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Real-life use of doravirine in ART-Experienced PLWH bearing drug resistance mutations: findings from a monocentric cohort study

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Introduction

- Doravirine (DOR), a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) exhibiting a unique resistance profile, which is determined by the innovative molecular structure. This characteristic allows the use of DOR even in PLWH with Drug Resistance Mutations (DRMs) who already experienced treatment failure with previous NNRTI (1, 2)
- DRMs associated with DOR seem to rarely occur and promising data result from study among naive PLWH in comparison with other ART regimen (3)
- Few real-world data are available to assess the efficacy of DOR-based ART with PLWH presenting DRMs. The aim of this study is to compare the use of DOR in presence and in absence of DRMs (4.)

Materials and Methods

Retrospective data of all >18 years old People Living With HIV (PLWH) who initiated a DOR-based antiretroviral treatment (ART) at the Infectious Diseases Clinic of A.O.U.C. Policlinico in Bari between January 1, 2021, and February 15, 2024, having a genotypic resistance test (GRT) archived in the clinic's database were collected. Viral sequences were analyzed using the HIV Sequencing Program of the Stanford HIV Resistance Database to obtain an updated profile of DRMs towards modern drug classes. Differences in immunovirological values, disease history, and ART of patients with and without DRMs were evaluated and compared via Chi-square test and Mann-Whitney U-test. The two groups will be mentioned as: PLWH without major DRMs (non- DRM group) and PLWH with major DRMs (DRM group)

Results

During the study period, 196 PLWH initiated a DOR-based ART. Among them, 131, mostly ART-experienced (120/131, 91%), had available viral genotype data. Of these, 29 subjects (22%) harbored at least one major DRM: 15 towards NRTIs, 10 towards PIs, 1 towards INSTIs, and 12 towards NNRTIs. Additionally, 12 PLWH (41%) showed resistance to two or more classes of antiretroviral drugs.

Demographics and medical history

Our population is mostly composed of cisgender males (72%) with a median age of 53 years (IQR 43-59). 82% are Italian. The most common comorbidities are dyslipidemia (48/131), followed by hypertension (33/131), chronic liver disease (21/131), osteopenia/osteoporosis (19/131), and diabetes (13/131).

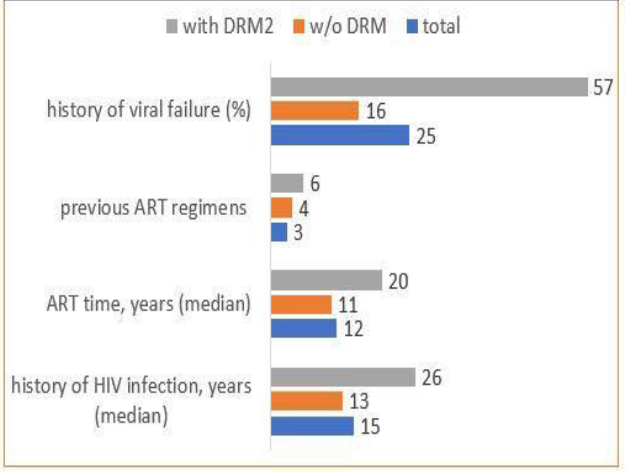
HIV infection characteristics

Overall, 75% of PLWH included in the analysis presented with the B-HIV1 subtype.

HIV transmission route was mainly heterosexual contact (42%), followed by male-to-male sexual contact (23%) and intravenous drug use (15%). An AIDS diagnosis was encountered in 29% of the total population. The CD4+ count shows a median nadir of 236 (IQR 105-374) cells/mL, and the viral load has a median zenith of 76,000 (IQR 24,541-270,000) copies/mL.

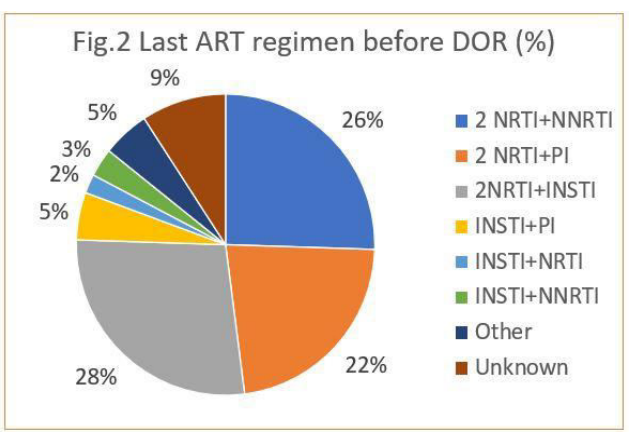
Notably, significant differences in the duration of HIV infection, and ARV treatment, the history of virological failure, and the number of previous ART regimens were observed comparing DRM and non- DRM groups as reported in Fig. 1.

Fig.1 differences between PWHIV with and without DRM



Concerning the last ARV regimen, at the time of switching to DOR they were homogeneous between the 2 groups, with the 3 most represented combinations being 2 NRTIs + INSTI, 2 NRTIs + NNRTI, and 2 NRTIs + PI (25%, 22%, and 27%, respectively). In Fig. 2, the percentages of all the regimens before switching to DOR in the total population are shown.

Fig.2 Last ART regimen before DOR (%)



DRM characteristics

In our study, 12 PLWH showed resistance to NNRTIs and still the clinician switched them to a DOR-based regimen. Of these, 11/12 were cisgender males with a median age of 60.5 years. 4 people switched from dual therapy. Of these, 5 were on an INSTI-based regimen (BIC or DTG), 6 on a PI-based regimen (DRV/cobi), and 2 on an NNRTI-based regimen (RPV or EFV). Only 2 ART switches were motivated by virological failure, while the rest were due to adverse event management (kidney failure, dyslipidemia, weight gain, and others). However, 8 PLWH had a previous history of virological failure, 5 received an AIDS diagnosis. 4 switched to dual therapy with DOR + INSTI. The most represented DRM was E138A (75%); others included E138G, K103N, Y181C, L100L, V106I, P225H, Y318F. 3 PLWH had more than one DRM.

DOR discontinuations

After a median follow-up time of 16 months (IQR 6-27 months) from the switch, 92% of PLWH were still on DOR. Among the 10 PLWH who changed from a DOR-based regimen, only 1 presented with virological failure. Of the remaining treatment switches, 1 was due to pregnancy, 2 to dual therapy simplification, 3 to medical reasons (dialysis initiation/drug interaction), and 3 to problems of treatment adherence (Tab.1). Notably, none of the discontinuations was observed in the group of PLWH bearing DRMs.

Tab. 1 Discontinuation reasons

discontinuation reason	n.	DOR-regimen
Poor adherence	2	DOR/TDF/3TC
	1	DOR + other agent
Virological failure	1	DOR/TDF/3TC
Pregnancy	1	DOR + other agent
Medical issue (drug-drug interaction/dialysis)	3	DOR/TDF/3TC
Semplification	1	DOR/TDF/3TC
	1	DOR + other agent

Conclusions

According to our preliminary results, the switch to DOR-based ART regimens seems to be applicable from each of the most common ART combination and promises to be highly effective also in presence of NNRTI-associated DRMs. However, the use of DOR needs to be assessed in naive PLWH as empirical therapy. Differences in efficacy and durability between DOR in dual and in three drug-regimens also deserve to be investigated.

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