Viral Response to Antiretroviral Therapy in a Patient Coinfected with HIV Type 1 and Type 2

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Clinical experience with the treatment of human immunodeficiency virus (HIV) type 2 (HIV-2) infection is limited, and even more scarce is information on therapy for patients coinfected with HIV type 1 (HIV-1) and HIV-2. Here, we describe the outcome for a coinfected patient in whom infection with both viruses was successfully controlled at the start of antiretroviral therapy, but for whom HIV-2 infection escaped control after a treatment simplification change while HIV-1 remained undetectable.

The prevalence of HIV-2 is low outside of West Africa. Nevertheless, it is in Western countries where HIV-2–infected patients have access to treatment. Clinical experience in treating HIV-2 infection is scarce, and the principles guiding use of HAART for HIV-1 infection are often applied to HIV-2 with minor changes. However, HIV-2 is naturally resistant to currently available nonnucleoside reverse-transcriptase inhibitors, and some other antiretrovirals may show less efficacy against HIV-2 than against HIV-1 [1, 2]. Herein, we describe 1 individual who was coinfected with HIV-1 and HIV-2 for whom HIV-1 replication but not HIV-2 replication was successfully controlled during HAART. This case illustrates that the presence of both viruses should be monitored, and HAART regimens must be designed with both viruses in mind.

Methods. The diagnosis of HIV-1 and HIV-2 coinfection was initially made by serological testing. Screening was performed using an EIA able to detect all known HIV variants (AxSYM HIV1/2 gO; Abbott); a synthetic peptide was used thereafter (PeptiLAV 1–2; Bio-Rad). Given the dual HIV-1 and HIV-2 reactivity, tests of the specimen were run in parallel with specific HIV-1 and HIV-2 Western blot assays (New Lav-Blot I and New Lav-Blot II; Bio-Rad). Dual serological infection was further confirmed by PCR with DNA extracted from PBMCs by use of specific HIV-1 and HIV-2 primers, as described elsewhere [3, 4].

The patient was observed for 36 months (from November 2001 to November 2004), and the clinical outcome, HIV-1 RNA levels, and CD4+ cell counts were recorded every 3–4 months. Plasma HIV-1 RNA level was measured using a commercial branched DNA assay (Quantiplex, version 3.0; Bayer).

Plasma HIV-2 RNA level was measured retrospectively in stored samples using EasyQ, version 1.1 (bioMérieux) [5]. This technique has proven to be a reliable measure of HIV-2 RNA level, with a detection limit of 50 copies/mL and a linear range of up to 10^6 copies/mL.

Drug-resistance mutations in HIV-2 were examined in the last 4 specimens. HIV-2 protease and reverse-transcriptase genetic regions were amplified using primers and conditions described elsewhere [4]. Amplicon products were analyzed using an automatic sequencer (Applied Biosystems). DNA sequences were analyzed, edited, and translated using the Sequence Navigator software, version 1.0.1 (Applied Biosystems). Encoded HIV-2 protein sequences were aligned and compared with HIV-2 wild-type consensus sequences obtained from GenBank. Primary and accessory drug-resistance mutations were examined on the basis of the latest International AIDS Society–USA guidelines [6]. HIV-2 subtyping was further characterized by phylogenetic analysis using these HIV-2 sequences.

Case report. This patient was an asymptomatic 44-year-old woman from Guinea Bissau in whom dual HIV-1–HIV-2 infection was diagnosed in November 2001. Her baseline CD4+ cell count was 112 cells/μL (CD4+ cell percentage, 7%), and her plasma HIV-1 RNA level was 3704 copies/mL. She initiated antiretroviral therapy 2 weeks after diagnosis; the regimen consisted of stavudine, lamivudine, and lopinavir boosted with ritonavir (LPV/r). The patient's immunological status improved, and the plasma HIV-1 RNA level decreased to less than the limit of detection within 8 weeks. It remained undetectable throughout the entire follow-up period (figure 1). During the 19 months after diagnosis, the CD4+ cell count increased to 592 cells/μL (CD4+ cell percentage, 16%). In July 2003, the patient was offered a simplified treatment regimen that consisted of stavudine, lamivudine, and efavirenz boosted with ritonavir (LPV/r). The patient's immunological status improved, and the plasma HIV-1 RNA level decreased to less than the limit of detection within 8 weeks. It remained undetectable throughout the entire follow-up period (figure 1). During the 19 months after diagnosis, the CD4+ cell count increased to 592 cells/μL (CD4+ cell percentage, 16%). In July 2003, the patient was offered a simplified treatment regimen that consisted of once-daily didanosine (250 mg), tenofovir (300 mg), and efavirenz (600 mg). Despite good adherence to her treatment regimen, the CD4+ cell counts began to steadily decrease, reaching 169 cells/μL in May 2004. Then, because of concerns...
Figure 1. Virological and immunological outcome in an HIV-1–HIV-2–coinfected individual receiving antiretroviral therapy. Genotypic changes with respect to wild-type HIV-2 reverse-transcriptase consensus sequence are shown in a box. HAART regimens are shown on top. Diamonds, plasma HIV-1 RNA level; squares, plasma HIV-2 RNA level; triangles, CD4+ T cell count. ATV, atazanavir; ddI, didanosine; d4T, stavudine; EFV, efavirenz; LPV/r, lopinavir boosted with ritonavir; TDF, tenofovir; 3TC, lamivudine.

about the deleterious interaction between didanosine and tenofovir [7], the former was replaced with lamivudine. No improvements in the CD4+ cell count were seen in the next few months, and treatment with LPV/r was resumed, replacing efavirenz. Three months later, the treatment regimen was changed again to lamivudine, atazanavir, and LPV/r; however, CD4+ cell counts remained low.

