Efficacy and safety of dolutegravir and doravirine dual therapy in the context of antiretroviral therapy switch: 48 weeks analysis

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BACKGROUND

Dual therapy in HIV represents an attractive opportunity for HIV-infected people in virologic suppression. Dual therapy regimens should achieve and maintain viral suppression and immunologic control while minimizing short- and long-term AEs, improve adherence and convenience, and reduce drug-drug interactions and costs. To date, there are few clinical data to support a dual regimen with dolutegravir and doravirine [1]. The individual efficacy of both doravirine and dolutegravir suggests that concomitant administration of these two molecules as part of an NRTI-sparing regimen could be a viable option, although to date there are no studies in the HIV-infected population. The aim of our study is to investigate whether a dual therapy regimen containing dolutegravir and doravirine is effective and safe.

METHODS

A prospective observational study lasting 24 months (February 2021-February 2023) is conducted at the Infectious Diseases Unit of University of Palermo to evaluate the efficacy, safety and tolerability of a two-drug antiretroviral scheme, containing dolutegravir and doravirine, in a cohort of patients with HIV infection and already on effective antiretroviral therapy.

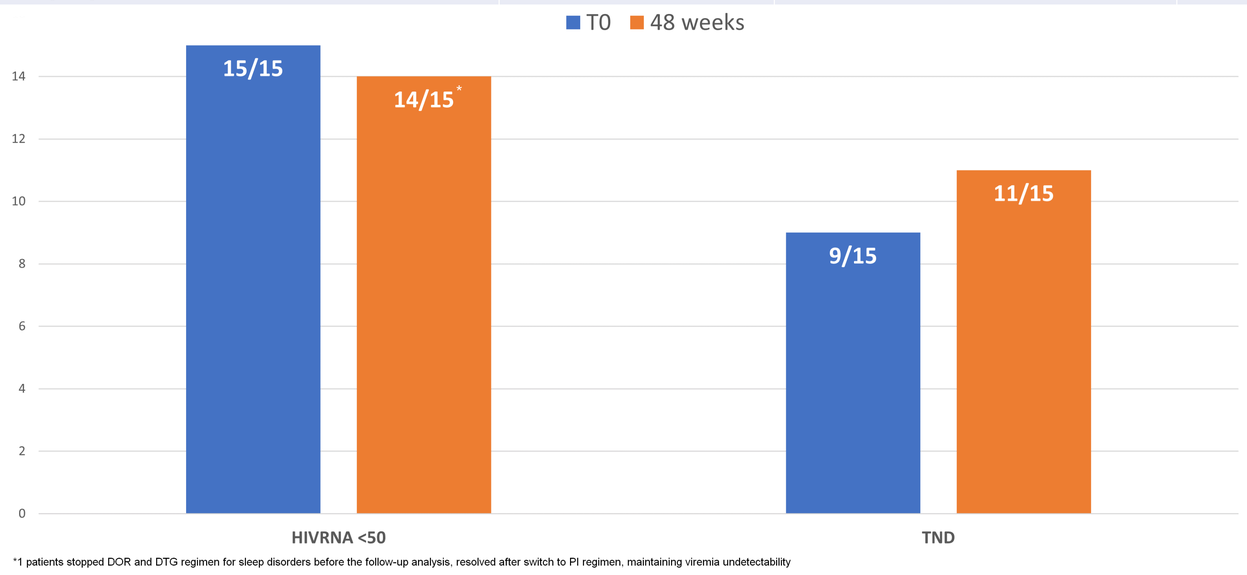
The primary endpoint of the study is maintenance of viral suppression at 48 weeks (± 6 weeks) with HIV-1 RNA <50 copies/mL. Secondary endpoints are: 1) percentage of participants without virological failure; 2) strategy success rate, defined as the percentage of participants without virological failure without interruption of study treatment; 3) genotypic resistance profile in case of virologic failure; 4) changes in CD4 cell counts, CD4/CD8 ratio, neutrophil-to-lymphocyte ratio (NLR) as a marker of systemic inflammation; 5) Estimated Glomerular Filtration Rate (eGFR), lipid profile, fasting glucose 6) clinical and laboratory adverse events.

RESULTS

Fifteen patients were included in this analysis, 10 (6.7%) males and 5 (33.3%) women. Mean age was 50.4 years (SD 12.2), with a mean lenght of HIV disease of 13.2 years (SD 7.94), mean nadir CD4 was 379/mmc (SD 201). Most frequent comorbidities were hypertension (40%), dyslipidemia (46.7%), osteoporosis and chronic kidney disease (13.3%), NCS disorders, metabolic syndrome, diabetes and HCV coinfection (6.7%). Switch to DOR and DTG were mainly due to high CV and metabolic risk (9/15, 60%). Antiretrovirals that patients were switched off were mostly integrase inhibitors (7/15, 46.7%), followed by boosted protease inhibitors (8/15, 53.3%). All 15 patients meets baseline criteria for HIV-RNA viremia <50 copies, 9/15 (60%) had complete suppression (TND). After 48 weeks, we observed a maintainance in viral suppression among all those who were undetectable at the baseline, 11/15 obtained TND. 1 patients stopped DOR and DTG regimen for sleep disorders before the follow-up analysis, resolved after switch to PI regimen, maintaining viremia undetectability. No significant changes in CD4, CD4/CD8 ration, lipid profile, renal function and neutrophil-to-lymphocite ratio were observed from the baseline.

