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Efficacy and safety of switching to co-formulated DOR/TDF/3TC in adult HIV-1-infected ART experienced: data from a single Italian Center in Florence, Italy

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Introduction

Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is also available co-formulated with tenofovir disoproxil (TDF) and lamivudine (3TC). Real-life data on DOR is lacking. The study aim is to evaluate the efficacy, safety, and metabolic impact of switching to DOR/TDF/3TC in a cohort of people living with HIV (PLWH) treated in a single center in Florence, Italy.

Materials and Methods

This is a retrospective, monocentric cohort study. We included all PLWH > 18 years old, antiretroviral therapy (ART) experienced switching to DOR/TDF/3TC with at least one follow-up visit at the Infectious and Tropical Diseases Unit in Careggi University Hospital, Florence. Study entry was the date of DOR/TDF/3TC initiation; exit was the discontinuation date, loss to follow-up, or the end of follow-up (March 2024). Virological failure (VF) was defined as two consecutive HIV-RNA >50 copies/mL detections or a single HIV-RNA >50 copies/mL followed by ART modification. However, those lost to follow-up weren't considered treatment discontinuations.

Results

We included 86 patients with a median FU of 2.43 years [IQR 1.5 – 3.4] with a maximum observation time of 4.5 years. At the switch, 81.4% (n=70) had undetectable HIV-RNA, while 18.6% (n=16) did not. No notable differences were observed between these groups. Demographic and clinical details are elucidated in Table 1. Notably, in 91.7% of PLWH, the pre-switching regimen was a 3-drug regimen, with tenofovir alafenamide (TAF) forming part of most backbones (54.7%). Over 60% of the cohort had at least one comorbidity, predominantly psychiatric disorders, followed by dyslipidemia and hypertension (Figure 1). We found 11 (12.8%) discontinuations attributable to various factors listed in Table 2, with an overall discontinuation rate of 5.34 per 100 patient-years [95%c 2.95 – 9.64]. Notably, two out of the 3 viral failures were PLWH who switched to DOR/TDF/3TC with detectable HIV-RNA. The only VF observed in PLWH who switched with HIV-RNA <50 cp/mL, occurred due to pre-existing mutations to TDF and 3TC (Table 2). Conversely, the majority (14 out of 16) of those starting with detectable viremia obtained undetectable levels after the switch. Figure 2 shows the probability of maintaining DOR/TDF/3TC up to 4 years. A focused analysis on individuals with over two years of follow-up showed significant reductions in total cholesterol and triglycerides without affecting creatinine levels (Table 3).

Table 1. Clinical/demographic characteristics of adults with HIV-1, ART experienced with HIV-RNA level <50 copies/mL, HIV-RNA level >50 copies/mL, switching to DOR/TDF/3TC in the Infectious and Tropical Disease Unit of Careggi University Hospital, Florence, Tuscany, Italy.

