APOBEC-Induced Mutations at Initiation of Cabotegravir + Rilpivirine for Two Patients Infected by HIV-1 Subtype CRF02: The Interest of Systematic Genotyping

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To the Editors:

More than 37 million people worldwide live with HIV.[1] With no effective vaccine available, controlling this pandemic still depends on antiretroviral therapy (ART). However, the need for daily and lifelong treatment exposes patients to noncompliance and treatment failure.[2] The results of the FLAIR, ATLAS, and ATLAS-2M studies demonstrating the noninferiority of switching from a conventional triple therapy to the long-acting injectable dual therapy cabotegravir + rilpivirine (CAB + RPV) opened a new era in antiretroviral therapy.[3,4] However, perfect treatment adherence is essential.[5,6] Any subtherapeutic serum concentration resulting from missed doses or discontinuation of injections risks the emergence of mutations and possibly resistance to one or both classes.[5–8] Therefore, strict recommendations limit the dual therapy CAB + RPV to adults infected by HIV-1 on a stable antiretroviral therapy for at least 6 months with no evidence of resistance and no history of virological failure with agents of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase strand transfer inhibitor (INSTI) class.[5,6]

The discovery in 2 of our patients of G140R and M230I mutations on genotyping before the switch calls for greater reflection on the value of systematic genotyping, on the one hand, and the practical measures to be adopted when genotyping reveals APOBEC-induced (apolipoprotein B mRNA editing enzyme and catalytic polypeptide-like) mutations, on the other hand. APOBEC-induced mutations consist of deleterious C-to-U mutations on HIV-DNA induced by the host APOBEC cytosine deaminases.[9] In both patients, we used Sanger sequencing for the reverse transcriptase (RT), protease (PR), and integrase (INT) regions in RNA and DNA, according to the Agence Nationale de Recherche sur le SIDA et les Maladies Infectieuses Emergentes (ANRS-MIE).

The first patient, aged 53, was diagnosed HIV-1 positive in 2008 with a viral load (VL) before treatment of 53,735 copies/mL (4.7 log) and a CD4 count of 202/mm^3 (17%). No pretreatment genotyping was performed. He was treated with tenofovir (TDF), lamivudine (3 TC), and efavirenz (EFV) between July 2009 and March 2014 then with TDF, emtricitabine (FTC), and RPV until May 2018 due to neuropsychological disorders attributed to Efavirenz; since 2019, he has been treated with tenofovir alafenamide (TAF), FTC, and RPV with an undetectable viral load since 2010 and an average CD4 rate of 454 cell/mm^3. Wanting to switch to an injectable dual therapy, the DNA genotyping performed at M156 of follow-up identified a CRF02 (AG) subtype carrying the G140R mutation in the integrase gene. The second patient was 19 years old and has been HIV-1 positive since 2017 with an initial VL of 63,160 copies/mL and a CD4 count of 176/mm^3. The pretherapeutic plasma RNA genotyping detected no resistance mutations. He has been treated with elvitegravir–cobicistat (EVG/c), FTC, and TAF combination therapy with an undetectable viral load since May 2019. The DNA genotyping test reperformed before switching to dual therapy revealed the G140R and M230I mutations on the integrase and reverse transcriptase genes, respectively. One of the limitations of DNA genotyping is the lack of knowledge of the interpretation of APOBEC mutations. Some of them are also mutations involved in resistance to CAB (G118R, E138K, G140R/S, and R263K) and RPV (E138K and M230I).[6,9] Both the G140R and M230I mutations detected in our patients are also APOBEC-induced mutations.[6,9–11] Only comparative analysis between the pretreatment genotyping and that performed before the switch can differentiate it from the APOBEC context and ensure an accurate management. Hence, the absence of the M230I mutation in the pretreatment genotyping for our second patient and its emergence on the preswitch genotyping with no prior exposure to NNRTIs suggest an APOBEC-induced mutation. This should intuitively not contraindicate RPV. However, the emergence of G140R after exposure to INSTIs (EVG) in the same patient raises additional concerns of a treatment-induced mutation. As for the first patient, due to lack of pretreatment genotyping, the G140R identified in the preswitch genotyping cannot, therefore, be formally associated solely with the APOBEC context. In view of the above, we refrained from introducing the dual therapy.

Knowing the key central position that integrase inhibitors play in the current antiretroviral treatment strategy,[12] in our opinion, it is important to perform at least one DNA genotyping (to be compared to previous ones) for patients eligible for dual injectable therapy to prevent therapeutic failure. However, the DNA genotyping remains a tool to be handled with caution because of its limitations. The ideal remains the cumulated RNA genotypes, collected throughout the therapeutic follow-up.

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