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Switch from etravirine to doravirine as a part of antiretroviral combination in virally suppressed people living with HIV: results of the French multicenter, observational SWEED study

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Background

- The simplification of ART is a crucial challenge for optimizing care of PWH.
- Etravirine (ETR), a second-generation NNRTI, has been used as a 'salvage therapy' in combination with other drugs for PWH with multidrug-resistant HIV who have experienced virological failure.[1] It is typically prescribed as a twice-daily dose, and is a potent enzyme inducer, leading to complex drug interactions.
- Doravirine (DOR), a next-generation NNRTI, has shown efficacy in both treatment-naïve and pretreated PLWH,[2-4] with durable viral control, good tolerability, and minimal weight gain. DOR resistance profile is distinct, with activity against strains resistant to other NNRTIs, such as those with K103N or Y181C mutations.[5]

STUDY MAIN OBJECTIVE:

- **DOR may replace ETR in maintaining viral control for virologically suppressed patients, even those previously exposed to NNRTIs. The main objective of the SWEED study was to determine if DOR-containing ART can maintain viral suppression in PWH previously treated with ETR-containing ART.**

Methods

- SWEED is a national, multicentre, observational study enrolling:
  - HIV-1 positive adults (18+ years);
  - On a regimen containing ETR (once or twice daily) combined with at least one other antiretroviral (except NNRTI);
  - Who switched to a regimen containing DOR with the same number of other antiretrovirals from 01/09/2019, in 10 French hospitals;
  - With viral suppression (pVL <50 copies/mL) for at least 12 months at the time of switching (one blip <200 copies/mL permitted);
  - At least 2 pVL measurements after switching and at least 48 weeks of follow-up;
  - Provided informed consent (non-opposition to participation).
- The primary outcome was the rate of virological failure (VF: confirmed pVL ≥50 copies/mL or single pVL ≥50 copies/mL with ART change) at W48. Secondary outcomes included: rate of strategy success rates (pVL <50 copies/mL with no ART change) at W48, occurrence of discontinuations due to side effects, changes in body weight and CD4 counts over the entire follow-up.
- Ethics Committee Approval Number: 023.02595.000228.

Results

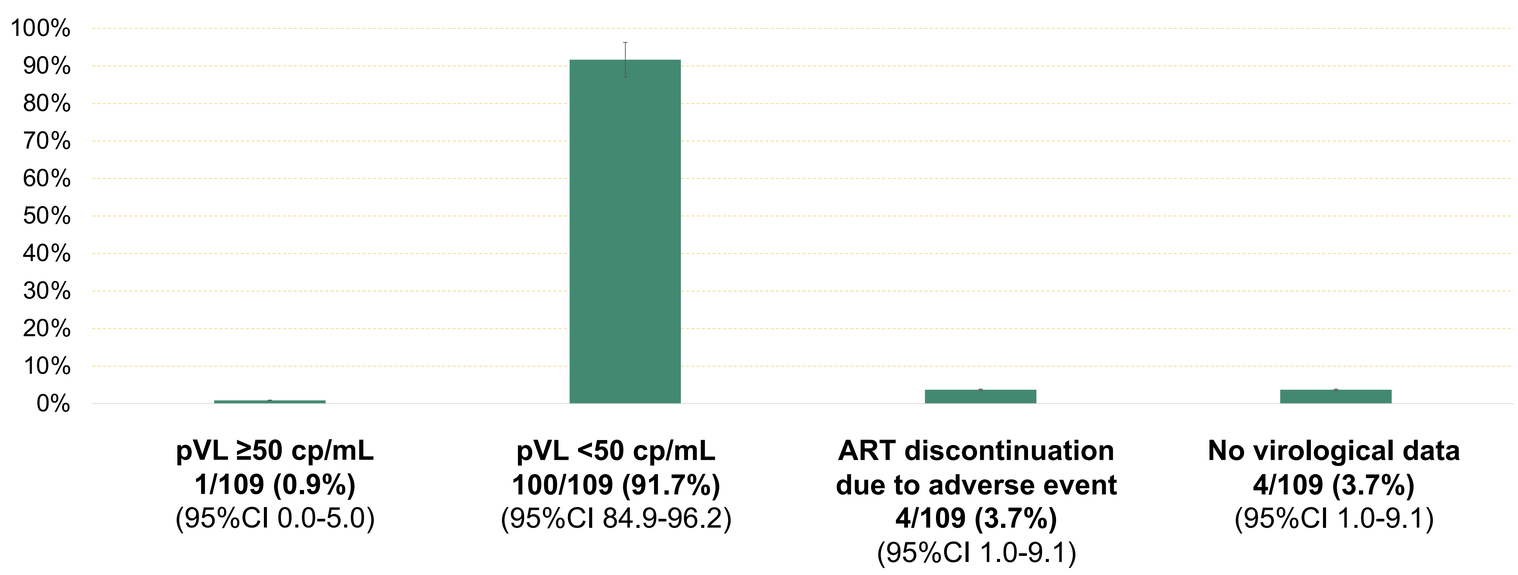
- 109 patients were included, their characteristics are detailed in the Table.

