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Commentary

Dolutegravir plus lamivudine for hiv treatment: Does the historical genotype really matter?

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The paradigm of antiretroviral therapy shifted in the last few years from the "mantra" of triple therapy to the possibility of using two-drug combination initially as maintenance strategies [1], and in fact as first-line regimens [2]. The possibility of such a shift was allowed by the availability of compounds with a high genetic barrier to resistance as "core agents", protease inhibitors, and the second-generation integrase inhibitor dolutegravir. This strategy looks at the avoidance of untoward long-term effects related to the exposure of antiretrovirals with regards to nucleos(t)ide reverse transcriptase inhibitors with potential metabolic [3], bone and renal toxicities [4]. Nevertheless, for a relevant percentage of patients, the possibility to switch to regimens composed of fewer drugs is challenged by the presence of archived genotypic mutations in their historical genotype.

In the recent article published in *EBioMedicine*, De Miguel and co-workers assessed the switch to dolutegravir plus lamivudine in patients without previous exposure to integrase inhibitors with and without previously acquired lamivudine resistance [5]. The study addresses a topic that continues to challenge physicians involved in the treatment of people living with HIV. In particular, the possibility of switching patients with a lamivudine containing dual regimen with and without previously archived lamivudine resistance in the historical RNA genotype. The authors selected only patients without a lamivudine resistance detectable at the time of the switch in the proviral DNA by Sanger sequencing. The authors concluded that dolutegravir plus lamivudine was effective in maintaining virological suppression despite the presence of lamivudine resistance mutations in the historical genotype and the presence of archived mutations assessed by next-generation sequencing.

Some limitations related to the pilot-study design warrant a mention. First, the small study population warrants us to interpret the findings with caution. The probability of virological failure at 48 weeks, which was the primary and endpoint is not a frequent event in patients who switch under virological control. The limited sample size may have influenced the results toward showing no difference between the groups. Second, the convenience sample from patients enrolled in a previous study (GEN-PRO [6]) could have introduced a selection bias by enrolling patients with a good adherence to antiretrovirals and with higher probability of treatment success. Third, the use of proviral DNA to guide clinical decision to change an antiretroviral regimen could be questionable. This strategy may not be feasible for the majority of clinical centers that manage people living with HIV including some high income countries, especially when we consider the use of next-generation sequencing. On one hand, the assumption that a negative detection of resistance at the time of the switch in the proviral DNA correlate with the time of viral suppression before the switch may sound reasonable, but on the other side, it may be questionable due to the possible presence of archived mutations not detected by the test or the fading away of latently infected cells. Nonetheless, the increased sensitivity provided by a next-generation sequencing facilitates more informed decision making to make the therapeutic switch is still a matter of debate. The findings of the present study confirm that there is no difference in virological failure in those with and without lamivudine resistance detected by next-generation sequencing [7].

Data from observational studies suggest that the time of viral suppression before the switch in patients under virological control with previous NRTIs resistance could be one of the most important factors in determining the risk of virological failure [8]. The study by De Miguel et al. underlines that patients with previous lamivudine resistance had a longer duration of viral suppression before the switch compared to those without lamivudine resistance (7.7 years vs 5.3 years) [5]. Thus, the prolonged viral suppression in patients with archived lamivudine resistance could have increased the probability of virological success when compared to those without resistance.

We also have to consider the growing evidence that NRTIs can contribute to treatment success in the presence of previous resistance, in the reverse transcriptase or other enzymes, when combined with a high-genetic-barrier anchor drug. While this effect could be

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class- or drug-specific, M184V/I data suggest that the duration of virological suppression has a critical role in decreasing the amount of previously resistant variants below a clinically relevant threshold.

Although these findings are preliminary, after combining them with those coming from observational studies [9, 10] we can suggest the possibility to simplify patients who have archived in their historical genotype lamivudine resistance to dolutegravir plus lamivudine as a maintenance regimen.

Declaration of competing interests

AG was a paid consultant for Mylan. SR received research grants to his Institution from ViiV Healthcare, Gilead Sciences and Janssen, outside the submitted work; he was also a paid consultant for ViiV Healthcare, Gilead Sciences, Merck Sharp and Dohme, Bristol-Myers Squibb, Janssen and Mylan. FC has nothing to declare.

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