was 134,684,400,000 IU/mL (11.13 log10) and alanine transaminase (ALT) was elevated at 262 IU/L (>4 times the upper limit of normal). Hepatitis C virus, hepatitis delta virus and HIV serology tests were all negative. He declined a liver biopsy, but in view of his raised transaminase and high viral load, entecavir 0.5 mg/day was initiated. A 4.4 log10 reduction in viral load was seen at 12 weeks. At 24 weeks, the drop in viral load from baseline was 5.1 log10, but with a substantial residual viral load of 10,027 IU/mL (Figure 1). Virological rebound (0.9 log10) was observed at week 27, which was associated with an ALT flare. A genotypic resistance test was performed using the samples from week 24 and week 27, both of which showed a genotype G virus with lamivudine-associated mutations V173L, L180M and M204V. In view of the lack of previous history of exposure to L-nucleosides, his pre-treatment baseline sample was also sequenced, and showed a mixed sequence of V173L, L180M and M204V. Careful scrutiny of the sequence also noted the presence of small amounts of M204V together with wild-type sequences (Figure 1). Interestingly, in the week 24 and 27 samples, no wild-type 173V and 180M were observed, whereas only small amounts of 204M were present, suggesting active selection of the pre-existing lamivudine-associated mutations by entecavir. Entecavir-specific resistance mutations at positions 169, 184, 202 and 250 were not detected. In view of the virological rebound, tenofovir was added to the regimen according to recent European Association For The Study Of The Liver clinical guidelines, resulting in a reduction in his hepatitis B viral load to 485 IU/mL and an improvement in his transaminitis (Figure 1).

As this patient was treatment naive, the presence of lamivudine-associated mutations at baseline suggested that he

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Composite chart showing changes in hepatitis B viral load and alanine transaminase (ALT) levels with time. The timing of the sequence analyses, treatment commencement and treatment change are indicated by arrows. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.
was infected with a virus with pre-existing resistance. V173L and L180M are compensatory mutations that increase the fitness of hepatitis B viruses harbouring mutations in the YMDD domain of the viral polymerase. It is of interest that while the YMDD domain mutation M204V was present as a minority species at baseline, V173L and L180M co-existed with the wild type as a mixed sequence in these two positions. While it is known that entecavir does not select lamivudine-associated mutations de novo,\(^6\) it is clear from this patient that pre-existing mutations were selected rapidly and resulted in virological rebound. Failure of entecavir was said to be rare and to occur only after 1–2 years of therapy.\(^3,6\) Hence, this is a case of early virological hepatitis B rebound on entecavir, through selection of lamivudine-associated mutations, but without developing any further entecavir-associated mutations in a treatment-naïve patient.

We feel it is essential to perform baseline resistance profiling on all patients started on entecavir even if treatment naive. The sequence tracing also needs to be carefully scrutinized as the mutations may appear as a minority species not obviously visible on population sequencing analysis.

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**References**


**Intraocular penetration of voriconazole and caspofungin in a patient with fungal endophthalmitis**

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Keywords: antifungal, ocular penetration, eye infection

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Sir,

Fungal infections of the eye are important causes of morbidity and loss of vision. Therapeutic options include intravitreally administered antifungals, ocular surgery and systemic antifungals. Until recently, intravitreal amphotericin B was the most common treatment option, along with vitrectomy. Only limited data are available describing voriconazole and caspofungin intraocular penetration, despite their increasing use in patients with fungal endophthalmitis.\(^1–3\) We report on the use of voriconazole and caspofungin in a patient with fungal endophthalmitis with measurement of plasma and intraocular concentrations of both drugs.

A 51-year-old monophthalmic man, was admitted with ulcerative keratitis of his left eye. Briefly, he had a complex ophthalmological history with recurrent corneal ulcerations treated with several penetrating keratoplasties, two limbal stem cell transplantations and finally loss of his right eye. As the patient only partially responded after 2 weeks with topical and systemic antibiotics, a keratolimbal transplantation was performed. Azathioprine and methylprednisolone were used to prevent rejection. Microscopy of the removed cornea showed fungi and intraconazole was started. However, after 1 week, inflammation persisted with development of hypopyon and visual acuity dropped to hand movements. The anterior chamber (AC) was flushed and amphotericin B (5 µg in 0.1 mL) was injected twice intracameraly. Microscopy of the AC taps showed fungal filaments. Cultures of aqueous humour on Sabouraud dextrose agar produced no growth. The infection spread from the AC into the vitreous, resulting in endophthalmitis. A pars plana vitrectomy was subsequently performed with intravitreal injections of voriconazole (50 µg in 0.1 mL). A few days later, the hypopyon recurred, with a new white feathery mass appearing in the AC.