basma.abdi@lns.etat.lu

734

No virological failure in patients living with HIV with past NNRTI resistance-associated mutations switched to doravirine-containing regimens

B. ABDI[1*], S. SALIBA[2], M. WIRDEN[1], A. FAYCAL[2], T. COCHERIE[1], R. PALICH[2], L. SCHNEIDER[2], S. SEANG[2], M.-A. VALANTIN[2], V. POURCHER[2], V. CALVEZ[1], A.MARCELIN[1], C. KATLAMA[2]

1. Sorbonne University, Virology department, Pitié-Salpêtrière hospital, AP-HP, Pierre Louis Institute of Epidemiology and Public Health (iPLESP), INSERM U1136, Paris, France,
2. Sorbonne University, Infectious Diseases department, Pitié-Salpêtrière hospital, AP-HP, Pierre Louis Institute of Epidemiology and Public Health (iPLESP), INSERM U1136, Paris, France

BACKGROUND

- Doravirine (DOR) is recommended in PWH with no prior resistance to any NNRTI.
- **We aimed to evaluate in real life the efficacy of DOR containing regimen in PWH with prior NNRTI virological failure (VF) and past NNRTI resistance associated mutations (RAMs).**

METHODS

- This observational study included PWH switched to a DOR-containing regimen between 30/09/2019 and 01/05/2022, with an HIV-1 RNA ≤50 cp/mL and past NNRTI-RAMs in RNA and/or DNA genotypes.
- For patients who had NNRTI-RAMs affecting the susceptibility to DOR, DNA genotyping was performed at the time of the switch to assess the persistence or clearance of previous NNRTI-RAMs over time.

➢ **Main outcome was the proportion of participants with VF at week 48 and week 96.**

➢ **Secondary outcomes evaluated the rate of viral suppression and transient virologic blip, RAMs in case of VF and side effects.**

RESULTS

- Data from **102** patients switched to DOR-containing regimen and followed for **at least 48 weeks**, were analyzed (Table 1).
- Reasons to switch patients to a DOR-containing regimen were: **drug burden reduction and prevention of long-term toxicities (n=60), weight gain on INSTI (n=15), side effects to prior ARV such as dyspepsia (n=10), CNS side effects (n=10) and arthralgia (n=3), or drug-drug interactions (n= 14).**

Table 1: Patients characteristics at baseline

Characteristics (at baseline)	Patients enrolled n=102
Age, years (median, IQR)	59 (51-63)
Male (n,%)	64 (63)
Time from HIV diagnosis, years (median, IQR)	26 (16-31)
ART duration, years (median, IQR)	22 (14-26)
Viral suppression duration, years (median, IQR)	7 (1-11)
Zenith HIV-1 RNA viral load, log_{10} cp/ml (median, IQR)	4.91 (4.29-5.46)
HIV-1 subtype B (n,%)	50 (49)
DOR-containing regimen at baseline (n, %)	
* Three drug regimen (3-DR)	63 (62)
DOR/TDF/3TC	56 (55)
*Two drug regimen (2-DR)	39 (38)
DOR + RAL	20 (20)
DOR + DTG	17 (17)

➢ **25% of patients had documented historical RAMs to DOR.**

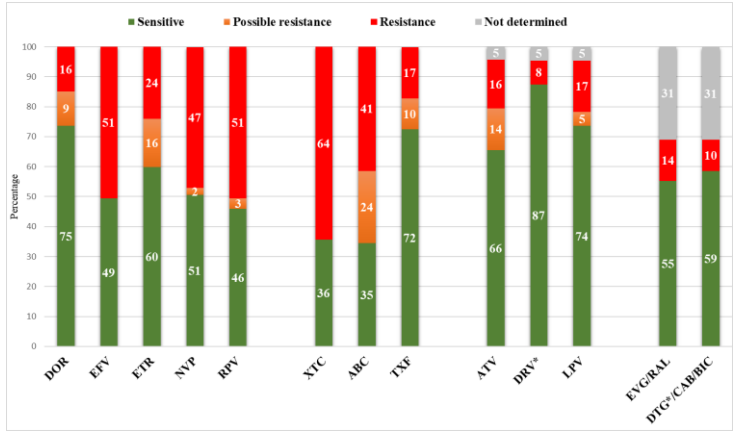
➢ **No virologic failure was detected at week 48 and neither at week 96.**

