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Short communication

Clinical outcome in resistant HIV-2 infection treated with raltegravir and maraviroc

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ABSTRACT

Therapy for infection with HIV-2 remains limited. We report an HIV-2-infected patient in whom genotyping demonstrated PI, NRTI and NNRTI resistance, with a subsequent response to raltegravir- and maraviroc-based therapy. Further studies are required to assess the clinical efficacy of maraviroc in HIV-2 infection.

Around 1 to 2 million people are infected with HIV-2, mainly in West Africa. Compared to HIV-1, HIV-2 infection results in lower viral loads, and slower progression to AIDS (Leligdowicz and Rowland-Jones, 2008). Treatment options in these patients are complex, as available antiretroviral therapies have been developed for the treatment of HIV-1 and because there is a paucity of controlled trials for treatment of HIV-2 (Gottlieb et al., 2008). Mutations conferring both PI resistance (in particular V71I) and NRTI resistance (in particular M184 V) in HIV1 have been shown to develop under drug pressure in patients with HIV-2, however, it is not clear whether this leads to clinical resistance (Ruelle et al., 2008). Similar observations have been made in the French ANRS cohort (Matheron et al., 2006). Genotypic studies in HIV-2 patients treated with AZT have shown a low prevalence of selection for mutations such as K70R associated with resistance *in vivo* in HIV-1-infected individuals (Adjé-Touré et al., 2003). Furthermore *in vitro* studies have shown that wild type HIV-2 has comparable susceptibility to HIV-1 for AZT as well as other nucleoside analogues in culture (Smith et al., 2008). Treatment of HIV-2-infected individuals with lamivudine selects for M184 V (van der Ende et al., 2003).

The HIV-2 protease shares only 50% nucleotide sequence identity with the HIV-1 equivalent, although its structure shows high similarity especially at the active site (Ohtaka and Freire, 2005) HIV-2 displays a number of naturally occurring polymorphism associated with PI resistance in HIV-1 and has been shown to have a high propensity for the development of PI resistance *in vitro* (Gustchina and Weber, 1991; Ntemgwa et al., 2007) although the clinical significance of this has not been determined. Furthermore HIV-2 has intrinsic resistance to non-nucleoside reverse transcriptase inhibitors. This is because there are significant differences in the binding pocket structure of the viral RT (Ren et al., 2002). Consequently this drug class has minimal activity against HIV-2 *in vitro* (De Clercq, 1993).

As a consequence of the reduced activity of first line HIV-1 antiretroviral agents against HIV-2 both *in vitro* and *in vivo*, there is considerable interest in the utility of newer drug classes for the treatment of HIV-2. We describe the first reported use of the CCR5 inhibitor maraviroc as a component of antiretroviral salvage therapy for a man with progressive HIV-2 encephalitis. HIV-2 viral load estimation was performed by real time PCR with brome mosaic virus internal control. Genotypic resistance assays were performed using in-house RT-PCR and sequencing.

A 48 year-old heterosexual West African male with HIV-2 infection was referred to our centre in 2006 with advanced HIV-2 infection and treatment failure. He had initially commenced antiretroviral therapy in April 2005 after an episode of cerebral toxoplasmosis, with 3TC and TDF and LPV/r. His baseline CD4 count at that time was 16 cells mm^{-3} with an HIV-2 viral load of 38,000 copies ml^{-1}, however there was no virological response with this regimen. At 6 months therapy was changed to TDF, FTC SQV/r which resulted in an initial rise in CD4 from 16 cells mm^{-3} to 60 cells mm^{-3} over 6 months; however, his viral load remained high at 37,200–80,700 copies ml^{-1}. On referral in October 2006 he was switched to TDF, FTC and DRV/r (Figure 1). In January 2007 his

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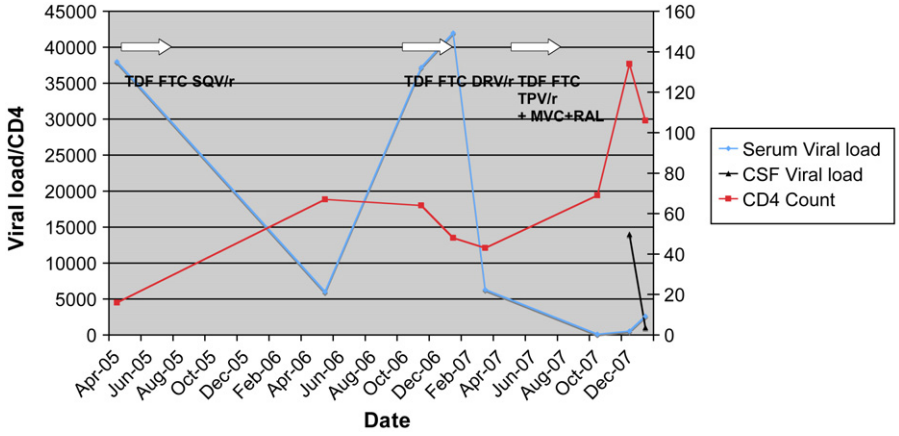

Fig. 1. Summary of response to antiretroviral therapy.
Viral load left-hand *Y*-axis expressed in copies mm^{-3}. CD4 cell count *Y*-axis right-hand side expressed in cells mm^{-3}. TDF tenofovir disoproxil fumarate, FTC emtricitabine, DRV darunavir, TPV tipranavir, MVC maraviroc, RAL raltegravir./r denotes ritonavir boosting.

