Correspondence

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HIV-1 escape in the central nervous system on elvitegravir-based antiretroviral therapy

Integrase inhibitors are increasingly used in combined antiretroviral therapy (ART) because of their high efficacy in inhibiting HIV replication and favourable tolerance profile. Elvitegravir is used with the pharmacokinetic enhancer cobicistat, associated with tenofovir and emtricitabine in a single-tablet regimen [1]. Very few data are available regarding the diffusion of elvitegravir in the central nervous system (CNS) [2,3]. Herein, we report a case of HIV-associated neurocognitive disorder (HAND) on elvitegravir-based treatment with virological escape in the CNS and the emergence of the elvitegravir-resistance mutation T66I in the cerebrospinal fluid (CSF).

A 45-year-old HIV-1 infected woman presented in September 2017 with rapidly progressive cognitive impairment and headache for a few weeks. Her HIV-1 subtype-B infection was discovered in 1993. She was negative for HBV and HCV. Her $CD4^+$ T cell count nadir was 130 cells/μl. She had a previous history of HIV encephalitis in 2014, following an 8-year interruption of ART. Her history of ART, viral load and drug-resistance mutation patterns is summarized in Fig. 1a. Since July 2016, she was successfully receiving tenofovir disoproxil fumarate [245 mg daily (q.d.)], emtricitabine (200 mg q.d.) and dolutegravir (50 mg q.d.), which had been switched in June 2017 to a single-tablet regimen of tenofovir alafenamide (10 mg q.d.), emtricitabine (200 mg q.d.) and cobicistat-boosted elvitegravir (150/150 mg q.d.). Plasma HIV-1 RNA was less than 1.3 log copies/ml at this time. She declared perfect adherence to treatment.

At admission in September 2017, HIV-1 RNA was 2.7 log copies/ml in plasma and 4.3 log copies/ml in CSF. CSF examination revealed 70 WBC/μl (all of whom were mononuclear cells), increased protein level of 96 mg/dl and normal glucose level of 2.87 mmol/l. All investigations looking for bacteria, mycobacteria, fungi and other viruses remained negative. Genotypic assessment of HIV-1 for drug resistance revealed M184 V mutation in the reverse transcriptase gene, both in blood and CSF. T66I mutation associated with resistance to elvitegravir was found in CSF. The integrase gene could not be amplified in blood samples due to low viral load. Phenotypic tropism assessment in blood and CSF revealed only CCR5-using viruses. Drug dosages by LC-MS/MS revealed tenofovir concentrations of 17 ng/ml in plasma (time, 24 h) and 2.77 ng/ml in CSF (time, 8 h); emtricitabine concentrations of 100 ng/ml in plasma (time, 24 h) and 140 ng/ml in CSF (time, 8 h); and elvitegravir of 540 ng/ml (total concentration) and 0.425 ng/ml (unbounded concentration, measure adapted from [4]) in plasma (time, 24 h), and 15.7 ng/mL (total concentration) in CSF (time, 8 h). Brain MRI was compatible with HIV-encephalitis (Fig. 1b). ART was changed in September 2017 to tenofovir disoproxil fumarate (245 mg q.d.), emtricitabine (200 mg q.d.), ritonavir-boosted darunavir [600/100 mg twice daily (b.i.d.)] and maraviroc (300 mg b.i.d.). Zidovudine (300 mg b.i.d.) was added in January 2018 because of incomplete virological control in CSF (HIV-1 RNA of 2.86 log copies/mL in CSF vs. 1.75 log copies/ml in plasma). In April 2018, both plasma and CSF HIV-1 RNA were less than 1.47 log copies/ml. All neurological symptoms progressively disappeared.

Herein, we report the first case of virological escape in the CNS on elvitegravir-based treatment associated with clinical HAND and the selection of T66I elvitegravir-resistance mutation in the CSF. Some factors could have contributed to this escape: this participant probably harboured HIV-1 strains with particular neurotropism, as she already had a past history of HIV-encephalitis; pre-existing M184 V emtricitabine-resistance mutation impaired the potency of the antiretroviral regimen. Virological escape in the CNS occurred 3 months after switching the integrase inhibitor from dolutegravir to elvitegravir, suggesting lower diffusion in the CNS and/or weaker virological potency of elvitegravir than dolutegravir in this case.

