A RANDOMIZED TRIAL OF DTG PLUS DRV/c AS A SWITCH STRATEGY IN SUBJECTS WITH MDR HIV-1

Poster-I02

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BACKGROUND

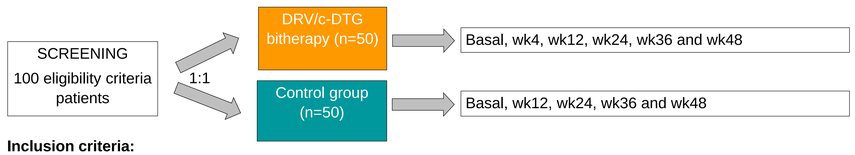
Dual therapy with DTG+DRV/c may be a suitable ART simplification strategy for treatment-experienced subjects with drug resistance mutations (DRM) because both drugs can be given once daily. They have high genetic barrier to resistance and less potential for pharmacological interactions than usual ART salvage regimens.

METHODS

Study design and patients

- Study design: This is an open label, multicenter, randomized pilot study to evaluate the efficacy and safety of switching to DTG+DRV/c as a 2-pill once-daily simplification strategy in well-suppressed and highly ART-experienced patients harboring archived DRM against at least 2 antiretroviral classes.

- Subjects who meet all eligibility criteria were randomly assigned to:
  - Experimental group: Bitherapy based on DTG (50 mg QD) plus DRV/c (800/150 mg QD).
  - Control group: Continuation of their current stable ART.



Inclusion criteria:

- Adults on ART containing at least 3 antiretroviral drugs.
- Confirmed HIV-1 RNA <50 c/ml for ≥6 months preceding the randomization.
- History of DRM against at least 2 antiretroviral classes, with no integrase-associated mutations or previous virological failure (VF) to INSTI-based regimens and no evidence of resistance to DRV (<15 points from Stanford dB score).
- Willing and able to be adherent during the study.

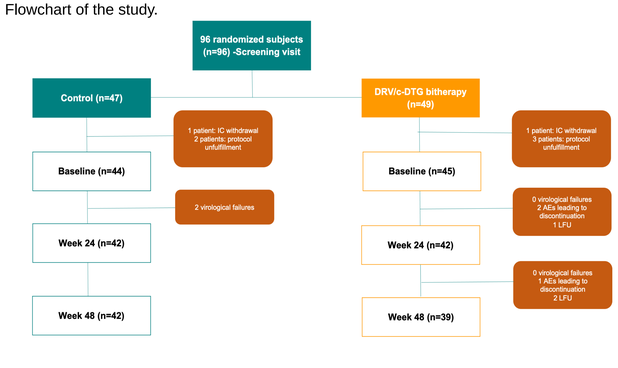
Endpoints:

- **Primary:** Percentage of subjects with HIV-1 RNA <50 c/mL at week 48 by TLOVR.
  - VF was defined as confirmed HIV-1 RNA ≥50 c/mL or a single determination of HIV-1 RNA >1000 c/mL.
  - Treatment adherence was self-reported by the patient by answering the adapted SERAD questionnaire
- **Secondary:** Sensitivity analysis at week 48 was done using the FDA snapshot algorithm:
  - Responders: patients with HIV-1 RNA <50 c/mL at week 48.
  - Non responders: HIV-1 RNA ≥50 c/mL, including participants with VF, blips (in window) or subjects who discontinued study drug because of reasons other than low efficacy, adverse event (AE) and death before week 48 with last available HIV-1 RNA ≥50 c/mL.
  - No virological data: Included participants who discontinued study drug before week 48 because of AE or death; ART discontinuation because of reasons other than low efficacy before week 48 with last available HIV-1 RNA <50 c/mL; and subjects who were still on study drug with missing HIV-1 RNA data at week 48 or lost of follow-up.

RESULTS

- A total of 100 subjects (50 subjects per group) were planned to be enrolled. This predefined sample size provided an 80% power with a one-sided significance level of 0.025 to detect a 90% of efficacy in the group of subjects treated with DTG + DRV/c, assuming 5% of participants lost to follow-up. The study was stopped because of poor enrollment after 2 years. We present the efficacy and safety results using available data.
- From 96 patients who were initially randomized during screening visit, 89 subjects were included and allocated to the study groups (figure 1)

Figure 1. Flowchart of the study.



