

## Antiretroviral Therapy

P 34

# Outcomes of doravirine-based regimens in virologically suppressed ART-experienced persons with HIV: data from the Icona Cohort

### Authors

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### ABSTRACT

**Background:** Randomized clinical trials demonstrated the efficacy of Doravirine (DOR) both in ART-naïve and pre-treated, virologically suppressed PWH. We aim to verify the outcome of ART-experienced virologically suppressed PWH on 3DR-DOR-including regimens in the real-world setting in Italy.

**Methods:** Observational study from the ICONA Cohort. Inclusion criteria: PWH ≥18 years-old, initiating DOR after July 2019 (availability of DOR in Italy) switched while virologically suppressed (HIV-RNA ≤50 cps/ml) from any other regimen to a 3DR-DOR-based regimen.

Primary endpoints: -time to treatment failure (TF): virological failure (VF: HIV-RNA >50 copies/mL in 2 consecutive determinations or single >1000 copies/mL followed by ART change) or DOR discontinuation for toxicity/failure; - changes in mean CD4, CD4/CD8, total cholesterol, LDL, HDL, Triglycerides after DOR switch. Reasons for DOR discontinuation were collected as reported by the treating physician.

The cumulative probability of TF was calculated by Kaplan-Meier curves.

Adjusted and unadjusted Cox regression models were used to estimate the risk of time to TF according to selected exposures of interest (sex, age ≥65 years, being born in Italy, previous NNRTI use and CD4 at first ART and at DOR switch).

Mixed linear models with random intercept and slope were used to estimate the mean CD4 and CD4/CD8 ratio and lipids changes from DOR initiation at different timepoints.

**Results:** A total of 640 PWH were included: 78% males, 7% age ≥65y, 82% born in Italy, 2.7% with CD4 <200 cells/mm<sup>3</sup> at DOR-switch, 29.4% with CD4 <200 cells/mm<sup>3</sup> at first ART start, 51% on previous NNRTI-based regimen, 88.3% with 3TC/TDF as backbone; 66% reached 96-weeks of follow-up and 42% the 144-weeks. Full

description in Table 1. In a median follow-up of 132 weeks (80-175), TF occurred in 40 cases (15 VF/discontinuation for failure and 25 discontinuations for toxicity: 7 gastrointestinal intolerance, 5 allergic reactions, 4 anxiety/insomnia, 3 osteopenia and 6 other): the probability of TF was 4.5% (95%CI 3.1-6.5) at 48w and 6.2% (4.5-8.6) at 96w. In the multivariable Cox analysis, sex, age, being born in Italy, CD4 at ART initiation, were not predictive of TF, while PWH with CD4<200/mm<sup>3</sup> at DOR switch had higher risk of time to TF (aOR 3.56, 95%CI 1.03-12.29); previous NNRTI-including ART was marginally protective (aOR 0.47; 95%CI 0.21-1.05) (Table2). Mean CD4 counts as well as the lipid parameters (cholesterol, LDL and triglycerides) showed improvements overtime, with significant improvements during follow-up (Figure 1).

**Conclusion:** In our single-arm study, switching to 3DR-DOR with undetectable HIV-RNA is a successful strategy that resulted only in 6.2% probability of treatment failure by 96 weeks. PWH with CD4<200/mm<sup>3</sup> should be treated with caution. The safe profile of DOR on lipid assets was also confirmed in our study.

**Table 1.** Characteristics of 640 PWH switching to DOR-based regimens

Age, median (IQR)	50 (42-56)
>65, n(%)	45 (7%)
Sex, Males n(%)	499 (78%)
Born in Italy, n (%)	522 (81.6%)
HCV-Ab pos, n (%)	63 (10.2%)
HBSAg pos, n (%)	38 (6.1%)
AIDS, n (%)	90 (14.1%)
CD4 ART start, median (IQR)	334 (184-498)
CD4 ART<200, n (%)	186 (29.4%)
HIV suppression, years, median (IQR)	7.1 (4.2-10.3)
Line of ART, median (IQR)	3 (2-5)
2nd line ART, n (%)	168 (26.2%)
CD4 DOR start, median (IQR)	736 (553-943)
CD4 DOR<200, n (%)	17 (2.7%)
Diabetes, n (%)	50 (7.8%)
CVD, n (%)	7 (1.1%)
NADMs	19 (3.0%)
Cholesterol, median (IQR)	193 (165-222)
HDL, median (IQR)	48 (40-57)
LDL, median (IQR)	123 (98-147)
Triglycerides, median (IQR)	111 (78-164)
BMI, kg/m <sup>2</sup> , median (IQR)	25.0 (22.8-27.8)
>30, n (%)	81 (14.8%)
DOR regimen, n(%)	
3TC,TDF,DOR	565 (88.3%)
FTC,TAF, DOR	62 (9.7%)
3TC,ABC,DOR	8 (1.2%)
FTC,TDF,DOR	5 (0.8%)
ART-class previous regimen, n(%)	
NNRTI	329 (51.4%)
INSTI	191 (29.8%)
PI	91 (14.2%)
Other	29 (4.5%)

Notes: CVD, cardiovascular diseases; NADMs, non AIDS defining malignancies;

**Table 2.** Unadjusted and Adjusted Hazard Ratios (HR) of TF by Cox regression model

	HR	95%CI	P	aHR <sup>†</sup>	95%CI	p
Sex, F (vs. M) <sup>§1</sup>	1.37	0.68-2.74	0.374	1.26	0.59-2.68	0.549
Country of birth, ITA (vs non-ITA) <sup>§2</sup>	0.83	0.38-1.8	0.636	0.92	0.41-2.05	0.837
Age >65 (vs <65 yrs) <sup>§3</sup>	0.71	0.17-2.95	0.638	0.87	0.21-3.69	0.853
NNRTI-class previous ART (vs Other) <sup>§4</sup>	0.35	0.18-0.7	0.003	0.47	0.21-1.05	0.065
CD4 ART initiation <200 cells/mm <sup>3</sup> (2200) <sup>§5</sup>	1.06	0.54-2.10	0.860	0.93	0.44-1.97	0.857
CD4 DOR initiation <200 cells/mm <sup>3</sup> (2200) <sup>§6</sup>	3.52	1.08-11.45	0.036	3.56	1.03-12.29	0.045

<sup>§1</sup> sex adjusted for nation of birth, age and year of first combination ART; <sup>§2</sup> Nation of birth adjusted for year of ART initiation, age and sex at birth; <sup>§3</sup> age adjusted for nationality, year of first combination ART and mode of HIV transmission; <sup>§4</sup> NNRTI-class pre CD4 nadir, line of ART, previous VF, year first ART, sex, age, nation, mode of HIV transmission; <sup>§5</sup> CD4 ART start adjusted for sex, mode of HIV transmission, HIV-RNA, year of first combination ART and nation of birth; <sup>§6</sup> Current CD4 adjusted for years of VS, line of ART, mode of HIV transmission, year first ART, sex, age;

**Figure 1.** Mean CD4 cell count (A), CD4/CD8 ratio (B), total cholesterol (C), HDL (D), LDL (E) and Triglycerides (F) after switch to DOR by linear mixed models

