Effectiveness and Safety of cobicistat-boosted darunavir-based antiretroviral treatment in an Italian Observational Cohort: the TMC114FD1HTX4003 – «ST.O.RE.» Study

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INTRODUCTION

Darunavir/cobicistat (DRV/c) is a protease inhibitor co-formulated with the booster cobicistat in fixed-dose combination (FDC), approved for the treatment of Human Immunodeficiency Virus–1 (HIV-1) infection. This FDC allows to reduce the pill burden of antiretroviral treatment (ART) and mistakes in drug administration.

STUDY DESIGN

"ST.O.RE" was a prospective, multicenter non-interventional, cohort study carried on HIV-1-infected, adult out-patients, being in stable ritonavir-boosted ARV-treatment with PIs (either darunavir 800 mg q.d.-based or not) since at least 12 months and virologically suppressed (HIV-RNA< 50 copies/ml) since at least 6 months. Patients were offered to enter this study once their treating physician had considered they were eligible to be administered DRV/c-based treatment as per DRV/c Summary of Product Characteristics. About 25 Infectious Diseases centers throughout Italy enrolled 348 patients. Patients were observed prospectively for 48±6 weeks after starting DRV/c-based regimen (**Figure 1**).

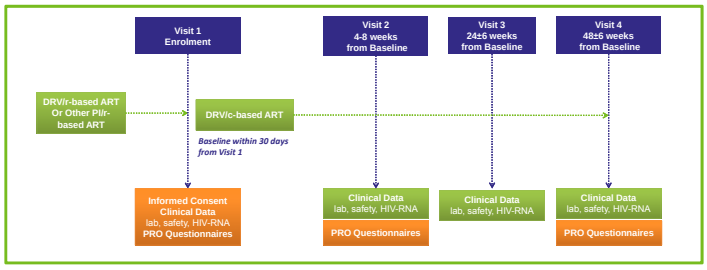


Figure 1: Study Design

OBJECTIVE

The primary objective of this study was to describe the effectiveness of this regimen, defined as virological suppression at 48 weeks, measured as maintenance of HIV-RNA<50 cp/ml as per FDA snapshot algorithm; virological failure (VF) was defined as HIV-RNA≥50 cp/ml. In addition, the study protocol established to analyze virological suppression according to TLOVR algorithm. Reasons for discontinuation and adverse events occurred during the study were also reported. Probability to remain in the study was also described. Analyzed reasons were: virological failure, adverse events and other reasons.

RESULTS

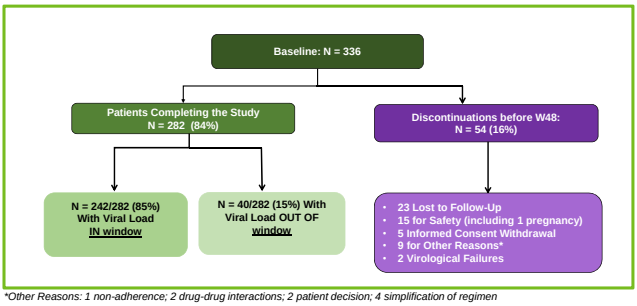
Out of **348** patients enrolled, **336** were included as evaluable for the analysis; 81.5% (274) started DRV/c- coming from a DRV/r-based regimen. 31% of patients are females. The main baseline characteristics are reported in **Table 1**.

Main baseline characteristics	Males (N=229)	Females (N=107)	Overall (N=336)	P
Age - Mean (SD)	49.6 (9.9)	48.5 (9.1)	49.2 (9.6)	-
White race - N (%)	218 (95.2%)	100 (93.5%)	318 (94.6%)	-
BMI - Mean (SD)	24.0 (3.2)	23.4 (4)	23.8 (3.5)	-
Ongoing and treated conditions - N(%)	111 (48.1%)	57 (53.8%)	168 (49.9%)	-
HCV Sero-positivity - N(%)	67 (29.0%)	25 (23.6%)	92 (27.3%)	-
Nr of years from the first HIV-1 positive test - Mean (SD)	13.2 (9.5)	16.9 (8.9)	14.4 (9.5)	0.0006*
Nr of years from the first ARV treatment - Mean (SD)	10.7 (7.6)	13.9 (7.4)	11.7 (7.6)	0.0002*
Nr of years from the first ARV treatment PIr based - Mean (SD)	6.9 (5.7)	8.4 (5.7)	7.4 (5.7)	0.0072*
Nr of years from virosuppression - Mean (SD)	4.7 (4)	5.8 (4.4)	5.0 (4.2)	0.0112*
CDC category C - N (%)	72 (31.4%)	25 (23.4%)	97 (28.9%)	-
CD4 Cell count - Median (Q1;Q3)	619 (448;883)	704 (535;917)	656 (465; 893)	-
HIV-RNA pre-HAART copies/ml - Mean (SD)	461558.7 (1380103) (N=154)	144505.4 (279534.1) (N=649)	368478.8 (1177524) (N=218)	-
CD4 Nadir (cell/mm³) - Mean (SD)	208.3 (170)	226.4 (154)	213.8 (165.3)	-
Transmission				
Intravenous Drug User	49 (21.4%)	16 (15%)	65 (19.3%)	0.1840**
Homosexual/ Bisexual	83 (36.2%)	0 (0%)	83 (24.7%)	
Heterosexual	61 (26.6%)	79 (73.8%)	140 (41.6%)	<0.0001**