IC, informed consent; AEs, adverse events; LFU, loss to follow-up

Table 1. Demographic and clinical characteristics

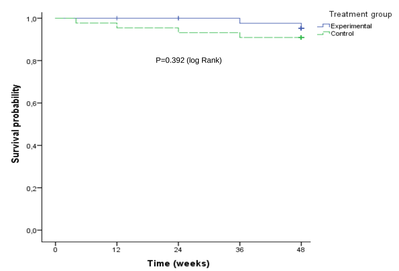
	Control (n=44)	DRV/c + DTG (n=45)	P valor
Male	32 (72.7)	36 (80.0)	0.462
Risk factor			0.736
MSM	16 (36.4)	18 (40.0)	
MSW	13 (29.5)	15 (33.3)	
IDU	12 (27.3)	10 (22.2)	
Others	3 (4.8)	2 (4.5)	
HCV co-infection	5 (11.4)	6 (13.3)	0.202
Age[a]	55 (50-60)	55 (50-61)	0.672
CD4 cell count (cells/mm^3)[a]	607 (429-961)	623 (493-901)	0.391
CD4 nadir (cells/mm^3)[a]	147 (61-217)	152 (77-269)	0.313
Years of infection[a]	25 (23-28)	25 (23-29)	0.403
ART at study entry			
DRV	28 (63.6)	33 (73.3)	
Other PI	3 (6.8)	0	
3TC/FTC	27 (61.4)	26 (57.8)	
TDF/TAF	23 (52.3)	17 (37.8)	
ABC	7 (15.9)	9 (20.0)	
ETV	9 (20.5)	13 (28.9)	
RAL	12 (27.3)	17 (37.8)	
DTG	13 (29.5)	17 (37.8)	

All values are expressed as No. (%) except when specified. [a]Median (interquartile range). [b]Including ritonavir

Abbreviations: MSM, men-sex-men; MSW, men who have sex with women; IDU, injecting drug use; HCV, hepatitis C virus; ART, antiretroviral treatment; DTG, dolutegravir; DRV/c, darunavir/cobicistat; PI, protease inhibitors; 3TC, lamivudine; FTC, emtricitabine; ABC, abacavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; ETV, etravirine; RAL, raltegravir.

Virological outcomes

Figure 2. Virological outcome at week 48 according to TLOVR analysis

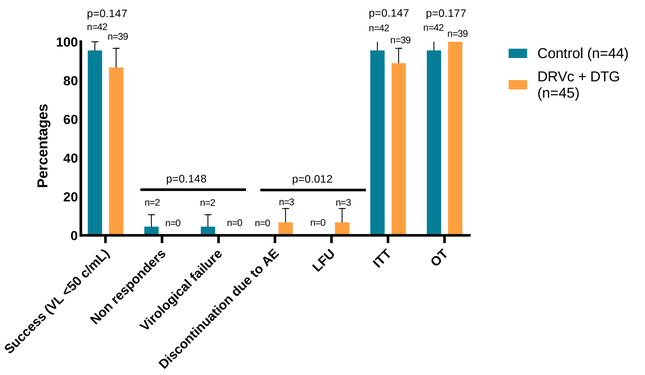


- There was no difference in the proportion of subjects maintaining HIV-1 RNA <50 c/mL at week 48 (95.6% vs 90.9%, log rank p=0.392)

CONCLUSIONS

- Dual therapy with DTG+DRV/c maintains viral suppression in highly treatment experienced subjects with multiclass drug resistance, as long as they retain DRV- and INSTI-susceptible HIV-1.
- More frequently observed AEs in the DRV/c+DTG arm has to be interpreted with caution due to the open label design.
- AES leading to treatment discontinuation were unfrequent.

Figure 3. Virological outcome at week 48 according to FDA snapshot analysis



VL, viral load; LFU, loss to follow-up; ITT: M = F, intention to treat: missing equal to failure; OT: M ≠ F, On-treatment: missing censored

- There was no VF in the DTG+DRV/c group, whilst there were 2 (4.5%) VF in the control group (p=0.147, snapshot analysis).
- Genotyping test was not performed in one patient with VF. No drug resistance mutations were detected in the other one.

Safety outcomes

Figure 4. Adverse events during follow-up

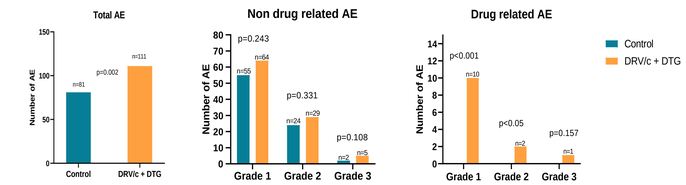
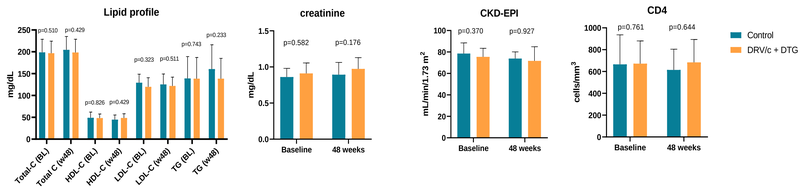


Figure 5. CD4 cell count and lipid and kidney profiles



- There were more overall and drug-related AEs in the group of DRV/c + DTG.
- Drug-related AEs associated with DRV/c + DTG were mainly Grade I and II.
- AEs leading to treatment discontinuation were observed only in 3 subjects from the DTG+DRV/c group (arthralgias, diarrhea, rash) and none in the controls.
- ART adherence remained above 98% in both study arms.

CROI Conference on Retroviruses and Opportunistic Infections

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