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EDITORIAL COMMENTARY

Antiretroviral Monotherapy for HIV: Game Over or Future Perspectives?

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(See the Major Articles by Bruan et al on pages 1489-97 and by Hocqueloux et al on pages 1498-505.)

When dolutegravir (DTG) based combination antiretroviral therapy (cART) received approval for the treatment of patients infected with human immunodeficiency virus type 1 (HIV-1) in 2013 (United States) and 2014 (Europe), the evaluation of DTG monotherapy as a maintenance treatment strategy made sense. Indeed, in none of the treatment-naive patients with virological failure in the DTG registration trials, genotypic resistance had been detected [1–4]. Also, during a phase 2 study of 10 days of DTG monotherapy, the plasma viral load of 7 of 10 patients decreased to below 50 c/mL [5]. Furthermore, at that time, the benefits of DTG as maintenance monotherapy could be substantial as tenofovir and abacavir related side effects could be bypassed, not to mention the potential cost savings. Unfortunately, DTG as maintenance monotherapy eventually bit the dust when it was given to patients who had initiated cART during the chronic phase of their human immunodeficiency virus (HIV) infection. Indeed, in 3 prospective clinical trials including a total of 208 patients, a switch to DTG monotherapy seemed to work in the short term but was clearly inferior to cART in the long term. Viral rebounds were observed despite excellent compliance and adequate DTG serum levels in 19 of the 208 patients, and although high-level DTG resistance was not observed, low- (n = 6) and intermediate-level (n = 2) resistance in integrase was documented [6–10]. In a recent meta-analysis that also included published case series, the 48-week virological failure rate of DTG monotherapy was 9% but was 0.7% in those switching to DTG based duo-therapy (adjusted odds ratio 0.1, 95% confidence interval 0.03–0.3) [11]. In the MONotherapy of TiviCAY (MONCAY) study published in this issue of Clin Inf Dis as well as in the DOlutegravir MONOtherapy (DOMONO) study, the risk of viral rebound during monotherapy was found to be higher in patients with a lower CD4 nadir and a higher HIV-DNA measurement. Both parameters indicate a more progressed disease state with a larger HIV reservoir. In addition, the large variation in the time to virologic failure observed during DTG monotherapy suggested that stochastic reactivation of a preexisting provirus containing a single INSTI-RAM may be the mechanism for breakthrough viremia. Taken together, these observations indicate that there may be a subgroup of HIV-1 infected patients that could be treated successfully with maintenance monotherapy—those with a smaller, less genetically diverse HIV reservoir. In the year 2019, the only way that the HIV reservoir size and its genetic diversity can be contained is by initiating cART during the acute phase of an HIV infection.

During this evolving knowledge on the effectivity of DTG monotherapy, the Swiss study on DTG as maintenance monotherapy was ongoing, and the results are published in this issue of *Clinical Infectious Diseases* [12]. In the study that they called *EARLY-SIMPLIFY*, Braun and colleagues postulated that the smaller genetic diversity and the smaller size of the HIV reservoir in patients who started cART during the acute phase of their HIV infection may allow for less intensive maintenance antiretroviral therapy. As such, they included patients from the Zurich Primary HIV Infection Study who all started cART within 180 days after their estimated date of infection [13]. To safeguard future treatment options, patients were monitored closely for virological failure and those with any form of treatment failure or documented genotypic resistance in the past were excluded. Furthermore, cerebrospinal fluid sampling was performed in a subset of patients to look for viral escape in the central nervous system. In sum, 101 patients were randomized, of which 68 switched to DTG monotherapy. One year after these 68 patients had switched to DTG monotherapy, the plasma viral load had remained <50 c/mL in all but 1 patient. Further information and analysis of this patient strongly suggested that this patient actually started cART during a chronic rather than an acute HIV infection. The lack of virological failures in this study is in sharp contrast with the rates of virological failure described above when used in patients who had

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Table 1. Proposed Set of Rules to Be Followed in Future Studies on Antiretroviral Maintenance Monotherapy

