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Dolutegravir-based monotherapy or dual therapy maintains a high proportion of viral suppression even in highly experienced HIV-1-infected patients

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Background: Dolutegravir is a powerful, well-tolerated integrase inhibitor with a high genetic barrier to resistance and may thus constitute the backbone of lightened regimens.

Methods: This was a monocentric, retrospective study. HIV-1-infected patients receiving dolutegravir as monotherapy (mDGV) or dual therapy (dDGV) were systematically identified. The primary outcome was the proportion of patients who maintained undetectable (<50 copies/mL) plasma HIV RNA [plasma viral load (PVL)].

Results: We identified 21 patients on mDGV (50 mg/day) and 31 on dDGV (50 or 100 mg/day, with atazanavir ± ritonavir, *n*=12; rilpivirine, *n*=11; maraviroc, *n*=3; lamivudine, *n*=3; darunavir/ritonavir, *n*=1; or abacavir, *n*=1). All of the patients were treatment experienced and 48% had experienced at least one virological failure. The baseline characteristics were as follows (for the mDGV/dDGV patients, respectively): 5%/29% had a history of AIDS; the median (IQR) highest PVL was 4.5 (4.3–5.5)/5.3 (4.7–5.6) log copies/mL; the median (IQR) nadir CD4+ count was 310 (280–468)/199 (134–281) cells/mm^3; 100% had undetectable PVL before the mDGV for a median (IQR) duration of 5.9 (3.5–9.9) years/81% had undetectable PVL before the dDGV for a median (IQR) duration of 3.7 (1.4–8.3) years; and the median (IQR) HIV DNA level was 2.7 (2.1–3.1)/2.9 (2.7–3) log copies/10^6 PBMCs. At the last follow-up visit, 100% and 97% of patients showed undetectable PVL following mDGV and dDGV, respectively [median (IQR) follow-up of 32 (29–45) and 50 (30–74) weeks, respectively].

Conclusions: In our experience, dolutegravir-based lightened regimens provided a high proportion of viral suppression, even in highly treatment-experienced patients.

Introduction

Currently, in high-income countries, most patients living with HIV who use a triple ART are virally suppressed, which allows them to reach normal life expectancy.[1,2] However, comorbidities are common among these patients and increase with age.[3] Therefore, reducing the number of antiretroviral drugs is essential to lower the long-term side effects and costs and limit interactions with comedications.

Dolutegravir is a powerful, easy-to-take, well-tolerated integrase inhibitor (INI), which offers a high genetic barrier to resistance and few drug–drug interactions.[4] Therefore, dolutegravir has the potential to replace ritonavir-boosted PI (PI/r) in lightened regimens, but still needs to be evaluated in this setting.

Here, we provide the first data in this field by reporting our experience with various dolutegravir-based lightened regimens (DBLR) in a real-life setting.

Methods

We conducted a retrospective, non-interventional study in a large (1250 beds) tertiary care centre in France. Using our electronic medical database (Nadis® software), we exhaustively identified all patients who received a DBLR, either as monotherapy or dual therapy. Patients with at least a plasma viral load (PVL) available ≥1 month after simplification,

which allowed us to determine the regimen's efficacy, were included in the study.

Of note, all decisions to switch to a DBLR were validated by the local HIV experts team, as recommended by French guidelines.[2] All participants provided written informed consent for the anonymous use of their clinical and biological data for biomedical research at the time their data were entered into the electronic database. Therefore, this study did not need to be approved by a research ethics committee.

The primary endpoint was the proportion of patients who maintained virological suppression (HIV RNA <50 copies/mL, US FDA Snapshot analysis with ITT analysis) at the last follow-up visit. Virological failure was defined as two consecutive PVL ≥50 copies/mL. Patient data were considered for analysis if the DBLR strategy was successfully continued; otherwise, data were censored at the time of failure or discontinuation. We also looked at very low-level viraemia (20 ≤ PVL < 50 copies/mL) during the follow-up period. The secondary endpoint was safety (serious adverse effects, AIDS-related events and death).

