RESIDUAL HIV-1 RNA, HIV-1 DNA, AND DRUG PLASMA Cmin IN DUAL DTG + 3TC, ANRS 167 LAMIDOL

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Background

- The dual-class therapy containing the integrase strand-transfer inhibitor (INSTI) dolutegravir and the nucleoside reverse transcriptase inhibitor (NRTI) lamivudine has been evaluated in the Agence Nationale de Recherche sur le sida et les hépatites virales (ANRS) 167 LAMIDOL trial
- ANRS 167 LAMIDOL trial showed an overall success rate at week 48 of 97% (95% CI: 94-100)[1]
- Even though this maintenance dual-class therapy has shown its effectiveness in maintaining virological suppression at 48 weeks, there are still questions about the risk of residual viremia and of cellular reservoir re-seeding due to the reduction of the number ARV drugs

Objectives

- The aims of this viro-pharmacological sub-study of the ANRS 167 LAMIDOL trial were to assess:
  - HIV cellular reservoir size at initiation and at W48 of DTG + 3TC
  - HIV residual viremia at initiation and at the different time-points of the follow-up of DTG + 3TC
  - Drug plasma concentrations at the different time-points of the follow-up of DTG + 3TC

Patients & Methods

- ANRS 167 LAMIDOL was a single-arm, prospective multicentre trial in HIV-1-infected patients who were virologically suppressed on a first-line cART based on two NRTIs and a third agent consisting of a boosted PI, an NNRTI or an INSTI with no change in regimen in the past for virological failure
- HIV total DNA was measured at D0 and W48 of DTG + 3TC using the real-time PCR kit GENERIC HIV DNA Cell® (Biocentric®, Bandol, France) with a limit of quantification [LOQ] of 10 copies/PCR
- Ultra-sensitive plasma viral load (USpVL) was performed to assess plasma residual viremia at D0, W24 and W48 of DTG + 3TC. The maximum volume of available plasma was centrifuged, the pellet was resuspended, and pVL was determined using COBAS® HIV-1, v2.0 (Roche Molecular Systems, Branchburg, NJ, USA). The LOQ depended on the amount of plasma volume available (3 copies/mL in 90% of cases). The limit of detection (LOD) was defined as an undetected PCR signal
- Total and unbound plasma DTG concentrations (24 hours the last drug intake C_{min}) were measured using UPLC-MS/MS
- Statistical analyses
  - Evolution of the USpVL over time was analyzed using a linear mixed effects model
  - Relationship between HIV DNA and USpVL was studied using linear regression

Table 1. Patients' characteristics

Male sex, n (%)	89 (85.6%)
Age, years, median, (min-max)	45 [24-71]
Mode of transmission, n (%)	
- MSM	73 (70%)
- Heterosexual	29 (28%)
- People Who Inject Drugs	2 (2%)
Time since HIV diagnosis, years, median (min-max)	6.2 [2.3-24.5]
Nadir CD4 count, cells/mm³, median (min-max)	339 [203-1155]
CDC stage (%) A/B/C	87.5%/8.7%/3.8%
cART duration, years, median (min-max)	4.5 [2-11]
Time on current cART, years, median (min-max)	4.0 [0.5-11.3]
NRTI backbone (FTC-TDF/ABC-3TC), n (%)	79/25 (76%/24%)
Duration of suppressed plasma HIV RNA* in years, median (min-max)	4.2 [2.0 -9.1]
CD4 count at enrollment, cells/mm³, median (min-max)	743 [373-1571]
Third agent in cART at screening, n(%)	
- NNRTI	58 (55.8%)
- PI	24 (23.1%)
- INSTI	22 (21.2%)
RAL/EVG/DTG	8/7/7

Results

HIV-1 DNA during the DTG + 3TC dual-class therapy

- Among the 104 patients receiving DTG +3TC, paired D0 and W48 HIV total DNA results were obtained in 100 patients
- Median (IQR) HIV DNA was 2.49 log_{10} copies/10^6 PBMC (2.17-2.95) at D0 and 2.52 (2.09-2.89) at W48 (p = 0.28; Wilcoxon paired test)
- HIV DNA was below the LOQ at D0 and W48 in two and four patients, respectively