HIV-2 viral load had fallen to 6000 from 80,700 copies ml^{-1}; however, his CD4 had also fallen to 48 cells ml^{-1} from 67 cells ml^{-1}. In addition he complained of weight loss and night sweats. HIV-2 genotype resistance testing demonstrated high-level resistance to NRTIs, NNRTIs and PIs, with the exception of intermediate resistance to tipranavir, and susceptibility to raltegravir (Table 1). On clinical review in April 2007 his CD4 count had fallen to 35 cells ml^{-3} and his viral load had risen to 42,000 copies ml^{-1}. At this stage he was noted to have cognitive impairment; MRI imaging demonstrated an encephalitic process affecting both cerebral hemispheres. CSF examination was negative for *Herpes* viridiae, JC and *Toxoplasma* PCR. A differential diagnosis of progressive multifocal HIV-2 leuko-encephalopathy was made.

In view of this patient's clinical progression and genotypic resistance profile, in September 2007 his regimen was changed to TDF, FTC, TPV/r, raltegravir and maraviroc salvage therapy. Over the next 2 months his serum viral load became undetectable and his CD4 count rose to 135 cells ml^{-3} by December 2007. However, his encephalopathy progress and repeated MRI showed increasing cerebral inflammation. In view of his neurological deterioration high dose steroids were commenced for possible immune reactivation inflammatory syndrome (IRIS) and repeat lumbar puncture and a paired CSF HIV-2 viral load estimation was performed. This demonstrated a CSF HIV-2 viral load of 14,100 copies ml^{-1} and a paired serum HIV-2 viral load of 530 copies ml^{-1}. To exclude development of CNS HIV-2 resistance secondary to impaired CNS drug penetration repeat paired serum and CSF HIV-2 viral load estimation and paired genotypic resistance assays were performed. These demonstrated a serum viral load of 1050 copies ml^{-1} and a CSF viral load of 2600 copies ml^{-1}. Paired genotypic resistance testing showed no significant differences between HIV-2 sequence in serum and CSF. Over the next 6 months his clinical condition stabilised; however, by August 2008 his viral load had increased to 73,740 and his CD4 count decreased to 97 cells mm^{-3}.

Table 1
Genotypic resistance assay on peripheral blood HIV-2 September 2007.

Nucleoside reverse transcriptase inhibitor polymorphisms	K65R, D67N, T69N, V118I, Q151M, M184V, L210N, T215S, K219E
Non-nucleoside reverse transcriptase inhibitor mutations	K101A, Y181L, Y188L, G190A, F227I
Protease resistance mutations	V32I, M46V, I47V, I50V, I54M, L76M, V82F, L90M, L10I, E35G, Q58E, A71L, G73A, L989V
Integrase resistance mutations	None

There have been recent cases demonstrating that raltegravir has utility as a part of salvage therapy for progressive HIV-2 infection (Garrett et al., 2008), however, this is the first published report of the use of maraviroc in this setting. The scientific rational for using integrase inhibitors to treat HIV-2 infection is evident since it has been shown *in vitro* that HIV-2 isolates have similar susceptibility to HIV-1 isolates as raltegravir and elvitegravir, despite 40% heterogeneity in integrase genes between the two viruses, and these drugs are generally well tolerated (Roquebert et al., 2008).

HIV-2 may use a wide range of coreceptors *in vitro* (Guillon et al., 1998; McKnight et al., 1998). HIV-2b may be tested for CCR5 or CXCR4 coreceptor use e.g. in U87-CD4 cell expressing appropriate coreceptors. It has recently been shown that progression of HIV-2 infection and CD4 cell depletion is strongly correlated with increased CCR5-expressing CD4 cells, and restriction of proviral DNA to memory-effector CD4 cells, thereby providing a rationale for the use of CCR5 inhibitors in this setting (Soares et al., 2006).

The progressive encephalitis reported here associated with an apparent failure to suppress viral replication in the CNS as determined by paired serum and CNS viral load estimation, could be due to viral escape mutations or poor CNS penetration of raltegravir and maraviroc. As we performed paired CSF and serum genotypic resistance assays, which demonstrated no significant difference in genotype at these sites, this suggests that apparent failure to control CNS replication was due to impaired CNS drug penetration rather than drug selection pressure.

Conflict of interest

None.

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