P041

Doravirine plus raltegravir (DOR/RAL) two-drug regimen as a maintenance ART in virally suppressed PWH: results of the international randomised DORAL trial

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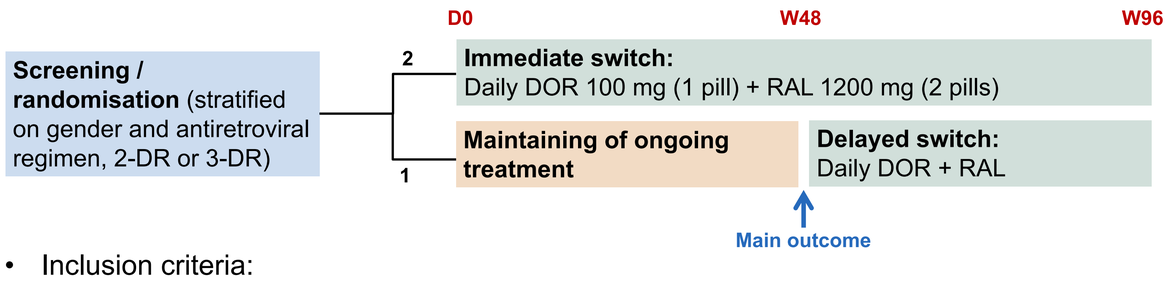
Background

- INSTI-based 2-drug regimens (2-DR) are increasingly being used for the treatment of HIV-1 infection. Leveraging the benefits of raltegravir (RAL),[1] a first-generation INSTI, and doravirine (DOR),[2-4] a next-generation NNRTI, both of which have a favourable tolerability profile and a neutral drug interaction profile, we aimed to evaluate the efficacy of these two molecules in combination as a 2-DR.
- **Here, we present the 48-week results of the DORAL trial, which aims to evaluate the virological efficacy of the DOR/RAL 2-DR as a maintenance treatment in virologically suppressed PWH.**

Methods

- DORAL is a prospective, international (8 centres in France, Italy and Spain), open-label, randomised trial where participants were randomly assigned (2:1) to switch to DOR/RAL (100 mg/1200 mg once daily) or to maintain their current regimen.



- Inclusion criteria:
  - HIV-1 positive adults (18+ years);
  - On a stable antiretroviral regimen containing at least 2 drugs for at least 6 months;
  - With viral suppression (pVL <50 copies/mL) for at least 12 months;
  - Naïve to doravirine;
  - With CD4 count ≥200/mm^3;
  - With no resistance to doravirine or raltegravir on all available HIV-RNA genotypes (genotype result was mandatory in cases of prior virological failure [VF] under NNRTI or INSTI);
  - Who provided a signed informed consent form.
- The primary endpoint was VF (defined as 2 consecutive pVL ≥50 copies/mL) at W48. Secondary outcomes included treatment success rate (pVL <50 copies/mL), tolerance and changes in body weight, CD4 counts, and CD4/CD8 ratio at W48.
- We initially planned to include 150 participants, but the final number of enrolments was 114 due to regulatory difficulties.
- As a reminder, a sub-study on the male genital compartment was carried out among 18 French participants: the results were presented at the EACS conference, Warsaw, Poland, 2023 (Abs. RA2.O5).
- Ethics Committee Approval Number: 6758.

Results

- From October 2020 to August 2023, 114 participants were included, and started study treatment (79 in the DOR/RAL arm and 35 in the continuing regimen arm).

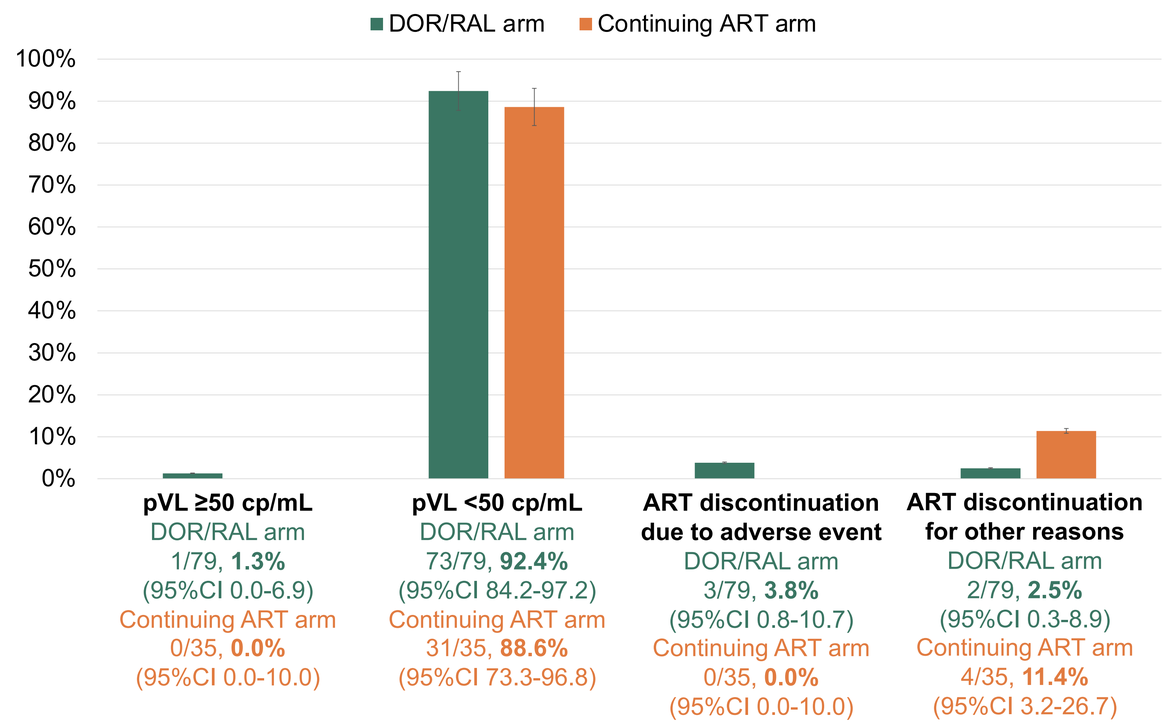
Table. Patient characteristics at inclusion.

