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Promising Results of Lamivudine + Dolutegravir Maintenance Therapy in ANRS 167 Lamidol Trial

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BACKGROUND

- Dolutegravir (DTG) is a potent integrase inhibitor (INSTI) with high genetic barrier
- The once daily (QD) DTG + 3TC combination is attractive , both drugs being safe, highly efficient and convenient

OBJECTIVES

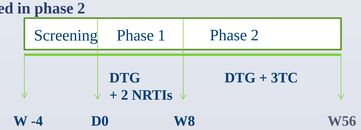
- To assess the efficacy and the tolerance of DTG + 3TC combination in HIV-1 infected patients with suppressed viral replication on first line antiretroviral therapy (cART)

METHODS

Trial design

Non comparative open-label, single arm, multicenter trial with 2 phases:

- **Phase 1** (8 weeks): third agent replaced by DTG 50 mg QD in combination with the current 2 NRTIs backbone
- **Phase 2** (48 weeks): DTG 50mg + 3TC 300mg QD for 48 weeks**. Only patients with plasma HIV RNA (pVL) ≤ 50 cps/mL at W8 were included in phase 2**



Main inclusion criteria

- HIV-1 infected adults (age > 18 yrs)
- Nadir CD4 cell count > 200/mm^3
- First line cART: 2 NRTIs plus either a NNRTI, a PI or an INSTI. A maximum of 2 modifications of cART for simplification and/or intolerance was allowed (except in the last 6 months), providing that there was not more than one modification for intolerance
- Wild type HIV-1 on pre-therapeutic genotype for NRTIs, NNRTIs, PIs and, when available, for INSTI
- pVL ≤ 50 cps/mL for at least 2 years, with at least 2 viral load determinations per year. Previous "blips" defined as 50 < pVL < 200 copies/mL and control < 50 cps/mL were allowed providing that their total number did not exceed 3 in the last 2 years and that they did not occur in the last 6 months
- Written informed consent
- Negative Hbs antigen
- Normal standard biological parameters

Main non-inclusion criteria

- Positive Hbs antigen and/or anti-Hbc antibody
- HIV-2 coinfection
- Hepatitis C co-infection needing treatment in the next 12 months
- HIV encephalitis, hepatic failure

Primary End-point

The primary end-point was the **proportion of patients in therapeutic success at W56 (i.e. after 48 W of DTG + 3TC)**.

Therapeutic failure was defined as one of the following:

- Virologic failure: pVL > 50 cps/mL, confirmed on a second sample 2 to 4 weeks later
- Interruption of the therapeutic strategy, whatever the reason
- Lost to follow-up
- Death

Statistical Analysis and Sample Size Calculation

To evaluate whether this strategy led to a >80% therapeutic success rate, and assuming an observed success rate of 90%, the inclusion of 95 patients in phase 2 would demonstrate the effectiveness of the strategy, with a 85% power and a type-I error of 0.05 (unilateral formulation). This number was increased to 100.

We planned to include 110 patients overall. Only patients who tolerated DTG and without any blip during phase 1 started the phase 2

Results are presented as n (%) or median [min-max].

RESULTS

Patients were enrolled from 10/1/2015 to 02/29/16 in 19 clinical centers.

