Transient viral load increase in HIV-1 infected patients treated with cobicistat-boosted darunavir regimen in an Italian observational, multicenter, prospective study (The TMC114FD1HTX4003 – "ST.O.RE." Study)

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INTRODUCTION

Treatment guidelines recommend HIV-1 RNA suppression below the limit of detection of the assay (generally <50 cp/mL) as a key goal of antiretroviral therapy. Transient viral load (TVL) increases, i.e. ≥ 50 cp/ml, are commonly observed in otherwise successfully treated patients.

Studies of HIV-infected children suggest that plasma virus during transient episodes in these patients originates from activation and expansion of latently infected cells (archived virus) and from ongoing viral replication, including the appearance and selection of new drug-resistant strains. This is not confirmed in the adult population. TVL is more frequently observed under PI-regimens; this may be due to release of defective virus particles detected by the assay even if not infective.

STUDY DESIGN

"ST.O.RE." was an Italian 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 800mg q.d.-based or not) since at least 12 months and virologically suppressed (HIVRNA< 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. Twenty-five Infectious Diseases centers throughout Italy enrolled 348 patients. Patients were observed prospectively for 48±6 weeks after starting DRV/c-based regimen with collection of viroimmunological parameters from clinical practice.

MATERIALS AND METHODS

We evaluated the rate and the effect of TVL increase during the entire duration of "ST.O.RE." study.
All available HIVRNA data, collected in patients on treatment, were included throughout 48 weeks of observation. TVL increase was defined as HIVRNA values ≥50cp/ml both single or confirmed measurements occurring anytime during the 48 weeks whether or not leading to virologic failure.
For the purpose of this analysis we split patients into two groups according to viral load (VL) levels: Group 1 VL ≥ 1000 cp/ml and Group 2 VL between 50-999 cp/ml.
We also analyzed the CD4 cell count, CD8 cell count, and CD4/CD8 ratio in patients showing TVL increase to observe potential change in immunological parameters. Immunological parameters considered for this analysis were values obtained during TVL and first visit post TVL.
Continuous data were presented as median and interquartile range (IQR). Comparisons between groups were performed using Wilcoxon rank-sum test and correlation analyses were performed by calculating Pearson coefficient. All tests were two sided and a p-value <0.05 was considered as statistically significant.

RESULTS

Out of 348 patients enrolled, 336 were included as evaluable for this analysis; 31% of them were females.
All patients were virosuppressed at baseline. Among 336 analyzed patients, 59% and 34% were on triple and dual regimens post-switch respectively. A total of 18/336 (5.4%) patients (11 on triple therapy – 63.6% of them had TDF/FTC as backbone) showed a TVL increase over the study. All of them were Caucasian; 12 were male (Table 1).
We observed TVL increase ≥ 1000cp/ml in eight patients (Group 1) while TVL between 50-999 cp/ml was reported in 10 (Group 2). Reported reasons for TVL increase were virological blip (a single measurement between 50-1000 cp/ml) in nine patients, non-adherence (VL ≥ 50 cp/ml and/or ≥1000 cp/ml in single or consecutive measurements during declared non-adherence period) in eight, virological failure in one during last visit of protocol (last HIV-RNA was detectable), drug-drug interactions (DDI) in one taking rifampicin and isoniazid.
We analyzed comparison between TVL increase and immunological status when CD4 and CD8 cell count were recorded in e-CRF. Data are shown in Table 2.

Table 1. Patients characteristics

Patient	Gender	ART therapy	TVL (cp/mL)	Reason of TVL	Concomitant therapy (Y/N)
1	M	DRV/c+TVD	80	virological blip	Y
2	M	DRV/c+TVD	19914	Non-adherence	N
3	M	DRV/c+TVD	81	virological failure	Y
4	M	DRV/c+KVX	33770	Non-adherence	Y
5	M	DRV/c+MVC	4127	Non-adherence	N
6	M	DRV/c+RAL	230	virological blip	Y
7	M	DRV/c+KVX	57	virological blip	Y
8	F	DRV/c+RAL	100	virological blip	Y
9	M	DRV/c+RAL	1990	Non-adherence	Y
10	M	DRV/c+RAL+MVC	189	virological blip	N
11	F	DRV/c+MVC	164	virological blip	N
12	F	DRV/c+TVD	73	Non-adherence	Y
13	F	DRV/c+TVD	53	virological blip	Y
14	M	DRV/c+TVD	7545	Non-adherence	N
15	M	DRV/c+TVD	134	virological blip	N
16	M	DRV/c+KVX	3155	DDI	Y
17	F	DRV/c+3TC	1264	Non-adherence	Y
18	F	DRV/c+3TC	102212	Non-adherence	N