	HIV RNA start <50 cp/mL (N=70)		HIV RNA start >50 cp/mL (N=16)		p	TOTAL (n=86)	
Italians, n (%)	45	64.3	9	56.3	0.549	54	62.79
Gender, n (%)					0.102		
• Female	5	7.1	4	25.0		9	10.5
• Male	57	81.5	11	68.7		68	79.0
• Transgender	8	11.4	1	6.3		9	10.5
Age at entry, median [IQR]	48.5	[40.7 - 57.0]	46.3	[35.6 – 54.1]		47.5	[39.9 - 56.6]
Risk of HIV transmission, n (%)					0.075		
• Heterosexual	11	15.7	4	25,0		15	17.4
• MSM	28	40.0	2	12.4		30	34.9
• Intravenous drug users	2	2.9	1	6.3		3	3.5
• Vertical	0	0	1	6.3		1	1.2
• Other/ Not known	29	41.4	8	50.0		37	43.0
AIDS diagnosis, n (%)	8	11.4	3	18.8		11	12.8
HIV-RNA Zenit, Log_{10} copies/mL, median [IQR]]	5.12	[4.57 – 5.42]	5.09	[3.96 – 5.93]	0.669	5.09	[4.56 – 5.62]
Nadir CD4 (cells/mL), median [IQR]	366	[180 - 510]	232	[126 - 403]	0.337	365	[156 - 499]
Years of HIV, median [IQR]	10.8	[4.0 – 16.2]	11.2	[4.0 – 21.8]	0.657	10.9	[4.0 – 16.2]
CD4+ T cells at baseline/µL, median [IQR]	740	[596 – 979]	779	[447 – 930]	0.467	742	[586 – 965]
CD4/CD8 cells at baseline/µL, median [IQR]	0.9	[0.6 – 1.2]	0.7	[0.5 – 1.3]	0.665	0.8	[0.5 – 1.1]
Previous 3D regimen	65	92.9	14	87.5	0.007	79	91.7
Type of pre-switch regimen					0.104		
• NNRTI	39	55.7	5	31.3		44	51.2
• PI	5	7.1	3	18.7		8	9.4
• INSTI	21	30.0	6	37.5		27	31.4
• NRTI + INSTI (2D)	3	4.4	0	0		3	3.4
• NNRTI + INSTI (2D)	1	1.4	0	0		1	1.2
• Other	1	1.4	2	12.5		3	3.4
Tenofovir in the backbone in the pre-switch regimen					0.253		
• TDF	18	25.7	7	43.7		25	29.1
• TAF	39	55.7	8	50.0		47	54.7
• No TXF	13	18.6	1	6.3		14	16.2
Number of previous ART regimens, median [IQR]	3	[2 – 4]	4	[2 – 5]	0.598	3	[2 – 4]
Coadministration of statins at baseline	8	11.4	1	6.3	0.542	9	10.5
Follow-up							
Discontinuation	9	12.9	2	12.5	0.969	11	12.8
Lost at Follow-up	6	8.6	1	6.3	0.759	7	8.1
Time of follow-up							
• <1 year	9	12.9	2	12.4		11	12.8
• 1-2 years	17	24.3	7	43.8		24	27.9
• 2-3 years	15	21.4	3	18.8		18	20.9
• >3 years	29	41.4	4	25.0		33	38.4

ART: antiretroviral treatment; MSM: males who have sex with males; PI: Protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitors; INSTI: integrase strand transfer inhibitor; 2D: two-drug regimen; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; TXF: Tenofovir

Figure 1. Comorbidities of adults with HIV-1, ART experienced, who switched to DOR/TDF/3TC, in the Infectious and Tropical Disease Unit of Careggi University Hospital, Florence, Tuscany, Italy.

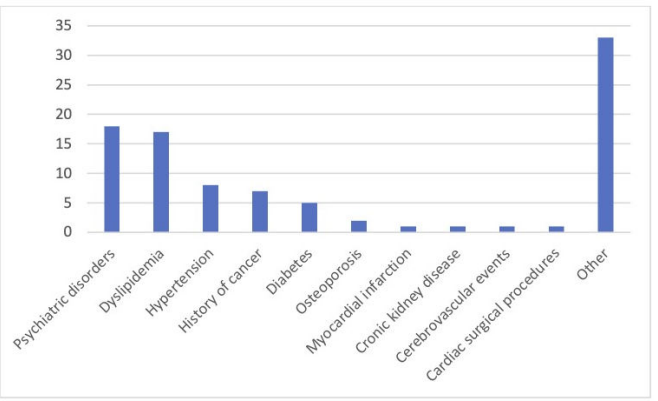


Table 2. Clinical characteristics of adults with HIV-1, ART experienced who discontinued DOR/TDF/3TC in the Infectious and Tropical Disease Unit of Careggi University Hospital, Florence, Tuscany, Italy.