General description of the population	
Variable	N=15
Age (year), mean ± SD (min-max)	50.4 ± 12.2 (27-71)
Male, n (%)	10 (66.7)
Time on ART (years), median (min-max)	13.2 (2-25)
CD4 Nadir, mean (min-max)	379 (40-656)
Baseline VL < 50 copies/mL, %	100%
Viral Load HIV, cop/mL, mean (min-max)	3.93 (0-31)
TND pre-switch, n (%)	9 (60%)
CD4 count at enrolment, (Cel/uL), mean (min-max)	692 (70-1119)
CD4/CD8 quotient at enrolment, mean ± SD (min-max)	1,14 ± 0,5 (0,13-2,2)
HBsAg positive (%)	0 (0%)
Use of proton pump inhibitors, n (%)	5 (33,3)
Comorbidities (each patients may have more than one)	
Dyslipidaemia	7 (46.7%)
Hypertension	6 (40%)
Peptic ulcer	2 (13.3%)
Chronic Kidney Disease	2 (13.3%)
Metabolic syndrome	1 (6.7%)
Osteopenia/Osteoporosis	2 (13.3%)
Depression/CNS symptoms	1 (6.7%)
Diabetes	1 (6.7%)
Previous ART regimen, Dual therapy n (%)	3 (20%)
Previous ART regimen, TAF based n (%)	8 (53.3%)
Previous ART regimen, n (%)	
DRV/c/TAF/FTC	4 (26.7)
BIC/TAF/FTC	3 (20)
DTG/ABC/3TC	3 (20)
DRV/c + DTG	1 (6,7)
DTG + ATV	1 (6,7)
DRV/r + ETR	1 (6,7)
ATV/b + TDF/FTC	1 (6,7)
DTG + TAF/FTC	1 (6,7)
Reason for change to DTG plus DOR, n (%)	
Hyperlipidaemia	4 (26.7)
Weight gain	3 (20)
CV risk	2 (13.3)
Use of proton pump inhibitors/DDIs	2 (13.3)
Simplified Regimen (pill-burden)	2 (13.3)
Adverse reaction in previous regimen	2 (13.3)

	Before switch	**After 48 weeks** (± 6 weeks)	**p-value**
CD4+, cell/mm3, mean (SD)	692 (284)	689 (232)	0.930
CD4/CD8 ratio, mean (SD)	1.13 (0.52)	1.23 (0.55)	0.230
Neutrophil-to-lymphocyte ratio NLR, mean (SD)	1.929 (0.829)	1.857 (0.770)	0.671
Total cholesterol, mean (SD)	197.2 (37.1)	188.9 (0.770)	0.365
HDL cholesterol, mean (SD)	55.1 (24)	55.0 (17.7)	0.977
T/HDL cholesterol ratio, mean (SD)	3.9 (1.13)	3.6 (0.8)	0.152
Fasting glucose, mean (SD)	82.4 (23.6)	95 (14.2)	0.161
Triglycerides, mean (SD)	132.8 (68.9)	112.5 (44.9)	0.140
Creatinine, mean (SD)	0.9 (0.2)	0.9 (0.2)	0.582
eGFR, mean (SD)	90.9 (21.5)	87.9 (17.2)	0.419



*1 patients stopped DOR and DTG regimen for sleep disorders before the follow-up analysis, resolved after switch to PI regimen, maintaining viremia undetectability

Summary of study result. a) Number of patients with HIV-RNA <50 copies/mL. b) Number of patients with HIV-RNA target not detected

CONCLUSIONS

Combination strategies with a good tolerability profile, an high genetic barrier and also the ability to be administered once-daily should be preferred in a setting such as the current SARS-CoV-2 pandemic. Doravirine is presented as a versatile molecule, the main feature of which is the low impact on serum lipids and carbohydrate profile, together with a distinctive resistance pattern. The combination of doravirine together with dolutegravir, a drug characterized by an excellent profile of potency, safety and long-term tolerability, appears to be a potential strategy in the setting of patients who require a regimen which maintains high virological efficacy but reduces long-term toxicity and pharmacological potentials.

References

1. Mazzitelli M, Sasset L, Leoni D, Putaggio C, Cattelan AM. Real life use of dolutegravir doravirine dual regimen in experienced elderly PLWH with multiple comorbidities and on polypharmacy: a retrospective analysis. Medicine (Baltimore). 2021;100:e28488.