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P132

Three versus two-drugs doravirine based regimens: a multicenter observational study

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Background

The aim of this study was to compare the effectiveness of three-drug (3DR) vs two-drug (2DR) doravirine (DOR)-based regimens.

Methods

Retrospective multicentric study including treatment-experienced people with HIV (PWH) who started regimen with DOR/lamivudine(3TC)/tenofovir dysoproxil(TDF) (single tablet regimen) or DOR+3TC (=baseline). Demographics, HIV-related characteristics, and metabolic parameters at baseline were compared. Reasons for treatment discontinuation and virologic failure (VF), defined as HIV-RNA>200 copies/ml for two consecutive measurements or HIV-RNA>1000 copies/ml, were analysed.

Results

Two-hundred-eighteen individuals were included: 171 (78.8%) in 3DR and 47 (21.6%) in 2DR. Clinical characteristics were shown in Table 1. PWH on DOR+3TC were older and with longer history of HIV infection and antiretrovirals exposure (p=0.01). Reasons for 2DR switch were mainly driven by metabolic issues and psychiatric symptoms. Lipids and creatinine values at baseline were similar in the two groups, while hypertension, diabetes, osteopenia/osteoporosis and chronic kidney disease were more prevalent in the DOR+3TC group (Figure 1).

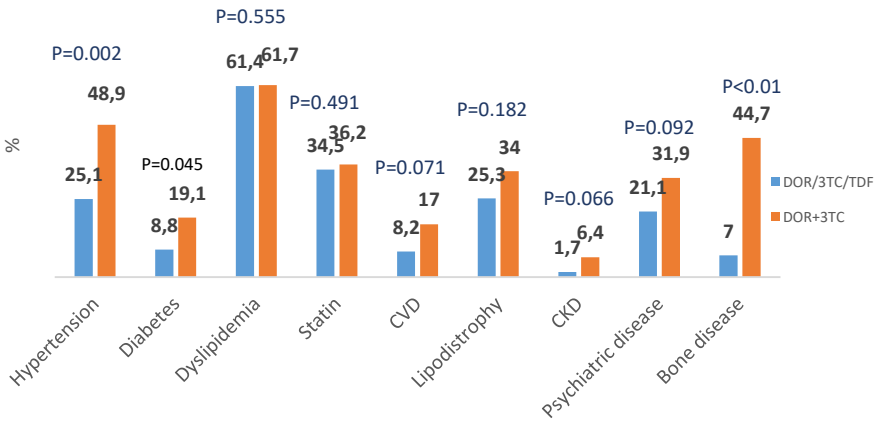
Table 1. Characteristics of PWH on DOR/3TC/TDF versus DOR+3TC

	DOR/3TC/TDF (n=171)	DOR+3TC (n=47)	p
Age, years (IQR)	50.9 (31.2-68.6)	55.9 (32.4-74.5)	0.0199
Males, n (%)	117 (68.0)	35 (74.5)	0.271
Ethnicity, n (%)			0.001
Caucasian	132 (77.2)	43 (91.5)	
African	28 (16.4)	0 (0)	
Asiatic	7 (4.1)	0 (0)	
Other	4 (2.33)	4 (8.5)	
Time since HIV diagnosis, years (IQR)	15.1 (2.4-34.2)	18.2 (5.4-37.1)	0.0107
HIV mode of acquisition, n (%)			0.037
Hetero	73 (42.7)	19 (40.4)	
MSM	76 (44.4)	14 (29.8)	
Other	22 (12.9)	13 (27.7)	
CD4 nadir, median (IQR)	287 (25-773)	240 (31-501)	0.223
HIV RNA zenith, median (IQR)	63150 (2,800-1,699,328)	30200 (5,100-500,000)	0.914
AIDS, n (%)	46 (29.3)	11 (26.8)	0.460
Time since ART initiation, years (IQR)	12.0 (1.8-26.4)	17.5 (3.5-29.6)	0.009
Duration VS, months (IQR)	104 (1-228)	105 (21-180)	0.549
Previous regimen, n (%)			
3DR	151 (88.3)	24 (51)	0.000
TXF	139 (81.3)	22 (46.8)	0.000
DOR	3 (1.75)	5 (10.6)	0.013
Other NNRTI	101 (59.1)	18 (38.3)	0.007
PI	64 (37.4)	13 (27.6)	0.131
INSTI	63 (36.8)	19 (40.4)	0.409
Reason for switch, n (%)			
Pill/drug reduction	53 (31.0)	21 (44.7)	0.092
Metabolic	67 (39.2)	25 (53.2)	0.102
Toxicity/intolerance	34 (19.9)	20 (42.5)	0.003
Bone	0 (0)	12 (25.5)	0.000
Psychiatric	14 (8.2)	13 (27.7)	0.001
Resistance/intensification	9 (5.3)	2 (4.2)	0.533
HBsAg pos, n (%)	8 (4.7)	-	
ASCVD risk score, median (IQR)	7 (1.0-25.3)	7.1 (1.1-47.7)	0.303
Body mass index, median (IQR)	25.7 (20.7-33.0)	25.3 (17.8-31.4)	0.482
Viro-immunological characteristics at baseline			
CD4 cell count, median (IQR)	698 (348-1,317)	778 (415-1,231)	0.340
CD4/CD8 ratio, median (IQR)	0.94 (0.23-1.76)	0.96 (0.39-2.05)	0.966
HIV RNA< 50 copies/ml	153 (94.4)	47 (100)	0.299
Full GSS*, n (%)	110 (91.6)	32 (82.1)	0.086
Previous acquired mutations to DOR, n (%)	2 (1.7)	3 (7.7)	0.090
Previous acquired mutations to 3TC, n (%)	8 (6.7)	7 (17.9)	0.006

