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Long-term durability of dolutegravir + darunavir/cobicistat dual regimen in highly antiretroviral-experienced people living with HIV (DoDaco study)

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Introduction/Summary

Dolutegravir (DTG) plus darunavir-cobicistat (DRV-c) dual regimen has been used as a simplified salvage option in treatment-experienced people living with HIV (PLWH), with history of virological failures and multiple class resistance. Two randomized trials and a few single arm ones have explored this combination in switch strategies in different settings.

Pharmakokinetic studies support this dual combinations

Long term data on this combination are missing. We report on the durability of this dual regimen assessed by treatment failure (TF) over time as a composite endpoint.

Study Design

Retrospective, observational, multicenter study in 6 Italian centres. PLWH who started DTG+DRV-c (DTG bid was allowed) for any reason since 2015 were included, regardless of HIV RNA levels. PLWH with active HBV coinfection requiring TAF/TDF or 3TC were excluded (entecavir was allowed)

Methods

Data were collected from electronic or hand written patients' records, according to each centre's organization, and sent by predefined excell files. Resistance-associated mutations (RAMs) were interpreted according to the Stanford HIVdb mutation list. The follow up was censored at Feb,28, 2024.

The primary endpoint was the TF defined as any reason of regimen discontinuation, including virological failure (VF) (i.e. confirmed HIV RNA ≥ 50 copies/mL or any detectable viral load followed by any treatment switch).

Secondary end-points were the reason for discontinuation, the emergence of resistance mutation at study drugs, the CD4 count increase, the impact of pre-exisiting mutation on the risk of failure and the impact on renal function and lipid profile

Basic descriptive statistics was used to describe the population's characteristics. Survival analysis with Kaplan-Meier estimator was used to assess the probability of treatment discontinuation over time. Multiple logistic regression was used to estimate the probability of TF at 1 year following the initiation of DTG+DRV-c

Results

A total of 283 individuals were included.

Table1 shows the patients' characteristics at study entry. A total of 73% and 60% of pts were already on boosted DRV and on dual therapy at study entry, respectively. A total of 9 (3.2%) patients were on DTG bid (2 also had entecavir). The median time (IQR) on virological suppression was 89 months (34-121) for those patients with undetectable VL at study entry. Participants had a median follow-up of 4 years since DTG+DRV-c initiation.

Results 2

Treatment Failure

A total of 80 patients discontinued the dual regimen during follow up. The reasons are listed in table 2

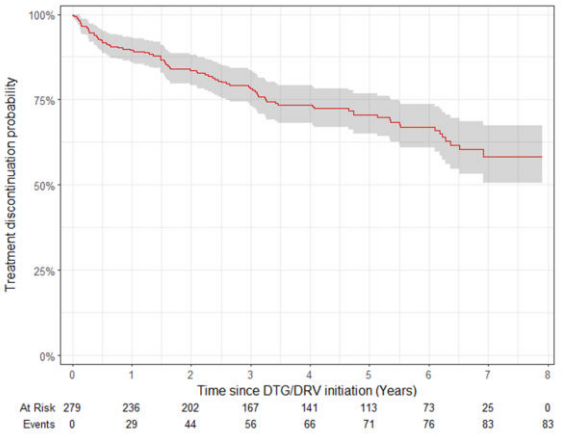
The probability of TF was 11%, 16%, 22%, 27%, 29%, 33%, and 42% after 1, 2, 3, 4, 5, 6 and 7 years of treatment, respectively (figure 1).

Table 2: Reasons for treatment discontinuation in 80 pts

Reasons	N. (%)
Virological failure	7 (8.7)
Death	18 (22.5)
Lost to follow up	8 (10)
Toxicity	11 (13.7)
Intolerance	9 (11.2)
Drug-drug interaction	9 (11.2)
HBV infection	2 (2.5)
Simplification	13 (16.2)
Patient's choice	2 (2.5)
SAE (PML)	1 (1.2)

Only 1 out of 7 individuals who had virological failure (VL range: 217 - 40,500 c/ml, mostly for lack of adherence) was genotyped (but unsuccessfully, his VL was 238 copies/ml)

Figure 1: Treatment failure with Kaplan–Meier estimator



- Median CD4 count increased from 576 to 686 cells/mL at month 72
- Two cases of HBV infections occurred during follow up, in unvaccinated subjects

Table 1. Baseline characteristics of patients starting dual regimen with DTG+DRV-c

Number of patients	283
Age, years, median (IQR)	60 (55-63)
Gender, male, n (%)	188 (66.4)
Risk factor for HIV acquisition, n (%)	
MSM	48 (17)
heterosexual	121 (43)
intravenous drug use	100 (35)
other, unknown	14 (5)
Comorbidities, n (%)	
none	72 (25)
1-2	178 (63)
3-5	29 (10)
>6	4 (1.4)
AIDS	102 (36)
Nadir CD4+T cell count, median (IQR)	152 (45-282)
Duration of HIV therapy, years, median (IQR)	24 (19-28)
Treatment lines n. (%)	
< 3	20 (7)
3-8	121 (43)
>8	128 (45)
Unknown	14 (5)
HIV Drug Resistance Mutations* n. (% tested)	
NRTI	205 (86)
NNRTI	157 (71)
PI	59 (37)
INI	18 (15)
Last ARV regimen, n (%)	
2NRTI+INI	29 (10)
2NRTI+NNRTI	18 (6.3)
2NRTI+PI	10 (3.5)
PI+INI	149 (53)
other	75 (27)
off therapy	2
CD4+T cell count at study entry, patients N. (%)	
< 200 cells	28 (10.5)
< 200-500 cells	81 (30.5)
> 500 cells	156 (57.7)
Baseline HIV RNA, n (%)	
<50 copies/mL	179 (67)
50-5000 copies/ml	58 (22)
Hepatitis B serology, n. (% tested)	
HBsAg +	7 (3.4)
HBsAb +	111 (53)
HbcAb +	80 (46)

Numbers are median (percentage), if not otherwise specified.
*Primary resistance mutations according to the Stanford HIVdb mutation list

Results 3

Factors associated to TF

At multiple logistic regression, after adjusting for age, sex, viral load at baseline and number of lines of therapy, the only factor associated with a reduced probability of TF after 1 year of treatment was an increase in CD4+T cell count of 50-unit from the baseline value (OR=0.947, 95%CI 0.9-0.992).

Safety

Median **TGs** (from 135 to 140 mg/dl) and median **total cholesterol** (from 200 to 197 mg/dl) levels were stable over 36 months. A total of 34% and 13% were on statins and/or fibrates, respectively.
Median **eGFR** decreased from 95.4 (baseline) to 87 and 86 ml/min at 6 and 12 month, respectively.

Conclusions

- Virological efficacy of this dual regimen was high in these highly-treated PLWH. Only 7 patients discontinued for VF (mostly for lack of adherence)
- Among the 80 pts who discontinued: one third for death or loss to F-up, while another third for drug related issues (toxicity, tolerability and drug interactions)
- Higher CD4 cells count was associated to lower risk of VF at week 48

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