Comparison of HIV-DNA decay in naïve patients starting dolutegravir plus lamivudine or dolutegravir-based triple therapy

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To the Editor,
Dolutegravir + lamivudine is the first two-drugs combination that has been recommended as a first-line regimen in selected treatment-naïve HIV patients, even though its long-term efficacy in this population has not been fully established and few data are available regarding its efficacy in controlling viral replication in reservoirs [1, 2].
HIV-DNA is a surrogate marker of the HIV cellular reservoir and a potential parameter for predicting the long-term success of Anti Retroviral Therapy (ART), because it has been related to residual viremia and low level inflammation independently of CD4+ count and HIV-RNA [3].
Currently, no data are available regarding HIV-DNA decay in ART-naïve patients starting treatment with dolutegravir + lamivudine. The aim of this study was to investigate differences in HIV-DNA decay in ART-naïve patients starting a dual regimen with dolutegravir + lamivudine versus a "standard" dolutegravir-based triple regimen.
This prospective, longitudinal, single-site study enrolled treatment-naïve adults (>18 years) who started a dual regimen with dolutegravir 50 mg + lamivudine 300mg once daily (2DR) or a triple regimen with dolutegravir 50 mg + emtricitabine (FTC)/tenofovir alafenamide (TAF) 200 mg/25 mg (3DR), based on clinician's decision, between June 2018 and January 2020. We quantified blood-associated total HIV-DNA at three different time points: before starting therapy (baseline, BL), at virological success (VS) (defined as the first HIV-RNA<50 copies/mL) and 6 months after VS (6mVS). HIV-DNA quantification was performed by droplet digital PCR, as previously described [4]. Results were expressed as $\log_{10}$HIV-DNA copies/10^6 leukocytes. All patients gave their informed consent and the study was approved by our local Ethics Committee (www.clinicaltrials.gov, number NCT02836782).
Non parametric tests were used to compare the medians between the two groups of patients (2DR versus 3DR) and to assess the change of $\log_{10}$ HIV-DNA and $\log_{10}$ HIV-RNA at the different time points within each group. Linear regression analyses explored predictors of HIV-DNA and HIV-RNA changes between BL and VS. Residual viremia (HIV-RNA <50 copies/mL) was categorized as a dichotomous variable: detectable (1-49 copies/mL) or undetectable (0 copies/mL).
We included 16 naïve patients, 6 in the 2DR-group and 10 in the 3DR-group. Patients' characteristics at baseline are showed in Table 1. All subjects were males (100%) with a median age of 33 years; 81% were Caucasian. Homosexual transmission was the main risk factor (69%) and subtype B was more frequent than non-B (56% *vs* and 31%). The two groups were homogeneous for the main characteristics, although patients in 3DR showed a significantly lower CD4/CD8 ratio (median 0.20

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vs 0.38, *p*=0.042); of note, baseline log_{10} HIV-DNA levels were similar in the two groups (3.86 and 3.99 in 2DR and 3DR, *p*=0.492).

During follow-up, all patients showed VS; 6mVS was available for 5 (83%) patients in 2DR and 9 (88%) in 3 DR, respectively.

Time to VS was similar in 2DR and 3DR [median 1.58 (interquartile range, IQR 1.23-4.07) and 4.4 (IQR 0.75-6.11) months, *p*=0.368). HIV-DNA and HIV-RNA changes at the three time points are shown in Figure 1.

At VS, HIV-RNA decreased significantly and to a comparable level in the 2DR and the 3DR groups [median 1.46 (IQR 1.09-1.60) and 1.05 (IQR 0.00-1.60) log_{10} copies/mL, *p*=0.368] and showed a similar delta change versus baseline: -3.50 (IQR -3.78/-3.25) in 2DR *vs* -4.59 (IQR -5.50/-3.17) in 3DR (*p*=0.181). No difference in the proportion of patients who reached undetectable viremia (HIV-RNA 0 copies/mL) (n=1/6, 16.6% in 2DR and n=3/10, 30% in 3DR, *p*=0.551) was observed. Both groups showed a significant CD4/CD8 ratio improvement and reached similar levels (0.48 in 2DR and 0.37 in 3DR, *p*=0.313).

At VS, HIV-DNA levels were comparable between groups [median 3.41 (IQR 3.07-3.51) in 2DR and 3.45 (IQR 3.32-3.74) in 3DR, *p*=0.492]; the median decay from baseline was similar in the two groups: -0.48 (IQR -0.61/-0.28) in 2DR *vs* -1.42 (IQR -1.13/-0.19) in 3DR, *p*=0.958.

Higher baseline HIV-RNA predicted a more pronounced decay of HIV-RNA at VS (mean change -1.296 per 1 log increase, 95% CI -1.855/-0.683, *p*<0.001). Similarly, higher baseline HIV-DNA levels were associated with greater decay in HIV-DNA at VS (mean change -0.469 per 1 log increase, 95% CI -0.671/-0.267, *p*<0.001). No types of regimen nor other demographic and clinical characteristics were associated to the decay of both HIV-RNA and HIV-DNA.