Trough plasma total concentrations of antiretroviral drugs were adequate [5]. Total concentration (Ct) measured during therapeutic drug monitoring usually represents a good substitute for unbound concentration (Cu). Through its ability to cross cell membranes to achieve pharmacodynamic activity, the Cu is considered as the pharmacologically active form [6]. In our case, high level of CSF-protein may have led to an increase in elvitegravir-bound concentration and therefore in the Ct, without modification of Cu. At equilibrium, Cu in the CSF is less than or equal to plasma Cu. Hence, on the basis of plasma Cu, it may be assumed that the Cu in the CSF was lower than the elvitegravir IC50 (3.9 ng/ml) [7]. This low exposure could explain the compartmentalized virological failure with emergence of elvitegravir-resistance mutation. The risk of virological escape in the CNS on elvitegravir-based regimen should be further

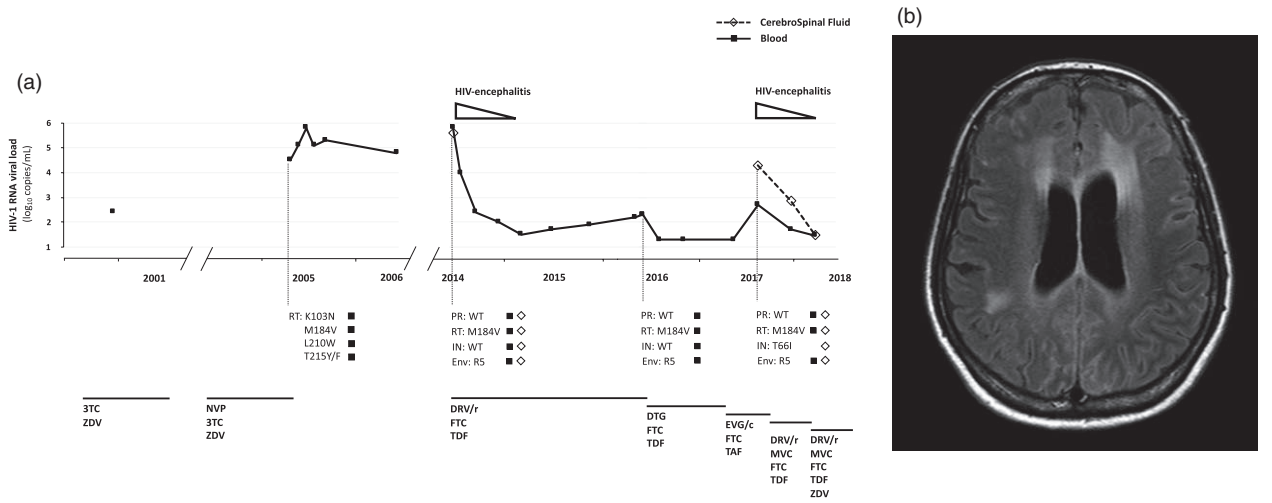

Fig. 1. (a) HIV-infection course. (b) Brain MRI. Axial brain MRI with contrast-enhanced FLAIR sequence in September 2017 showing mild cerebral atrophy and periventricular white matter lesions compatible with HIV-encephalitis, and leptomeningeal enhancement associated with meningitis. 3TC, lamivudine; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; *Env*, envelope gene; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; *IN*, integrase gene; MVC, maraviroc; NVP, nevirapine; *PR*, protease gene; R5, CCR5-using viruses; *RT*, reverse transcriptase gene; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; WT, wild-type; ZDV, zidovudine. Black square, measure in peripheral blood; open diamond, measure in CSF.

estimated, in an era in which integrase inhibitors are becoming the main third agent of combined ART.

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Conflicts of interest

There are no conflicts of interest.

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