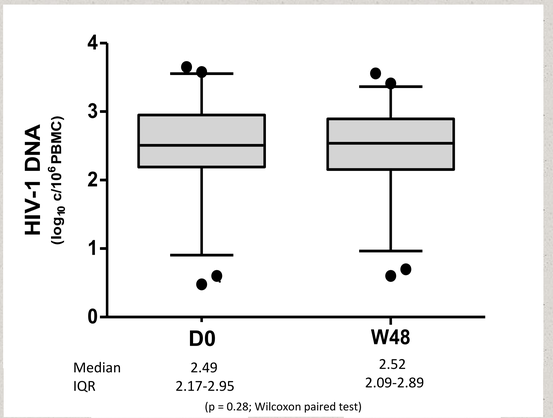

Figure 1. Total HIV-1 DNA at Day 0 and W48 of the DTG + 3TC dual-class therapy (Whiskers 2.5%-97.5%)

Residual viremia

- Residual viremia was measured in 101, 101 and 99 patients at D0, W24 and W48 of DTG + 3TC, respectively
- The proportion of patients with USpVL <LOD was 38%, 41% and 49% at D0, W24 and W48 (Table 2), respectively
- Among the 97 participants with USpVL available at the three time points, USpVL did not change over time (p = 0.11; paired McNemar test)
- An association was observed between HIV total DNA and USpVL (Spearman correlation; rho = 0.15; p = 0.01)

Virology USpVL	D0 (n = 101)	W24 (n = 101)	W48 (n = 99)
USpVL < LOD	38%	41%	49%
LOD < USpVL < LOQ	30%	30%	21%
USpVL > LOQ	32%	29%	30%

Table 2. Description of the ultra-sensitive plasma viral load

Pharmacology median (IQR 25-75%)	D0	W24	W48
Total DTG Cmin (ng/mL)	1677 (1301-2224; n = 87)	1815 (1322-2227; n = 93)	1710 (1237-2216; n = 88)
Unbound DTG Cmin (ng/mL)	3.6 (2.7-5.1; n = 85)	3.6 (2.6-5.2; n = 92)	3.4 (2.3-5.0; n = 88)

Table 3. Description of DTG plasma C_{min}

Drug plasma concentrations

- All total plasma DTG C_{min} except one, exceeded the in vitro protein-binding adjusted IC_{90} values (64 ng/mL)[2]
- Thus, overall, plasma DTG C_{min} were considered as adequate in almost all patients, suggesting a high level of treatment adherence (Table 3)
- Free fraction of DTG in plasma was approximately 0.2%
- No association was observed between plasma DTG C_{min} and USpVL (Spearman correlation; rho = 0.197; p = 0.07)

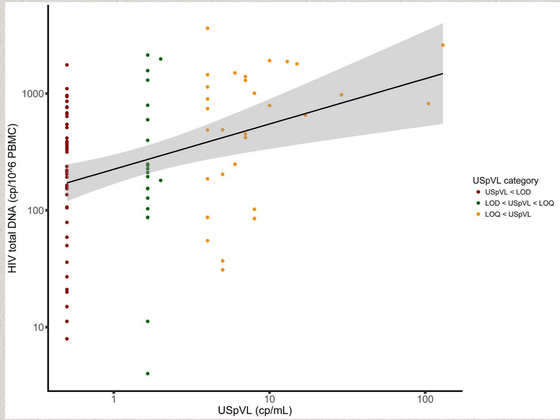

Figure 2. Linear regression line between HIV-1 total DNA (copies/10^6 PBMC) and USpVL (copies/mL) at W48

Conclusions

- No change was observed, during the first year of DTG + 3TC maintenance dual-class therapy, in residual viremia level or in HIV cellular reservoir size in patients with no history of virological failure and with stable and adequate plasma DTG C_{min}
- These findings are in accordance with those described in others maintenance dual-class therapy : ANRS 163 ETRAL[2] for HIV cellular reservoir size and SWORD trial for residual viremia[3]
- Thus, these findings are reassuring regarding the potency of a maintenance dual-class therapy with DTG, not only in maintaining plasma virological suppression but also at the level of residual viremia in patients fully adherent
- As described under triple-class therapy, we observed a positive relationship between residual viremia and HIV cellular reservoir size under the maintenance DTG + 3TC dual-class therapy

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