The data collected at baseline (i.e. the day patients switched to a DBLR) included demographic characteristics, medical history, duration of HIV infection, CDC stage, coinfection with hepatitis viruses, current CD4+ cell count and nadir, current PVL and highest value, HIV DNA level in PBMCs, serum creatine phosphokinase (CPK) and creatinine level, duration and type of previous line(s) of combined ART, duration with undetectable (i.e. <50 copies/mL) PVL, history of virological failure (and drug resistance-associated mutations, if any) and reasons for switching to a DBLR. Follow-up data (i.e. after switching to a DBLR) included relevant clinical events, CD4+ count, PVL, CPK and serum creatinine levels, genotype at failure (if any) and ART changes (if any). Blood samples were taken at 1–4 month intervals, as recommended by national guidelines.

Data are expressed as the median (IQR), mean ± SD, *n*, % or *n* (%). Continuous variables were compared using a paired *t*-test or the Wilcoxon test.

Results

From January 2013 to August 2015, 621 patients under ART were followed in our department; of these, 154 (25%) received dolutegravir. Fifty-two patients received a DBLR (all were able to be evaluated and were included in the study), either as monotherapy (50 mg once daily, $n=21$) or as part of dual therapy ($n=31$). In the latter group, dolutegravir was given at 50 mg once daily ($n=26$) or twice daily (100 mg/day, $n=5$) in association with rilpivirine ($n=11$), atazanavir ($n=8$), atazanavir/ritonavir ($n=4$), darunavir/ritonavir ($n=1$), maraviroc ($n=3$), lamivudine ($n=3$) or abacavir ($n=1$). The main characteristics and outcomes of the patients are summarized in Tables 1 and 2, according to the strategy. All the patients were treatment experienced at baseline and 25 (48%) had experienced at least one virological failure. In those 25 patients who had previously failed, the frequency of archived mutations for resistance to at least one drug among NRTI, NNRTI, PI/r or any of these classes was 68%, 60%, 16% and 80%, respectively. More importantly, nine patients had previously failed under a regimen containing raltegravir. A genotype was available at baseline for seven patients. Mutations encoding INI class resistance were evidenced in five patients (N155H, $n=4$; V72I, $n=4$; G163R, $n=1$; E157Q, $n=1$; and L74I, $n=1$). All viruses remained susceptible to dolutegravir.

Overall, the entire duration on the DBLR accounted for 45 patient-years [median (IQR) follow-up: 39 (29–55) weeks]. During follow-up, 179 PVL assays were performed: 177 (99%) showed <50 copies/mL and 173 (97%) showed <20 copies/mL. At the last visit, all of the patients except one had a PVL <50 copies/mL [global success rate: 98% (95% CI: 90%–100%), Snapshot analysis] and were continuing with the strategy (details are given in Table 1). A single patient experienced a confirmed virological failure while using dolutegravir/maraviroc and this treatment was subsequently stopped. This non-compliant woman had previously failed with raltegravir and had an N155H mutation. She admitted to taking half the pills she was prescribed while taking the DBLR. At week 79, her PVL increased to 736 copies/mL and genotyping revealed additional mutations (V72I+F121Y+S147G) encoding resistance to dolutegravir plus a CXCR4 tropism.

No patient experienced serious adverse effects, AIDS-related events or died during the follow-up period. Overall, the mean estimated glomerular filtration rate (MDRD study equation) did not significantly change from baseline to the last visit (from 89 ± 26 to 87 ± 23 μmol/L, respectively; $P=0.15$). CPK was found to be slightly elevated (grade I) in 13% of patients, none of whom complained of muscular pain.

Discussion

This study reports the first observational data on DBLR, mainly in the setting of a maintenance strategy in long-term suppressed patients. Overall, these regimens were safe and proved effective regarding immunovirological control, even in heavily pretreated patients. Of note, all patients who achieved the 24 week follow-up visit ($n=19$ and $n=30$ with dolutegravir as monotherapy and dolutegravir as dual therapy, respectively) had undetectable PVL. A single patient failed (at week 79) in the dual-therapy group due to a combination of poor adherence, previous INI mutation and poorly effective antiretroviral partner.