All treatment decisions made for this patient had been based on the virological assessment of HIV-1 RNA level using a commercial assay. However, information on plasma HIV-2 RNA level had been ignored. We retrospectively measured the plasma HIV-2 RNA level, using a new real-time nucleic acid sequence–based amplification (NASBA) method [5]. The HIV-2 load was 7433 copies/mL at the time of diagnosis and became undetectable after HAART initiation. The plasma HIV-2 load remained undetectable during the first 18 months of therapy. However, it began to increase in April 2003 (to 165 copies/mL), and in all subsequent samples, HIV-2 was detectable, at one point reaching a level of 6800 copies/mL (figure 1). The HIV-2 load decreased sharply (to 91 copies/mL) after introduction of lamivudine, atazanavir, and LPV/r, the patient’s last treatment regimen.

To prove that values provided using EasyQ specifically reflected the HIV-2 RNA level and not the HIV-1 RNA level, we used primers specific to HIV-2 and HIV-1 to amplify separately the pol genetic regions from each virus. The same extracted RNA was used for these differential experiments. The sample collected at diagnosis was positive for both HIV-1 and HIV-2. In contrast, the final follow-up samples yielded positive results only with the HIV-2–specific primers. Furthermore, DNA analysis of these samples revealed wild-type HIV-2 reverse-transcriptase sequences before the initiation of HAART and the appearance of the rtK65R and rtI118V mutations in the HIV-2 reverse transcriptase at month 23; no changes were observed in the HIV-2 protease. Finally, the phylogenetic analysis showed that this patient was infected with HIV-2 subtype A. (The GenBank accession numbers for the sequences generated in the study are AY940172, AY940173, and AY940174).

Discussion. There is little experience with the use of antiretroviral therapy for HIV-2 infection, and there is even less experience with using it to treat HIV-1–HIV-2 coinfection [8–10]. The care of individuals with either HIV-2 infection alone or dual infection has been hampered by the difficulty of measuring plasma HIV-2 loads. The lack of an approved test for determining the HIV-2 load has confined experimental tests to few research laboratories [11–13]. We have recently tested a new commercially available method [5] that was originally designed to measure a wide range of HIV variants for the quantitation of plasma HIV-2 RNA level. Very good results for detection of HIV-2 were obtained, with a wide dynamic range (from 50 to 10^6 copies/mL). Moreover, the method was equally effective at detecting HIV-2 subtypes A and B, which are the most prevalent worldwide [14].

In coinfected patients, it is generally believed that HIV-1 outcompetes the lower-replicating HIV-2 virus [15]. This assumption, along with the frequent reports of low viral loads in most studies that involve HIV-2–infected persons (compared with those that involve HIV-1–infected persons) [10–13, 15], has suggested that in vivo immunodeficiency must be driven mainly by HIV-1 in coinfected persons. Accordingly, treatment rules applied to HIV-1 infection may have been considered a priority in coinfected persons.

In the patient described here, the initial reduction and attainment of undetectable HIV-1 load, which was maintained
during the entire follow-up period, was complicated by immunological deterioration that began to occur after replacement of the protease inhibitor with efavirenz. Although it is quite effective against HIV-1, efavirenz is not active against HIV-2 [16]. Moreover, the weak genetic barrier of tenofovir-didanosine most likely explains the rapid selection of the rtK65R mutation in HIV-2. It is important to note that, in our patient, the rtK65R mutation appeared within 3 months after virological failure, even though the patient had a relatively low HIV-2 load. A recent report has highlighted the fact that this mutation could be selected more frequently in HIV-2 than in HIV-1 [17], as was previously described for the rtQ151M mutation [1, 4], which also compromises the antiviral efficacy of many nucleoside analogue inhibitors.

Finally, it should be highlighted that no resistance mutations developed in the HIV-2 protease in all tested samples obtained from our patient. However, the fact that wild-type HIV-2 protease already has amino acid substitutions that have been associated with either primary (proM46I) or secondary (proL10V, proV32I, proM36I, proA71V, or proG73A) resistance in HIV-1 raises the question of whether available HIV-1 protease inhibitors might have the same efficacy against HIV-2. Some reports have suggested that HIV-2 does not respond equally well to distinct protease inhibitors [1, 2, 18]. Changes noticed in the viral protease in our patient, as well as in others [19, 20], suggest that HIV-2 could be more prone to acquire multidrug resistance to available protease inhibitors. All of this information should be taken into consideration when deciding which antiretroviral regimens should be prescribed to HIV-2–infected patients. Our case further illustrates that, in HIV-1–HIV-2–coinfected individuals, both viruses should be taken into account when assessing treatment decisions and outcome. Drugs known to be active against HIV-2 should be given, and periodic measurement of HIV-2 loads must be performed.

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References