



**HAL**  
open science

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

Bruce Shinga Wembulua, Nadia Valin, Sidonie Lambert-Niclot, Estelle Nerozzi-Banfi, Thibault Chiarabini, Jean Luc Meynard, Karine Lacombe

## **► To cite this version:**

Bruce Shinga Wembulua, Nadia Valin, Sidonie Lambert-Niclot, Estelle Nerozzi-Banfi, Thibault Chiarabini, et al.. APOBEC-Induced Mutations at Initiation of Cabotegravir + Rilpivirine for Two Patients Infected by HIV-1 Subtype CRF02: The Interest of Systematic Genotyping. *Journal of Acquired Immune Deficiency Syndromes - JAIDS*, 2023, 92 (3), pp.e17-e18. 10.1097/QAI.0000000000003148 . hal-04086754

**HAL Id: hal-04086754**

**<https://hal.sorbonne-universite.fr/hal-04086754>**

Submitted on 7 Sep 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

### To the Editors:

More than 37 million people worldwide live with HIV.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> However, perfect treatment adherence is essential.<sup>5,6</sup> 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.<sup>5-8</sup> 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.<sup>5,6</sup>

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.<sup>9</sup> 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<sup>3</sup> (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<sup>3</sup>. 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<sup>3</sup>. The pretherapeutic plasma RNA genotyping detected no resistance mutations. He has been treated with elvitegravir-cobicistat (EVC), 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).<sup>6,9</sup> Both the G140R and M230I mutations detected in our patients are also APOBEC-induced mutations.<sup>6,9-11</sup> 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 (EVC) 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,<sup>12</sup> 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.

**Bruce Shinga Wembulua, MMed<sup>a</sup>**  
**Nadia Valin, MMed<sup>a</sup>**  
**Sidonie Lambert-Niclot, PhD<sup>b</sup>**  
**Estelle Nerozzi-Banfi, MD<sup>a</sup>**  
**Thibault Chiarabini, MMed<sup>a</sup>**  
**Jean Luc Meynard, MMed<sup>a</sup>**  
**Karine Lacombe, MMed<sup>a,b</sup>**

<sup>a</sup>Department of Infectious and Tropical Diseases, Saint Antoine Hospital, Paris Cedex, France

<sup>b</sup>Sorbonne Université, Pierre Louis Institute of Public Health, Paris Cedex, France

<sup>c</sup>Institute of Medicine and Applied Epidemiology, Paris, France

### REFERENCES

- UNAIDS. *UNAIDS Global AIDS Update 2021 - Confronting Inequalities - Lessons for Pandemic Responses from 40 Years of AIDS (reliefweb.int)*; 2021.
- Benson C, Wang X, Dunn KJ, et al. Antiretroviral adherence, drug resistance, and the impact of

The authors have no funding or conflicts of interest to disclose.

- social determinants of health in HIV-1 patients in the US. *AIDS Behav.* 2020;24:3562–3573.
3. Rizzardini G, Overton ET, Orkin C, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR trials. *J Acquir Immune Defic Syndr.* 2020;85:498–506.
  4. Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet.* 2021;396:1994–2005.
  5. HAS. *Avis de la commission de la transparence Rekambys 900mg du 21 avril 2021.* Available at: <https://www.hassante.fr/upload/docs/evamed/CT18976Planning%20CT%20fin%202020-2021.pdf>. Accessed April 10, 2022.
  6. European Medicines Agency. *Vocabria, INN-Cabotegravir: Summary of Product Characteristics.* Available at: <https://www.ema.europa.eu/en/documents/productinformation/vocabria-epar-product-informationfr.pdf>. Accessed April 10, 2022.
  7. Charpentier C, Peytavin G, Cuzin L, et al. Les inhibiteurs de l'intégrase in Katlama C., Jade. *VIIH, Hépatites virales et Santé sexuelle.* Paris: EDP Sciences; 2020:308–318.
  8. Ndashimye E, Li Y, Reyes PS, et al. High-level resistance to bictegravir and cabotegravir in subtype A- and D-infected HIV-1 patients failing raltegravir with multiple resistance mutations. *J Antimicrob Chemother.* 2021;76:2965–2974.
  9. Stanford university HIV drug resistance database. *HIV-1 Signature APOBEC Mutations.* Available at: <https://hivdb.stanford.edu/page/apobec/>; 2021. Accessed May 05, 2022.
  10. *Stanford University HIV Drug Resistance Database: NNRTI Resistance Comments.* Available at: <https://hivdb.stanford.edu/dr-summary/comments/NNRTI/>. Accessed May 05, 2022.
  11. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. Update of the drug resistance mutations in HIV-1. *Top Antivir Med.* 2019;27:111–121.
  12. *WHO. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach July 2021.* Available at: <https://www.who.int/publications/item/9789240031593>. Accessed June 01, 2022.