

## Commentary

# Dolutegravir monotherapy: when should clinical practice be clinical research?

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In this issue of *Antiviral Therapy*, Oldenbuettel *et al.* [1] report the results of a retrospective study conducted at a single centre in Munich in which 31 HIV-infected patients whose viral loads were suppressed on standard antiretroviral therapy (ART) were switched to monotherapy with the integrase inhibitor, dolutegravir. At 24 weeks, efficacy was 94% by intention-to-treat analysis. One patient chose to discontinue monotherapy despite virological suppression; another experienced virological failure with emergence of two integrase mutations (Q148H and G140S).

Before discussing the potential clinical implications of the findings, it is important to address the ethical issues associated with the study as reported. The authors state that patients were switched to dolutegravir monotherapy based on the 'clinical judgement of the treating physician' and that ethics committee approval and informed consent were obtained only for the purpose of the retrospective analysis. However, since dolutegravir monotherapy is a virtually untested treatment approach not recommended in current European or US ART guidelines, it is surprising that 31 patients could be identified at a single centre who were treated in this way as part of standard clinical care. Reasons for switching are discussed, but none of them seem to require the use of dolutegravir monotherapy. For example, gastrointestinal side effects, nephrotoxicity and drug interactions are mentioned, but these are commonly encountered in clinical practice and can be addressed by switching to other standard multi-agent regimens. Similarly, lipodystrophy and anaemia are mentioned, but they are not recognized toxicities of any of the currently recommended antiretroviral agents. As such, the clinical rationale for making a switch to monotherapy is unclear. What motivated these decisions? How were the potential benefits and risks to individual patients balanced? Were specific medication changes discussed with colleagues who had HIV expertise? How were patients engaged in making a

decision to be treated with an unproven and non-standard single drug regimen? Were they made aware of the risks? Was there explicit informed consent for this clinical choice? The answers to these important questions are not found in the paper.

Although the study is described as retrospective, the authors refer to the '24-week study period' and Table 1 presents data collected at weeks 4, 12 and 24. Laboratory testing included gamma-glutamyl transferase (GGT), CD8 count and CD4/CD8 ratio, and lipid panels, tests that would not necessarily be ordered in routine clinical practice in all patients within a 24-week period, at least in most US clinics. The unusual regimen and the precision of laboratory monitoring raise the question of whether this study was what might be called a 'pre-planned retrospective analysis', in which patients were switched to an investigational regimen presumably as part of standard medical care but with plans for analysing the data retrospectively. Obtaining ethics approval and consent after the fact for the purpose of analysing and reporting previously collected data certainly simplifies the ethics approval process, which would otherwise include prospective evaluation of the risks and benefits of the proposed intervention and the requirement for a formal informed consent process. However, avoiding these protections for interventions that ought to be reviewed in advance is ethically problematic. While there can be confusion over what constitutes clinical practice versus research, using dolutegravir monotherapy and systematically evaluating it is clearly research. While physicians are generally free to prescribe drugs for off-label indications or to use non-recommended regimens in routine practice when it is deemed clinically appropriate, this is not the case for research, in which patients must be prospectively informed of the experimental nature of the therapy, of the risks and benefits of that therapy, and of the fact that the primary purpose of the proposed intervention

and monitoring are for research and not necessarily their individual benefit.

The authors cite three other studies of dolutegravir monotherapy, one from Spain [2] and two from France [3,4]. All three are small, single-centre, retrospective or observational studies. When originally presented, the Spanish study by Rojas *et al.* [5], involving 33 patients, was described as a ‘24-week pilot study’ with specific and timed laboratory studies and inclusion criteria. However, in the published paper, it was described as a retrospective, non-interventional study for which ethics committee approval was not required. The French Katlama study [3], involving 28 patients, does not mention ethics committee approval but states that all patients were informed and gave consent to ART modification. The French Gubavu study [4], involving 21 patients, does not mention ethics committee approval or consent.

In sharp contrast to these reports of retrospective monotherapy data, there was a carefully designed and conducted Argentine study (PADDLE) [6] in which 20 treatment-naïve patients with baseline HIV RNA <100,000 copies/ml were prospectively treated with a two-drug combination of dolutegravir and lamivudine. Results from that early pilot trial have been promising enough that two larger scale trials are now in progress in the US. Since lamivudine is a generic drug with virtually no toxicity, it seems more appropriate to study the two-drug combination before prematurely jumping to monotherapy. It should also be noted that in all four of the reports of monotherapy studies, patients would have been switched to dolutegravir monotherapy before the first presentation of the dolutegravir/lamivudine data in October 2015 [7].

As stated above, physicians are not bound to follow treatment indications or guidelines when caring for patients. However, when their practice departs from the standard of care, it should be for sound reasons that they can articulate and justify to their peers and patients, especially when the therapy being prescribed is as untested and even as ‘radical’ as dolutegravir monotherapy. In research, the standards for oversight and informed consent are far higher. There is nothing wrong with reporting retrospective or observational data, which can often serve as a stimulus for future prospective clinical trials, but it is important that these studies be truly retrospective or observational. The monotherapy studies to date raise two questions. First, if dolutegravir monotherapy is really being prescribed routinely in some centres, what is the evidence base for that clinical approach, and to what degree do patients understand that it is not a standard-of-care regimen? Second, are patients being placed on experimental regimens primarily for research purposes without being adequately informed of the experimental nature of their therapy and of their participation in research?

As for dolutegravir monotherapy, four small studies have now demonstrated virological failure with the emergence of new integrase resistance in 5 (4.4%) of 113 patients. In contrast, no integrase resistance has been reported in any of the much larger cohorts and trials of patients taking dolutegravir in combinations with other agents. Furthermore, the approval of tenofovir alafenamide makes it possible for almost all patients to take a recommended nucleoside backbone [8,9]. Finally, a two-drug regimen of dolutegravir and lamivudine is now being carefully studied in two larger clinical trials. In light of these considerations, it seems hard to justify the use of dolutegravir monotherapy in clinical practice. If monotherapy is to be studied at all – and the scientific rationale is debatable at best – it should be in the context of carefully controlled clinical prospective trials that maximize patient safety and include a robust informed consent process.

## Disclosure statement

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