➢ **No blip was observed, and all patients (100%) maintained an HIV-1 RNA levels of ≤50 copies/mL.**

➢ **There were no significant changes in CD4 count (p=0.98) or the CD4/CD8 ratio (p=0.36).**

- **25/102 (25%)** patients had documented historical RAMs to DOR: possible resistance in 9/25 (36%) or major resistance in 16/25 (64%) (Figure1).
- Major mutations were V106A (n=1) and Y188L (n=1), or at least two resistance mutations, predominantly involving the L100I, K103N, Y181C, and G190A/E mutations (Table 2).
- **Median time since the last detection of NNRTI-RAMs was 12 years (5-17).**

Figure 1: Cumulative of historical antiretroviral resistance-associated mutations



- 16 PWH discontinued the DOR-containing regimens within a median delay of 3 weeks (IQR 11-30): pregnancy (n=2), patient preference (n=2) and adverse events (n=12).
- A total of **87 PWH** and **86 PWH** completed **48**- and **96-weeks** follow-up respectively.

➢ **Over 2 years follow-up, no virologic failure occurred neither at week 48 (0/87, 0%) nor 96 (0/86, 0%).**

Table 2: Virological characteristics of patients having doravirine resistance associated mutations in the past

PWH	DOR-containing regimen	Past NNRTI-RAMs profiles	Resistance interpretation: ANRS-MIE /Stanford	Time since the last detection of NNRTI-RAMs (years)	Detection of archived NNRTI-RAMs at moment of switch
1	DOR/TDF/3TC	E138G; Y181C+H221Y	I/ I	15.3	ND
2	DOR+DTG/3TC	V179I+Y181C+G190A+H221Y	I/ IR	0,0	V179I+Y181C+G190A+H221Y
3	DOR + DTG	Y181C+G190A	I/ I	7,8	ND
4	DOR + DTG	K103N; K101E+Y181C+G190A	I/ IR	6,7	K103N
5	DOR + RAL	L100I+E138A+Y181C+G190A	I/ IR	19,1	ND
6	DOR/TDF/3TC	Y181C+H221Y	I/ IR	11,6	ND
7	DOR/TDF/3TC	Y181C+H221Y	I/ IR	13,5	ND
8	DOR + RAL	A98S+K101E+G190A	I/ I	12,2	A98S
9	DOR+ DRV/r + MVC	V90I; K101E+Y181C	I/ I	17,3	ND
10	DOR/TDF/3TC	L100I+K103N	R/ IR	18,5	ND
11	DOR + ABC/3TC	E138A+ V179I+Y181C+M230L	R/ R	8,0	ND
12	DOR/TDF/3TC	K103N+Y181C+H221Y	R/ I	0,0	ND
13	DOR + DTG	Y181C; K103N +H221Y+M230L	R/ R	16,2	ND
14	DOR + DTG	L100I+K103N	R/ IR	17,7	ND
15	DOR + DTG	Y188L	R/ R	0,1	ND
16	DOR + DTG	L100I+K103N	R/ IR	19,0	K103N
17	DOR/TDF/3TC	V179D+G190A/S+H221Y	R/ I	15,8	ND
18	DOR + DTG/3TC	A98G+K103N+Y181C	R/ IR	19,9	ND
19	DOR+ 3TC+ MVC	L100I+K103N	R/ IR	1,8	K103N
20	DOR/TDF/3TC	E138K+G190E	R/ R	0,0	E138K+G190E
21	DOR + DTG	K101E±K103N+V179I+Y181C +G190A+H221Y	R/ R	4,8	ND
22	DOR/TDF/3TC	V106A	R/ R	4,4	ND
23	DOR/TDF/3TC	K103N+Y181C	R/ SP	18,4	ND
24	DOR/TDF/3TC	G190E	R/ R	0,0	G190E
25	DOR/TDF/3TC	K103N+Y181C	R/ SP	0,0	K103N+Y181C

ANRS-MIE algorithm interpretation: I= possible resistance; R= resistance, Stanford algorithm interpretation: SP: Potential Low-Level Resistance I: Low-Level Resistance I R: Intermediate Resistance R: High-Level Resistance, ND= archived RAMs not detected at moment of switch

CONCLUSION

❖ **This is the first real-world study up to 96 weeks follow up to provide a new insight about the use of DOR-containing regimens as a treatment in long term suppressed patients whom viruses harbored specific NNRTI-RAMs in their history.**