ARV Therapies and Therapeutic Strategies

INDEPENDENT REPORTING ON EACS 2017

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

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PROMISING RESULTS OF DOLUTEGRAVIR + LAMIVUDINE MAINTENANCE IN ANRS167 LAMIDOL TRIAL

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Abstract PE9/11

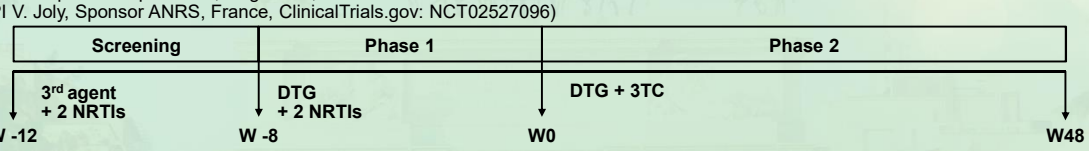
INTRODUCTION

- Dolutegravir (DTG) is a potent integrase inhibitor (INSTI) with high genetic barrier and favorable pharmacokinetic profile
- The once daily (QD) DTG + 3TC combination is attractive, both drugs being safe, highly efficient and convenient
- We assessed the efficacy and the tolerance of DTG + 3TC combination in HIV-1 infected patients (Pts) with suppressed viral replication on antiretroviral therapy (cART)

PATIENTS AND METHODS

Trial design

- Non comparative open-label, single arm, multicenter trial
  (PI V. Joly, Sponsor ANRS, France, ClinicalTrials.gov: NCT02527096)



Selection criteria

- Main inclusion criteria:
  - HIV-1 infected adults >18 yrs, nadir CD4 count >200/mm^3
  - Current cART: 2 NRTIs plus a NNRTI, a PI or an INSTI. Max. 2 modifications of cART for simplification/intolerance allowed
  - Wild type HIV-1 on pre-therapeutic genotype for NRTIs, NNRTIs, PIs and, when available, for INSTIs
  - Plasma HIV-RNA (pVL) ≤50 cps/mL for ≥2 yrs. Blips <200 cps/mL allowed (max. 3 in the last 2 yrs, none in the last 6 months)
  - Written informed consent
  - Normal standard biological parameters
- Main non-inclusion criteria: HIV-2, HCV, or HBV co-infection

Primary Endpoint

- % Pts with therapeutic success at W48
- Therapeutic failure was defined as one of the following:
  - Virologic failure: 2 consecutive pVL > 50 cps/mL, 2-4 Wks apart
  - Interruption of the therapeutic strategy, whatever the reason
  - Lost to follow-up
  - Death

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RESULTS

- 110 pts included in 19 centers from 10/01/2015 to 02/29/2016
  - 3 Pts w/ pVL>50cps/mL and 3 AEs leading to withdrawal from trial

  ➔104 Pts included in Phase 2 (Table 1)

Table 1: Baseline Characteristics of Pts Included in Phase 2	N = 104
Age (yrs)	45 [24-71]
Male	89 [85.6%]
MSM	73 [70.2%]
Duration since HIV diagnosis (yrs)	6.2 [2.3-24.5]
Nadir CD4 count per mm^3	399 [203 - 1155]
Time from 1st cART (yrs)	4.5 [2-11]
Duration of virologic success (yrs)	6.2 [6-24]
CD4 cell count per mm^3	768 [346 - 1615]
Duration on current cART (yrs)	4.0 [0.5-11.3]
3rd agent in the current cART,	
- NNRTI	58 (55.8%)
- PI	24 (23.1%)
- INSTI	22 (21.2%)
(RAL, EVG, DTG): (n)	(8, 7, 7)
RAL: raltegravir, EVG: elvitegravir,	

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RESULTS (CONT'D)

Table 2: Patients with ≥ 1 Value of pVL > 50 cps/mL During Phase 2

Patient	Baseline				Follow-up			
	Previous ART	INSTI RAM	Visit	pVL (cps/mL)	End Point	Plasma Drug Levels (ng/mL)	RAM	Modification of ART
60-010	TDF/FTC+RAL then ABC/3TC+RAL	Absence	W4 W8 W16 W24 W32 W40 W48	84 77 38 56 52 100 99	Virological failure at W4	At W4 (at 12h): DTG 2401 3TC 299	NA (RNA and DNA)	ABC/3TC+DTG at W8 RAL+ETR at W32
78-005	TDF/FTC+RPV then TDF/FTC+EFV	Absence	W32 W40 W48	59 <50 55	Therapeutic failure at W40	At W32: DTG 908 3TC 130	RNA: L74V/L (resistance ABC) DNA: M230I (resistance RPV) and V106I (polymorphism)	TDF/FTC+DTG at W40 (investigator decision)
60-001	ABC/3TC/fAPV then ABC/.3TC/RAL	Absence	W24 W28 to W48	51 <50	Blip	NA	NA	No
62-006	TDF/FTC+EFV then TDF/FTC+RPV	NA	W40 W43 W48 W52 (control)	67 <50 130 <50	Blip	At W48 (at 10h): DTG 2616 At W52 (at 11,5h): DTG 529	No RAM for RT NA for INSTI	No

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ENDPOINTS AND ADVERSE EVENTS

Endpoints

- Success rate: 97% [IC95% : 94-100]. 3 therapeutic failures:
  - 1 virologic failure at W4 (Table 2)
  - 1 lost to follow-up at W32
  - 1 strategy interruption at W40 (Table 2)
- 3 additional blips during Phase 2 in 2 Pts (Table 2)
- Between W-8 and W48:
  - Increase in total (p=0.01) and HDL -cholesterol (p=0.006)
  - No change of LDL -cholesterol (p=0.3) and triglycerides (p=0.08)
- Increase of CD4 count (p=0.0003) but no change of CD4/CD8 ratio (p=0.08) between W-12 and W48
- Decrease of creatinine clearance between W-8 and W48 (p=0.0003)

Adverse events

- **9 severe AEs** reported among 110 Pts among 110 Pts included in Phase 1
  Phase 1: 1 Pt with suicidal ideation, withdrawn from trial
  Phase 2: 7 Pts, not related to study treatment, 1 Pt with depressive disorder related to study treatment (no discontinuation)

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CONCLUSION

- In this population of virologically suppressed patients without previous virological failure, switching to DTG+3TC combination was relatively safe, effective and well tolerated at W48 of treatment.
- Ancillary studies on seminal VL and cART concentrations are ongoing

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