RESULTS - Continued

Table 2. Comparison of Immunologic Parameters in the 18 Patients with TVL

	Group 1 HIVRNA≥1000 Median (IQR) n=8	Group 2 HIVRNA<1000 Median (IQR) n=10	P for comparison*
HIV RNA Mean (SD)	5836 (24270) 21747 (34413)	90.5 (91.0) 116 (61)	0.0004
CD4	725 (520)	560 (459)	
CD4 post	322 (302)	592 (373)	
Change	-280 (270)	-53 (149)	0.01
CD8	890 (711)	859 (231)	
CD8 post	831 (482)	922 (749)	
Change	-142 (662)	-46 (782)	0.39
CD4/CD8	0.68 (0.21)	0.48 (0.49)	
CD4/CD8 post	0.40 (0.31)	0.50 (0.96)	
Change	-0.195 (0.394)	0.0 (0.07)	0.001

IQR: Interquartile Range; SD: Standard Deviation
* Wilcoxon rank sum test

CD4 cell count and CD4/CD8 ratio decrease were statistically significant in patients with TVL≥1000cp/ml as compared to those with TVL <1000cp/ml (Table 2). We found a negative correlation, albeit barely significant, between TVL and CD4/CD8 change (rho=-0.50 p=0.056) (Table 3).
CD8 cell count values was underreported during the "ST.O.RE." study therefore negative correlation can't be confirmed despite significance level found.

Table 3. Correlation between HIVRNA and immunological parameters

Immunological Parameters	Pearson Correlation Coefficient Rho	P value
CD4	0.12	0.65
CD4 post	-0.15	0.6
Change	-0.31	0.23
CD8	-0,15	0.61
CD8 post	0,4	0.15
Change	0.38	0.16
CD4/CD8	0,47	0.08
CD4/CD8 post	-0.30	0.29
Change	-0.50	0.056

CONCLUSIONS

In our study throughout 48 weeks, TVL increase occurred infrequently: 18/336 patients (5.4%). All virological blip and two non-adherence re-suppressed with the same antiretroviral regimen after TVL.

TVL increase (≥1000 cp/ml) appears to affect the immunological status with possible increase of immune activation and inflammation.

THE ST.O.RE. STUDY GROUP
We acknowledge all the patients participating in the study and all the investigators.

Massimo Andreoni-Policlinico Tor Vergata, Roma; Andrea Antinori-INMI L. Spallanzani, Roma; Francesco Castelli-ASST degli Spedali Civili, Brescia; Annamaria Cattelan-AOU Padova, Padova; Roberto Cauda-Fondazione Policlinico A.Gemelli, Roma; Maurizio Celesia-ARNAS Garibaldi, Catania; Lucio Cosco-A.O. Pugliese Ciaccio, Catanzaro; Antonella d'Arminio Monforte-ASST Santi Paolo e Carlo, Milano; Andrea De Luca-A.O.U. Senese, Siena; Giovanni Di Perri-Ospedale Amedeo di Savoia, Torino; Elio Manzillo O. Cotugno, Napoli; Andrea Gori- Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan Infectious Diseases Unit, Milan Italy; ; Adriano Lazzarin-Ospedale San Raffaele, Milano; Giordano Madeddu-A.O.U. Sassari, Sassari; Renato Maserati-Fondazione IRCCS Policlinico San Matteo, Pavia; Maurizio Mineo-A.O.U. Policlinico Giaccone, Palermo; Giancarlo Orofino-Ospedale Amedeo di Savoia, Torino; Giovanni Penco-EO Ospedali Galliera, Genova; Barbara Menzaghi-Ospedale di Circolo, Busto Arsizio; Diego Ripamonti-ASST Papa Giovanni XXIII, Bergamo; Giuliano Rizzardini-Ospedale Luigi Sacco, Milano; Stefano Rusconi-Ospedale Luigi Sacco, Milano; Teresa Antonia Santantonio-A.O.U. Ospedali Riuniti, Foggia; Gaetana Sterrantino-A.O.U. Careggi, Firenze; Vincenzo Vullo-Policlinico Umberto I, Roma.

«STORE» study was funded by Janssen-Cilag SpA, Italy