* Genotipic Resistance test available for 120 individuals on DOR/3TC/TDF and 39 individuals on DOR/3TC

Abbreviations: 3DR, three-drug regimen; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; GSS, genotypic susceptibility score; MSM, men who have sex with men.

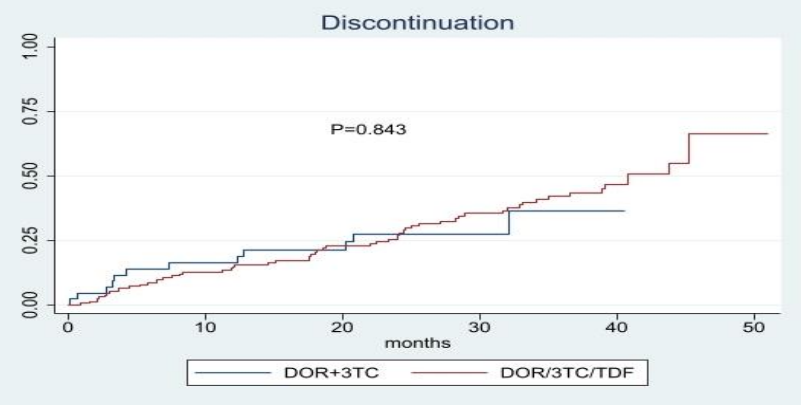
Figure 1. Metabolic characteristics of PWH on DOR/3TC/TDF or DOR+3TC at baseline



CVD, cardiovascular disease; CKD, chronic kidney disease; bone disease defined as presence of osteopenia or osteoporosis by means of DEXA

Discontinuations were 59 (35%) in DOR/3TC/TDF and 12 (25.5%) in DOR+3TC (logrank=0.834) (Figure 2), with median time to discontinuation of 18.2 months (2.1-40.8) vs. 5.8 months (0.13-32.1) (p=0.017). Main reasons for discontinuation were toxicity/intolerance [24/59 (40.6%) in 3DR vs 5/12 (41.6%) in 2DR] (p=0.597), reduction in pill/drug burden [18/59 (30.5%) vs 2/12 (16.6%)] (p=0.276) and virological failure/increase of genetic barrier [9/59(15.3%) vs. 5/12(41.6%)] (p=0.051). During a 25 months (IQR 2.8-44.3) follow-up period, 3 VF (1.7%) occurred in the 3DR group leading to discontinuation and emergence of resistance mutations in 2. During a follow-up of 23.8 months (2.8-37.7), 1 VF (2.1%) was reported in the 2DR group with emergence of N348I (with no impact on DOR susceptibility) while 2 blips led to treatment intensification. Genotypic susceptibility score <2 was reported in 7 out of 39 individuals with available genotypic resistance test on 2DR mainly for the presence of archived M184V but 3 individuals showed also DOR mutations: of these, 4 maintained virological suppression until last available follow-up (median 19.2 months).

Figure 2. Discontinuation according to 3DR versus 2DR doravirine (DOR)-based regimens



Conclusions

DOR/3TC/TDF and DOR+3TC were comparable in terms of effectiveness and durability. DOR+3TC might be an option in case of complex interplay of metabolic disorders and history of intolerance, exclusively if full known susceptibility to the regimen and reinforced adherence.