Table. Patient characteristics at inclusion (n=109)

Age, years, median (IQR)	59 (53-65)
Gender, n (%)	
- Male	86 (79)
- Female	23 (21)
Country of birth, n (%)	
- France	85 (78)
- Other	24 (22)
Transmission group, n (%)	
- Heterosexual	35 (32)
- MSM	53 (49)
- Other	21 (19)
CDC stage C, n (%)	33 (30)
CD4 nadir, cells/mm^3 (IQR)	157 (83-243)
Time from HIV diagnosis, years, median (IQR)	29 (22-32)
Time from ART initiation, years, median (IQR)	25 (20-27)
Past exposure to NNRTIs, n (%)	
- Nevirapine	46 (42)
- Efavirenz	43 (40)
- Rilpivirine	12 (11)
- Etravirine (inclusion criteria)	109 (100)
Previous virological failure, n (%)	
- Under NRTI	69 (63)
- Under NNRTI	45 (41)
- Under PI	43 (39)
- Under INSTI	7 (6)
Duration of viral suppression, years, median (IQR)	13 (9-17)
CD4 count, cells/mm^3 (IQR)	653 (463-858)
CD4/CD8 ratio, median (IQR)	0.8 (0.6-1.3)
Body weight, kg, median (IQR)	75 (68-88)
Body mass index, kg/m^2, median (IQR)	24.4(21.9-27.3)
Kind of ETR-based ART before switching, n (%)	
- 2-drug regimen	58 (53)
Including RAL+ETR	*48 (44)*
- 3-drug regimen	46 (42)
Including 2 INTIs + ETR	*31 (28)*
- 4-drug regimen	3 (3)
- 5-drug regimen	2 (2)

- Of the 109 patients, 97 (89%) had at least one comorbidity requiring treatment. The most prevalent comorbidities were: hypertension (n=49, 45%), dyslipidaemia (n=46, 42%), diabetes (n=23, 21%), depressive syndrome (n=21, 19%), dysthyroidism (n=10, 9%), and chronic renal failure (n=8, 7%).
- 45/109 (41%) patients had past VF on NNRTI.
- 91/109 (84%) patients had at least one resistance genotype available, including 42/91 (46%) with at least one documented viral mutation to NNRTIs. The most prevalent mutations were: K103H/N/S/T/R (24%), V179D/F/L/M/T (13%), K101E/H/I/P/R (10%), Y181C (10%) and G190A/C/Q/S/T/V (9%). Overall, past mutations led to full resistance and possible resistance to nevirapine, efavirenz, rilpivirine, etravirine and doravirine in 31 (34%) and 1 (1%), 31 (34%) and 0 (0%), 22 (24%) and 2 (2%), 12 (13%) and 7 (8%), 12 (13%) and 5 (5%) of cases (French ANRS-MIE algorithm, v.35).
- After switching, as requested by the protocol, the proportion of participants with 2, 3, 4 and 5-drug regimens remained the same. The four most frequent DOR-containing ART were: DTG+DOR (n=30, 28%), RAL+DOR (n=23%), DOR/3TC/TDF (n=20, 18%) and 3TC/ABC+DOR (n=11, 10%).
- **Median follow-up after switch to DOR-containing ART was 30 months (IQR 19-47).**

Figure. Proportion of patients with virological failure, therapeutic success and ART discontinuations at W48 (FDA Snapshot)



- **Only one VF occurred at W23** (pVL=186 confirmed 382 copies/mL) under DOR+DTG+ATV/r; no genotype was performed, and no plasma drug concentrations were available at failure; pVL was resuppressed without ART change; **therefore, virological failure rate was 0.9% (95%CI 0.0-5.0) at W48.**
- There were 4 treatment discontinuations before W48 due to adverse events, leading to a strategy success rate of 91.7% (95%CI 84.9-96.2) at W48. These adverse events were: neuropsychiatric disorders (n=2) palpitation and muscle pain (n=1), gastrointestinal disorder (n=1).
- No additional VF occurred between W48 and the end of follow-up.
- 13 additional treatment discontinuations occurred between W48 and the end of follow-up: adverse events (n=3: renal failure, hepatic cytolysis and neuropsychiatric disorder), doctor's decision (n=7), patient's decision (n=2), and death non attributable to ART (n=1).
- There were no significant changes in body weight (+0.0 kg, p=0.58) and CD4 counts (-14 cells/mm^3, p=0.88) over follow-up.

Conclusions

- **DOR-containing ART were capable to maintain a high rate of virological suppression (only one VF) in PWH with past NNRTI resistance, within 2-DR (53%) or 3-DR (42%), after switching from ETR containing ART.**
- **Doravirine confirms its potent efficacy in patients with a long history of ARV. Its once-daily dosing, good safety profile and absence of drug-drug interactions are advantages for patients.**
- Limitations: retrospective observational study, with non-comparative arm, and small population size.

REFERENCES: **Yazdanpanah**, *CID*, 2009, **Molina**, *Lancet HIV*, 2020, **Orkin**, *CID*, 2019, **Johnson**, *JAIDS*, 2019, **Feng**, *AAC*, 2015

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