** Wilcoxon Test; **Fisher Exact Test; P-values express significant difference between male and female patients*

Table 1 – Demographic Characteristics

Patients' disposition is shown in **Figure 2**:



**Other Reasons: 1 non-adherence; 2 drug-drug interactions; 2 patient decision; 4 simplification of regimen*

Figure 2: Patients' Disposition

RESULTS - Continued

Virological results are shown in **Figure 3**:

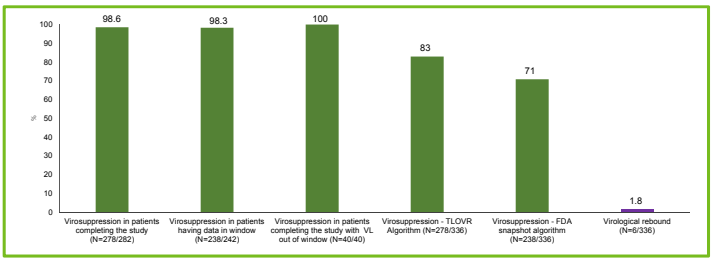


Figure 3: Virological Results; *VL = Viral Load*

282/336 (84.5%) patients completed the study; of them, 242 had data in window at Visit 4 (48±6 weeks) and 238 (98.3%) had an HIV-RNA<50cp/ml. According to TLOVR algorithm, 278/336 patients (83%) were virosuppressed after 48±6 weeks. Six virological failures occurred during the study (1.8%), all of them due to lack of adherence (2 before Visit 4), so no resistance test was performed; one patient changed therapy due to virological failure after week 48 (81 cp/ml – not confirmed). Forty-six out of 54 (85.2%) patients withdrawn from the study were virosuppressed by the time of discontinuation.

Probability to remain in the study is shown in **Figure 4** (Kaplan-Meier Analysis).

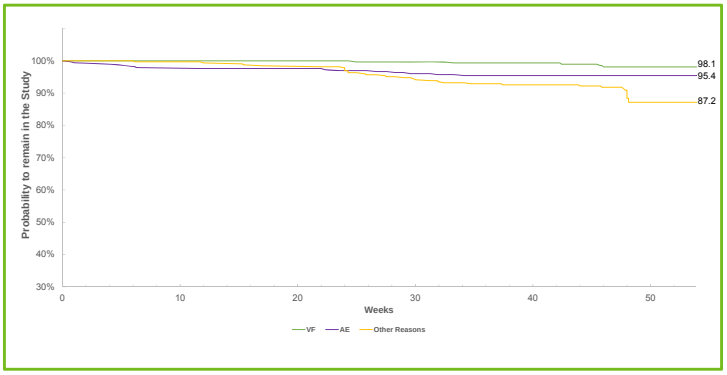


Figure 4 – Kaplan-Meier Curves; AE = Adverse Events; VF = Virological Failure

Twenty serious adverse events (SAE) were reported during the study, none related to DRV/c. Two of them (anaplastic lymphoma and Hepatitis A) led to study discontinuation. One patient discontinued the study due to pregnancy; fourteen patients (4.2%) discontinued due to 20 adverse events in total. Only six patients (1.8%) discontinued due to adverse drug reaction to DRV/c. No special safety issues were registered. Details are provided in **Table 2**.

Patient	AE Description	Grade	SAE (Yes/No)	Relationship with DRV/c
1	Anaplastic large-cell lymphoma	4	Yes	Not Related
2	Hepatitis A	3	Yes	Not Related
3	Neck pain	2	No	Not Related
4	Epistaxis	1	No	Not Related
5	Proteinuria	2	No	Not Related
6	Lipid metabolism disorder	2	No	Not Related
	Gastro-oesophageal reflux disease	2	No	Doubtful
7	Pain in extremity	1	No	Doubtful
8	Hypercholesterolaemia	1	No	Doubtful
9	Malaise	2	No	Possible
	Myalgia	2	No	Possible
	Anxiety	2	No	Possible
10	Diarrhoea	2	No	Possible
11	Gastrointestinal disorder	1	No	Possible
12	Pruritus	1	No	Probable
13	Dyspepsia	2	No	Very Likely
	Nausea	2	No	Very Likely
14	Nausea	2	No	Very Likely
	Dyspepsia	2	No	Very Likely
	Vomiting	2	No	Very Likely

Table 2 – Adverse Events leading to study discontinuation

CONCLUSIONS

This study has confirmed in clinical practice the high virological suppression and good safety profile of DRV/c, as shown in pivotal trials[1,2] suggesting that this regimen is an effective option for patients in daily practice, ensuring virosuppression and good tolerability.

References:
1. Tashima et al. AIDS Research and Therapy 2014, 11(1):39-50
2. Orkin et al. The Lancet HIV 2018, 5(1):PE23-PE34

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