A Case of Cerebrospinal Fluid Viral Escape on a Dual Antiretroviral Regimen: Worth the Risk?

To the Editor—Among human immunodeficiency virus (HIV)-infected patients on antiretroviral therapy (ART), incomplete viral suppression in cerebrospinal fluid (CSF) may occur even with undetectable plasma viremia [1–4]. Treatment simplification with "less-drug regimens" may favor adherence and reduce toxicity, but raises concerns on lower central nervous system (CNS) drug penetration and subsequent CNS viral escape [5, 6], as in the case we report herein.

A 47-year-old HIV-infected woman, receiving different ART regimens since 2002, in 2007 withdrew emtricitabine due to lower-limb neuropathy, and maintained plasma viral control with darunavir/ritonavir 600/100 mg twice daily and tenofovir (in February 2013: HIV RNA <40 copies/mL; CD4 lymphocyte count, 508 cells/μL). In March 2013, she was hospitalized after complaining of lower-limb weakness and pain, headache, dizziness, and dysarthria. Brain magnetic resonance imaging (MRI) showed extensive signal abnormalities (Figure 1*A*); lumbar puncture revealed CSF total protein of 76 mg/dL with oligoclonal immunoglobulin G bands, normal glycorrhachia, and cell count. CSF cultures and examinations for opportunistic infections (*Cryptococcus neoformans*, Epstein-Barr virus, cytomegalovirus, human herpesvirus 8, JC virus) were negative, and the CSF HIV RNA load was 2715 copies/mL. Genotypic testing showed the presence of multiple protease inhibitor (PI)–associated mutations (V32I, I54V, V82A, I84V, L10I, L33F, K20R, M36I) conferring intermediate resistance to darunavir, and nucleoside/nucleotide reverse transcriptase inhibitor–associated mutations (M41L, T215Y, V90I), conferring intermediate resistance to tenofovir. Thus, antiretroviral treatment was changed with darunavir/ritonavir 600/100 mg twice daily plus raltegravir 400 mg twice daily plus etravirine 200 mg twice daily. Two months later, the patient reported significant symptom improvements: the CD4 count was 759 cells/μL; both plasma and CSF HIV RNA were undetectable. One year later, brain MRI showed clear improvements in radiological signs (Figure 1*B*).

To our knowledge for the first time, here we describe a case of CSF viral escape in an HIV-infected patient on suppressive ART with a dual regimen. Previous cases of CSF viral escape (with or without neurological symptoms) were reported in patients with incomplete plasma HIV RNA suppression, or treated with suboptimal ART [1, 2]. Compared to others, this case clearly illustrates the improvements of neurological symptoms and radiological signs (Figure 1*A* and 1*B*) after switching ART, guided by genotypic resistance testing on CSF. Recently, a higher CNS penetration effectiveness ranking score of ART has been associated with lower levels of CSF HIV RNA, as well as improvements in neurological and cognitive functions [7, 8]. Meanwhile, new therapeutic schemes have been proposed for patients on suppressive therapy to reduce toxicity and costs, such as switching to dual regimens or to boosted PI monotherapy [5, 9]. These approaches may, however, be limited by lower CNS drug penetration, potentially leading to CSF viral escape (already described with boosted PI monotherapy) [5, 6]. In this report, the results of HIV genotyping in CSF suggest a CNS virus compartmentalization, with subsequent selection of

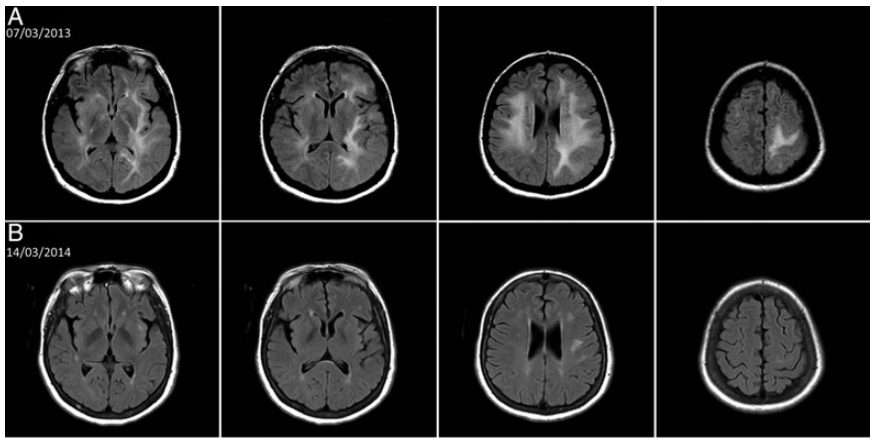

Figure 1. Brain MRI images before (*A*) and 48 weeks after (*B*) combination antiretroviral therapy switch. *A*, Axial brain magnetic resonance imaging (MRI) demonstrating extensive signal abnormalities in the white matter of the cerebral hemispheres and in both the middle cerebellar peduncles. *B*, Axial brain MRI showing absence of alterations in the cerebral peduncles and a reduction of the areas of altered signal in the cerebral white matter with the persistence of small areas of lesion.

resistant variants replicating intrathecally. Notably, significant clinical and radiological improvements were obtained by ART optimization and consequent viral suppression in CSF.

Caution is needed with simplification strategies, especially when treating people with a long ART history and previous neurological events; CSF viral escape should be ruled out in HIV-infected patients with suppressed plasma viremia presenting with neurological symptoms.

Notes

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Davide Mangioni,[1] Antonio Muscatello,[1] Francesca Sabbatini,[1] Alessandro Soria,[1] Marianna Rossi,[1] Luca Bisi,[1] Nicola Squillace,[1] Carlo De Grandi,[2] Andrea Gori,[1] and Alessandra Bandera[1]

Divisions of [1]Infectious Diseases, Department of Internal Medicine, and [2]Neuroradiology, Department of Diagnostic Radiology, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy

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Correspondence: Davide Mangioni, MD, Division of Infectious Diseases, Department of Internal Medicine, San Gerardo Hospital, 20900 Monza, Italy (d.mangioni@campus.unimib.it).

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