1. First limit the study population to patients with a high CD4 nadir (>200–350/mL) and a low viral load zenith (<100.000/mL) or patients that started cART during a primary HIV infection.
2. Monitor plasma viral load at least at 2, 4, 8, 12, 18, 24, 36, and 48 weeks.
3. Limit study population to patients with all antiretroviral classes available as treatment options.
4. Limit study population to patients that are virologically suppressed for >12 months.
5. Limit study population to patients that have shown optimal cART compliance in the past.
6. Inform patients that undetectable = uninfectious does not apply to them during the trial.
7. Inform patients that they may lose the entire drug class that is being studied.
8. Reassess patients' willingness to continue the trial when new insights become available.
9. Provide a biologically plausible hypothesis why the drug to be studied as monotherapy could work in the particular patient population (eg, very high genetic barrier against the development of resistance to the drug).

Abbreviations: cART, combination antiretroviral therapy; HIV, human immunodeficiency virus.

started cART during the chronic phase of their HIV infection. Several hypotheses might account for this observation. As mentioned above, the smaller genetic diversity of HIV in the patients included in the Swiss study may be one of the explanations. Indeed, if virological failure during monotherapy is the consequence of stochastic reactivation of a replication competent virus that harbors a mutation in integrase that makes the virus less susceptible to DTG, the chances of failure will be substantially less if the genetic diversity in the patient is smaller. However, whether or not a smaller reservoir size is the key to success remains uncertain and is a question that cannot easily be answered. Indeed, only the replication competent part of the reservoir is relevant here. Therefore, additional analyses on the proportion of HIV-DNA positive peripheral blood mononuclear cells (PBMC) carrying replication competent virus would provide the necessary insights. Meanwhile, when looking at the copy number of the median total HIV-DNA in PBMC as reported in the Swiss study, it was very comparable to what was observed in the DOMONO study (2.25 vs 2.19 copies/10e6 PBMC) [14]. It is therefore unlikely that a relatively simple HIV-DNA measurement alone would be able to predict if a maintenance monotherapy strategy will work. Apart from viral factors, a more preserved immune system with less exhausted anti-HIV immune responses of the patients in the current study could be an important explanatory factor for the success of DTG monotherapy as well.

Although the study by Braun and colleagues suggests that a subgroup of patients might exist for which simplification to DTG monotherapy works, the study should only be considered a first proof of concept. Also, given the fact that most of the failures during DTG monotherapy in the other studies were observed after week 24, a longer follow-up is needed before more definite conclusions can be drawn.

Where do we go from here with DTG or other future monotherapy studies? Despite the results from the *EARLY-SIMPLIFY* study, DTG as maintenance monotherapy should no longer be considered a treatment option for patients outside or even inside the context of a clinical trial. The only exception may be in a specific subset of patients as studied in *EARLY-SIMPLIFY* or patients with favorable reservoir and host characteristics that we must first gain a further understanding on. Also, although this may seem obvious, giving monotherapy to patients while other treatment options exist is only acceptable after ethics committee approval. The patient should be informed about the worst-case scenario that may follow study participation, which is losing the entire drug class under study. Although the idea of losing an entire drug class may frighten physicians, during the informed consent process of the DOMONO study we learned that patients on a suppressive cART regimen were often willing to accept a small risk of losing a drug class given that all the DOMONO patients had all other antiretroviral drug classes as potential future treatment options available. We therefore think that studies on monotherapy remain acceptable from an ethical point of view provided that the drug has a (very) high genetic barrier against the development of resistance and that a stringent set of common-sense rules are followed to protect the patient's safety (Table 1). This is illustrated by the fact that all 10 patients who developed virological failure during the DOMONO study became and have remained virologically resuppressed soon after they restarted their preceding cART regimen. Also, none of the 100 DOMONO patients have told us that they regretted their study participation. Instead, many of them have repeatedly mentioned how sad it was that the DTG monotherapy failed, and they would be happy to participate in future studies. However, as physicians and researchers, primum non nocere should prevail over these understandable sentiments.

Note

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