To date, lightened strategies (monotherapy or dual therapy) are largely based on PI/r, alone or with an NRTI, NNRTI, INI or maraviroc.[1,2,5] Of all the PI/r used, boosted darunavir (darunavir/r) has been most widely tested as a monotherapy.[6] There is no direct comparison between darunavir/r and dolutegravir as monotherapy or dual therapy. Notably, in the FLAMINGO trial in which dolutegravir and darunavir/r were compared with two NRTI, dolutegravir was found to be superior to darunavir/r in terms of efficacy.[7]

The INI class has been increasingly recognized as a first-line option, especially because of its good efficacy and tolerability.[1,2] In combination with two NRTI, the INI class was found to be superior to PI/r in a large study, even though raltegravir, which was used in this trial, showed a low genetic barrier.[8] Dolutegravir is not only as efficient and well tolerated as raltegravir as a first-line strategy, it is also more powerful in pretreated patients because its high genetic barrier allows it to maintain antiviral activity against most mutated strains.[9,10]

In fact, dolutegravir is the most powerful antiretroviral drug ever marketed, resulting in a 2.5 log copies/mL PVL drop after 10 days when given as monotherapy in untreated patients.[11] In one study, at the end of this monotherapy, 70% of patients had a PVL <50 copies/mL and a post-treatment effect was observed up to 72 h.[11] Even in patients with highly resistant viruses, a short monotherapy of dolutegravir quickly decreased the PVL by a mean of −1.43 log copies/mL.[12] Interestingly, similar to darunavir/r, dolutegravir is characterized by a high affinity to its target, resulting in strong and sustained binding.[4] As a consequence, *in vitro* selection of mutants resistant to dolutegravir is very difficult.[4] To date, no emergent dolutegravir-resistant virus has ever been

Table 1. Characteristics and outcomes of patients on DBLR

Characteristics	Dolutegravir combined with another ARV ($n=31$)	Dolutegravir monotherapy ($n=21$)
Before DBLR		
age, years	53 (48–61)	47 (41–65)
male	17 (55%)	13 (62%)
duration with HIV infection, years	17 (11–24)	11 (5–16)
CDC stage		
A	18 (58%)	17 (81%)
B	4 (13%)	3 (14%)
C	9 (29%)	1 (5%)
coinfection		
HBV	2 (6%)	1 (5%)
HCV	2 (6%)	2 (10%)
CD4 count nadir, cells/mm^3	199 (134–281)	310 (280–468)
highest PVL, log copies/mL	5.3 (4.7–5.6)	4.5 (4.3–5.5)
prior lines of ART, *n*	7 (4–11)	5 (3–7)
prior virological failure(s)		
with any regimen	20 (65%)	5 (24%)
with a regimen including INI	8 (26%)	1 (5%)
last regimen		
dual therapy	14 (45.2%)	6 (28.6%)
triple therapy	15 (48.4%)	15 (71.4%)
quadruple therapy	2 (6.5%)	—
last PVL <50 copies/mL	25 (81%)[a]	21 (100%)
duration PVL <50 copies/mL, years	3.7 (1.4–8.3)[b]	5.9 (3.5–9.9)
last CD4 count, cells/mm^3	702 (495–867)	768 (563–936)
last CD4/CD8 ratio	0.8 (0.5–1.1)	1.4 (0.9–1.5)
last HIV DNA, log copies/10^6 PBMCs	2.9 (2.7–3.0)	2.7 (2.1–3.1)
reason for changing to DBLR		
simplification	18 (58.1%)	15 (71.4%)
adverse reaction/toxicity	6 (19.4%)	6 (28.6%)
virological failure	6 (19.4%)	—
drug–drug interactions	1 (3.2%)	—
After DBLR		
total follow-up, weeks	50 (30–74)	32 (29–45)
CD4 count increase at last visit, cells/mm^3	8 (−72 to 88)[c]	1 (−122 to 91)[c]
all PVL values	107 (100%)	72 (100%)
<20 copies/mL	102 (95%)	71 (99%)
20–49 copies/mL	3 (3%)	1 (1%)
50–199 copies/mL	1 (1%)	—
≥200 copies/mL	1 (1%)	—
last PVL <50 copies/mL	30 (97%)[d]	21 (100%)[e]
ΔeGFR, mL/min/1.73 m^2	−4.5 (−11 to 4)[c]	0 (−6 to 6)[c]