Figure 1: Study Flow Chart

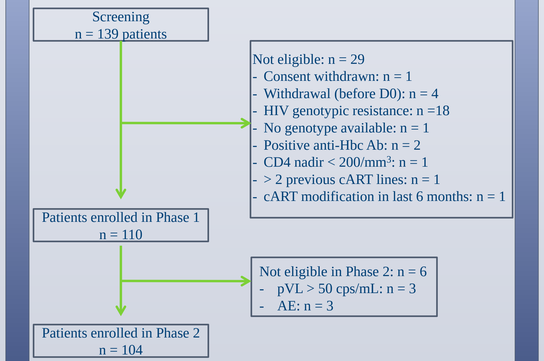


Table 1: Phase 2 Patients Baseline Characteristics

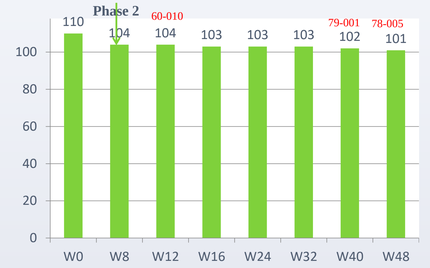
	N = 104
Age (Yrs)	45 [24-70]
Male	89 [85.6%]
MSM	73 [70.2%]
Duration since HIV diagnosis (Yrs)	6.3 [2.3-24.5]
Time on current cART (Yrs)	4.0 [0.5-11.3]
Nadir CD4 cell count per mm^3	399 [203 – 1155]
CD4 cell count per mm^3	743 [373 – 1571]
Third agent in the current cART, - NNRTI - PI - INSTI (RAL, EVG, DTG): (n)	 58 (55.8%) 24 (23.1%) 22 (21.2%) (8, 7, 7)
CDC stage A	91 (87.5%)
RAL: raltegravir, EVG: elvitegravir,	

Table 2: Patients with ≥ 1 value of pVL > 50 cps/mL during Phase 2

Patient	Baseline		Follow-up					
	Previous ART	INSTI RAM	Visit	pVL	End Point	Plasma drug levels	RAM	Modification of ART
60-010	TDF/FTC+RAL then ABC/3TC+RAL	Absence	W12 W16 W24 W32 W40 W48 W56	84 cps/mL 77 cps/mL 38 cps/mL 56 cps/mL 52 cps/mL 100 cps/mL 99 cps/mL	Virological failure at W12	At W12 (at 12h) DTG 2401 ng/mL 3TC 299 ng/mL	Not amplifiable (RNA and DNA)	ABC/3TC+DTG at W16 RAL+ETR at W40
78-005	TDF/FTC+RPV then TDF/FTC+EFV	Absence	W40 W48 W56	59 cps/mL < 50 cps/mL 55 cps/mL	Therapeutic failure at W48	At W40: DTG 908 ng/mL 3TC 130 ng/mL	RNA: L74V/L: resistance to ABC DNA: M230I and V106I	TDF/FTC+DTG at W48 although pVL < 50 cps/mL (investigator decision)
60-001	ABC/3TC/fAPV then ABC/.3TC/RAL	Absence	W32 From W36 to W56	51 cps/mL < 50 cps/mL	Blip	NA	NA	No
62-006	TDF/FTC+EFV then TDF/FTC+RPV	NA	W48 W51 W56 W60 (control)	67 cps/mL < 50 cps/mL 130 cps/mL < 50 cps/ml	Blip	At W56 (at 10h): DTG 2616 ng/mL At W60 (at 11,5h): DTG 529 ng/mL	No RAM for RT NA for INSTI	No

TDF: tenofovir, FTC: emtricitabine, RAL: raltegravir, ABC: abacavir, fAPV: fosamprenavir, EFV: efavirenz, RPV: rilpivirine, ETR: etravirine, NA: not available, RAM: resistance associated mutation

Figure 2: Patients in Therapeutic Success



All patients have reached **W48 of the study, i.e. W40 of dual therapy**. 101/104 = 97%) are in therapeutic success).

At W48, therapeutic strategy has failed in 3 patients:

- Pt 60-010: virologic failure at W12 (W4 dual therapy)
- Pt 79-001: lost to follow-up at W40 (W32 dual therapy)
- Pt 78-005: treatment modification at W48 (W40 dual therapy) decided by the investigator

101 patients are still on study treatment and the last visit of the last patient is planned for 03/27/2017

Table 3: Serious Adverse Events

N patients	Type of event	Related to study treatment	Strategy interruption
Phase 1			
1	Suicide ideation	1/1	Yes
Phase 2			
2	Grade 4 CK elevation after fitness activity	1/2	No
1	Grade 4 depression	1/1	No
3	Hospitalization*	0/3	No
1	Grade 4 ALT elevation due to acute hepatitis C	0/1	No

* Planned hospitalization for digestive endoscopy (1 Pt), management of diabetes (1 Pt); hospitalization for polyarthritis (1 Pt)

CONCLUSION

- Switching to DTG + 3TC combination maintained virologic suppression at W40, was safe and well tolerated in this population of selected patients without previous virological failure
- Longer follow-up and comparative trials are needed to evaluate more precisely the role of this attractive maintenance strategy in HIV care

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