Previous regimen	Gender	HIV RNA Viral load in cp/mL at switch to DOR/TDF/3TC	Subtype	Major mutations on the last genotype	Cause	Time to discontinuation in years	Post- regimen
DRV/r + TDF/FTC	F	TND	B	Not detected	Osteopenia	3.3	3TC/DTG
DRV/c/TAF/FTC	M	30	B	Not detected	Switch to LA CAB+ RPV	1.8	LA CAB + RPV
DRV/c/TAF/FTC	M	TND	NA	Not detected	Switch to the previous regimen that was suspended for major interactions with DAA in HCV coinfection	0.3	DRV/c/TAF/FTC
DRV/c/TAF/FTC + DTG	F	115	B	Not detected	Virological failure in poor adherence	0.3	DRV/c/TAF/FTC + DTG
RPV/TAF/FTC	M	<20	B	Not detected	Pill dimensions	1.0	RPV/DTG then LA CAB + RPV
RPV/DTG	M	22	B	41L 62V 65N 67E 70R 103T 184I 210W 215N 215S 215Y 69SA/G	Virological failure	1.3	RPV/DTG + DRV/c
TDF/FTC + DTG	M	TND	NA	Not detected	Lactose intolerance (excipient in DOR/TDF/3TC)	4.0	3TC/DTG
BIC/TAF/FTC	M	108	B	Not detected	Virological failure	1.5	DRV/c/TAF/FTC
RPV/TAF/FTC	M	TND	NA	NA	Frequent Blips HIV RNA 50-100 cp/mL	2.5	RPV/DTG
RPV/TAF/FTC	M	TND	NA	NA	DDI (TDF with lenalidomide inducing severe nephropathy) in MM treatment	4.3	RPV/TAF/FTC
BIC/TAF/FTC	M	26	NA	Not detected	Gastrointestinal intolerance	0.03	EVG/c/TAF/FTC then LA CAB + RPV

TND: toget not detected; M: Male; F: Female, NA: Not Available. TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; 3TC: Lamivudine; DRV: Darunavir; RPV: Rilpivirine; DTG: Dolutegravir; BIC: Bictegravir; CAB: Cabotegravir; EVG: Elvitegravir; LA: Long acting.; DAA: direct-acting antivirals; DDI: Drug-Drug Interaction; MM: Multiple Myeloma

Figure 2. Probability of remaining free from treatment discontinuation for all causes in adults with HIV-1 ART experienced switching to DOR/TDF/3TC in the Infectious and Tropical Diseases Unit at Careggi Hospital, Florence.

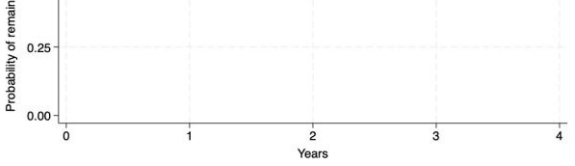
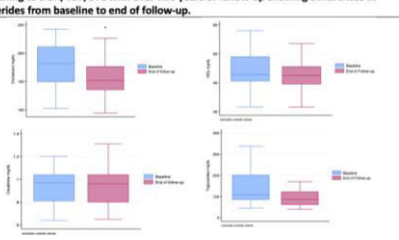


Table 3. **Focused analysis on PLWH switching to DOR/TDF/3TC with over two years of follow-up showing Differences in cholesterol, HDL, creatinine and triglycerides from baseline to end of follow-up.**



	PLWH switching to DOR/TDF/3TC with more than 2 years of FU at baseline blood exams (N=51)	PLWH switching to DOR/TDF/3TC with more than 2 years of FU at the end of Follow-up (N=51)	p
Triglycerides mg/dL, median [IQR] Normal ranges: <150 mg/dL normal; 150-199 mg/dL borderline; 200-500 mg/dL high; >500 mg/dL very high	107 [85 -201]	85 [61 – 122]	<0.001
Cholesterol mg/dL, median [IQR] Normal ranges: <200 mg/dL desiderable; 200-240 mg/dL borderline; >240 mg/dL high risk	181 [149 - 211]	151 [135 – 176]	<0.001
HDL mg/dL, median [IQR] Normal ranges: >60 mg/dL low risk; 40-60 mg/dL borderline; <40 mg/dL high risk	45 [41-58]	45 [39-51]	0.448
Creatinine mg/dL, median [IQR] Normal ranges: 0.7 – 1.2 mg/dL	0.97 [0.81 – 1.04]	0.96 [0.8 – 1.04]	0.938

Conclusions

Switching to DOR/TDF/3TC was effective across varying baseline HIV-RNA levels, demonstrated good tolerability, and was associated with a marked improvement in serum lipid profiles.

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