eGFR, estimated glomerular filtration rate calculated using the MDRD formula; HBV/HCV, hepatitis B/C virus.
Values are given as median (IQR) or *n* (%).
[a]Six patients had detectable PVL at baseline: 66, 76, 711, 850, 2410 and 6750 copies/mL, respectively.
[b]For the 25 patients with undetectable PVL at baseline.
[c]No statistical difference between baseline and last follow-up visit.
[d]Twenty-nine out of 31 patients (94%) also showed <20 copies/mL.
[e]All showed <20 copies/mL.

reported in a patient in whom dolutegravir was prescribed as a first INI.[13] Nevertheless, patients in whom a first-generation INI has failed may have a selected pathway leading to cross-resistance, including dolutegravir,[12] as illustrated by our failing patient. Of note, two recent communications reported 4 patients out of 61 (6.6%) who failed with dolutegravir as monotherapy within the first 24 weeks of follow-up: all of them had been exposed to a first-generation INI (i.e. raltegravir or elvitegravir).[14,15]

Table 2. Antiretroviral strategies used at baseline in the 52 patients who switched to DBLR

ARV regimen at baseline (before patients switched to DBLR)	Active ARV drugs at baseline	Number of patients who switched to dolutegravir associated with another ARV	Number of patients who switched to dolutegravir monotherapy
1 EI+1 INI	2	1	
1 EI+1 PI/r	2	1	
1 INI+1 NNRTI	2	3	1
1 INI+1 NRTI	2		1
1 INI+1 PI	2	3	2
1 INI+1 PI/r	2	5	
2 NRTI	2		2
2 PI/r	2	1	
1 EI+1 INI+1 NNRTI	3	1	
1 EI+2 NRTI	3	1	
1 INI+1 NRTI+1 NNRTI	3	1	
1 INI+2 NRTI	3	5	9
1 INI+2 PI/r	3	1	
2 NRTI+1 NNRTI	3	1	6
2 NRTI+1 PI	3	2	
2 NRTI+1 PI/r	3	3	
1 INI+2 NRTI+1 NNRTI	4	1	
1 INI+2 NRTI+1 PI/r	4	1	

ARV, antiretroviral; EI, entry inhibitor.

This work has important limitations. Mainly, this was a retrospective uncontrolled study, with limited sample size and short duration of follow-up that combined patients with heterogeneous medical histories and potential biases. However, the fact that we did not select patients on stringent immunovirological criteria supports the potential for the broad success of DBLR strategies. Our findings now need to be validated by randomized controlled trials and long-term data.

The long-term survival of patients with HIV compels us to rethink treatment and to lighten it.[16] In our experience, dolutegravir has the capacity to structure lightened strategies. Because the few cases of virological failure were seen in patients who had previously been exposed to a first-generation INI, we believe that DBLR should be restricted to those in whom dolutegravir is used as the first INI, in particular with the monotherapy. Otherwise, such regimens should be very closely monitored.

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Transparency declarations

T. P. has served as a clinical trial principal investigator for Gilead Sciences and has served on advisory boards for Bristol-Myers Squibb, Gilead Sciences and ViiV Healthcare. L. H. has served as a clinical trial principal investigator for Bristol-Myers Squibb, Gilead Sciences and ViiV Healthcare and has served on speaker bureaus or advisory boards for Bristol-Myers Squibb, Gilead Sciences and ViiV Healthcare. All other authors: none to declare.

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Author contributions

C. G. and L. H. participated in the conception and design of the study. T. P., M. N., J. B., C. M. and L. H. included the patients in the study. C. G. and L. H. collected the clinical data. L. H. and T. P. analysed and interpreted the data. J. G. and V. A.-F. performed the virology analysis. C. G. and L. H. wrote the manuscript. All the authors reviewed, revised for content and approved the final version of this paper.

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