For patients whose samples were available at 6m VS, both HIV-RNA and HIV-DNA levels remained stable as compared to VS within the 2DR and the 3DR group (*p*=0.068 and 0.889 for HIV-RNA, and

Table 1 - Characteristics of patients at the time of first-line therapy initiation (baseline)

	2DR n=6	*3DR n=10*	*p*
Male gender, n (%)	6 (100)	10 (100)	1
Age, median (IQR) years	32.9 (26.9-44.8)	33.3 (28.6-45.4)	0.875
Caucasian, n (%)	4 (67)	9 (90)	0.274
Not Caucasian	2 (33)	1 (10)	
Risk factor			0.33
Homo/bi-sexual	5 (83)	6 (60)	
Heterosexual	1 (17)	4 (40)	
HIV Subtype			0.872
B	4 (67)	5 (50)	
non-B	2 (33)	3 (30)	
Unknown		2 (20)	
CD4 count, median (IQR) cells/mm^3	289 (206-496)	157 (20-428)	0.220
CD8 count, median (IQR) cells/mm^3	791 (662-891)	618 (279-1429)	0.635
CD4/CD8, median (IQR)	0.38 (0.25-0.66)	0.20 (0.10-0.30)	0.042
HIV-RNA, median (IQR), Log_{10} copies/mL	4.90 (4.43-5.14)	5.40 (4.88-5.93)	0.073
HIV-DNA/106 leukocytes BL, median (IQR), Log_{10} copies	3.86 (3.49-4.04)	3.99 (3.59-4.70)	0.492
Time elapsed between HIV diagnosis and first-line therapy initiation, median (IQR)	0.25 (0.18-21)	0.48 (0.30-3.00)	0.220
Starting first-line therapy within two months from HIV diagnosis, n %			0.869
Yes	5 (83)	8 (80)	
No	1 (17)	2 (20)	
CDC stage C, n (%)	0 (0)	4 (40)	0.074

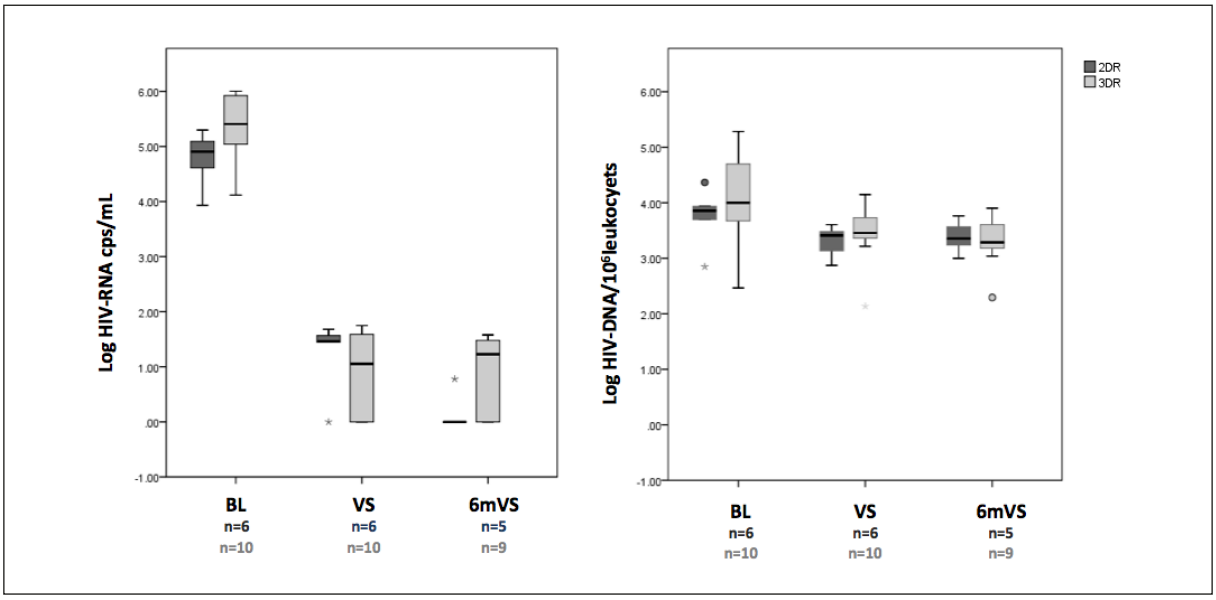

Figure 1 - HIV-RNA and HIV-DNA decay at the three different time points according to the DTG-based dual (2DR) vs triple therapy (3DR) groups. The boxes represent the 25th and 75th quartiles, the median is presented as a line inside the box. The whiskers represent values within ± 1.5% IQR. Circles and stars show the outliers with values between 1.5% to 3% the IQR, and >3% IQR, respectively.

p=0.686 and 0.314 for HIV-DNA, respectively), with no difference between the two groups (*p*=0.298 for HIV-RNA and *p*=1.000 for HIV-DNA). To the best of our knowledge, this is the first study that has explored the impact of dolutegravir + lamivudine as first-line regimen on HIV-DNA levels. In line with data previously observed in ART-naïve patients starting a standard three-drug regimen, we showed that 2DR determined a significant HIV-DNA decay at VS, and this decrease was similar to that observed for 3DR; no further decrease was observed at 6m VS [5,6]. These data suggest that, at least in the short term, using dolutegravir + lamivudine is not detrimental for controlling the HIV reservoir, although these conclusions are limited by the small sample size and short follow-up of the study.

These preliminary findings warrant the implementation of larger studies to fully verify their clinical implications.

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Conflict of interest
None

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