	Total (N=114)	Immediate switch arm (N=79)	Delayed switch arm (N=35)
Age, years, median (IQR)	57 (49-65)	58 (50-65)	56 (47-61)
Gender, n (%)			
- Male	81 (71)	57 (72)	24 (69)
- Female	33 (29)	22 (28)	11 (31)
Country of inclusion, n (%)			
- France	53 (46)	36 (46)	17 (49)
- Italy	37 (33)	27 (34)	10 (28)
- Spain	24 (21)	16 (20)	8 (23)
Transmission group, n (%)			
- Heterosexual	49 (43)	35 (44)	14 (40)
- MSM	48 (42)	32 (40)	16 (46)
- Other	17 (15)	12 (16)	5 (14)
CDC stage C, n (%)	21 (19)	14 (18)	7 (21)
CD4 nadir, cells/mm^3 (IQR)	246 (125-350)	267 (112-350)	234 (144-363)
Time from HIV diagnosis, years, median (IQR)	21 (13-28)	21 (13-28)	22 (15-28)
Time from ART initiation, years, median (IQR)	18 (11-25)	19 (10-25)	17 (11-24)
Viral suppression, years, median (IQR)	10 (6-15)	9 (5-14)	13 (7-15)
CD4 count, cells/mm^3 (IQR)	700 (549-914)	730 (550-927)	685 (503-822)
CD4/CD8 ratio, median (IQR)	1.1 (0.8-1.5)	1.1 (0.9-1.5)	1.1 (0.7-1.4)
Body weight, kg, median (IQR)	75 (65-86)	77 (66-85)	72 (61-86)
Body mass index, kg/m^2, median (IQR)	25.3 (22.6-28.3)	25.4 (23.1-28.1)	24.7 (21.9-29.0)
(continued…)	**Total (N=114)**	**Immediate switch arm (N=79)**	**Delayed switch arm (N=35)**
Antiretroviral strategy prior to inclusion, n (%)			
- INSTI-based 3-drug regimen	42[a] (37)	31[b] (40)	11[c] (32)
- NNRTI-based 3-drug regimen	28 (24)	20 (25)	8 (23)
- bPI-based 3-drug regimen	9 (8)	5 (6)	4 (11)
- 2-drug regimen	35[d] (31)	23[e] (29)	12[f] (34)

NOTES. a. Including 29 participants already receiving raltegravir. b. Including 21 participants already receiving raltegravir. c. Including 8 participants already receiving raltegravir. d. Including 31 participants already receiving raltegravir. e. Including 19 participants already receiving raltegravir. f. Including 12 participants already receiving raltegravir.

- Over 48 weeks, there was one VF (1.3%, 95%CI 0.0-6.9) at W12 in the DOR/RAL arm (pVL=91 copies/mL confirmed 89 copies/mL), in a participant with adequate plasma drug concentrations at VF, and no resistance to NNRTI or INSTI documented at baseline. At VF, a E138A mutation was detected in the HIV-RNA within the reverse transcriptase gene. pVL was resuppressed after resumption of nevirapine-based 3-drug previous regimen. There was no VF (0%, 95%CI 0.0-10.0) occurred in the continuing regimen arm.
- **The difference in proportion of VF between the DOR/RAL arm and the continuing ART arm was 1.3% (95%CI -1.2 to 3.8).**
- The proportion of participants who maintained virological suppression at week 48 was 92.4% (95%CI 84.2-97.2) in the DOR/RAL arm and 88.6% (95%CI 73.3-96.8) in the continuing regimen arm.

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



- Two drug-related grade 3-4 adverse events occurred in two participants in the DOR/RAL arm (severe anxiety and panic disorder).
- The 6 participants who discontinued ART for reasons other than adverse events made this decision, usually in agreement with their doctor, in order to simplify their regimen (switching from 3 pills to 1 pill).
- There were no significant differences in the changes in body weight (+0.08 kg versus +0.04 kg, p=0.51), CD4 counts (+37 cells/mm^3 versus +26 cells/mm^3, p=0.076), and CD4/CD8 ratio (+0.04 versus +0.03, p=0.912) between arms at W48.

Conclusions

- **This prospective, international clinical trial shows a high rate of virological success of the DOR/RAL 2-DR (92% after switching to DOR/RAL, compared to 89% when maintaining ongoing ART, due to higher rate of discontinuations).**
- Tolerability was excellent. Given its the neutral drug interaction profile, this combination could be proposed for PWH with comorbidities and concomitant medications that carry a high risk of drug interactions, including cancer patients undergoing chemotherapy.
- DOR has the advantage of remaining effective against viral strains that are resistant to other NNRTIs,[5] and could therefore be used in patients who do not have access to all current treatment options. A sub-study of archived resistance in the HIV-DNA of participants in the DORAL study is ongoing.
- Limitations: The study was not powered to demonstrate the non-inferiority of this strategy. However, it does position this 2-DR as a potential alternative in specific cases.

REFERENCES: **1. Rockstroh**, *CID*, 2011, **2. Molina**, *Lancet HIV*, 2020, **3. Orkin**, *CID*, 2019, **4. Johnson**, *JAIDS*, 2019, **5. Feng**, *AAC*, 2015

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