

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

Véronique Joly<sup>1,2</sup>, Charles Burdet<sup>2</sup>, Roland Landman<sup>2,3</sup>, François Raffi<sup>4</sup>, Christine Katlama<sup>5</sup>, André Cabié<sup>6</sup>, Aida Benalycherif<sup>3</sup>, Gilles Peytavin<sup>1,2</sup>, Diane Descamps<sup>1,2</sup> and Yazdan Yazdanpanah<sup>1,2</sup>

<sup>1</sup>Hôpital Bichat, Paris, France, <sup>2</sup>Inserm, Iame, UMR 1137, Paris, France, <sup>3</sup>IMEA, Paris, France, <sup>4</sup>CHU Hotel Dieu, Nantes, France, <sup>5</sup>Université Pierre et Marie Curie, Paris, France, <sup>6</sup>CHU Fort de France, Fort de France, France

## 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

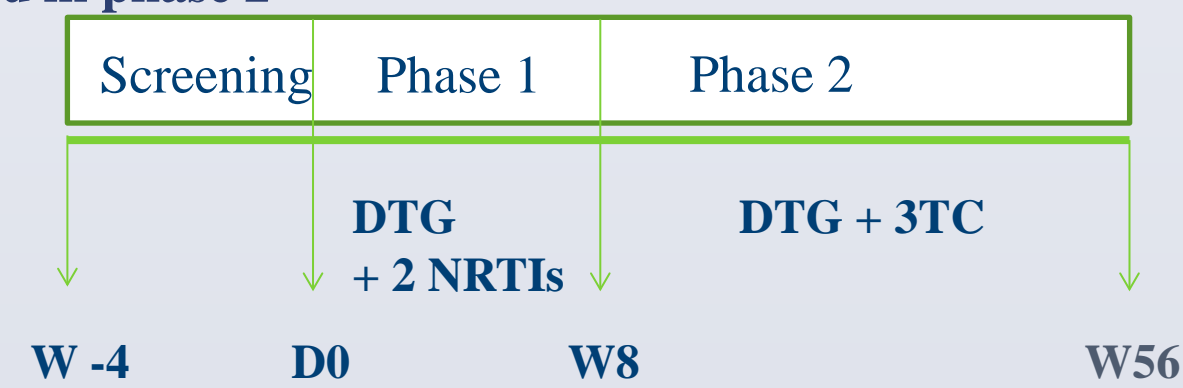
- To assess the efficacy and the tolerance of DTG + 3TC combination in HIV-1 infected patients with suppressed viral replication on first line antiretroviral therapy (cART)

## 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<sup>3</sup>
- 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

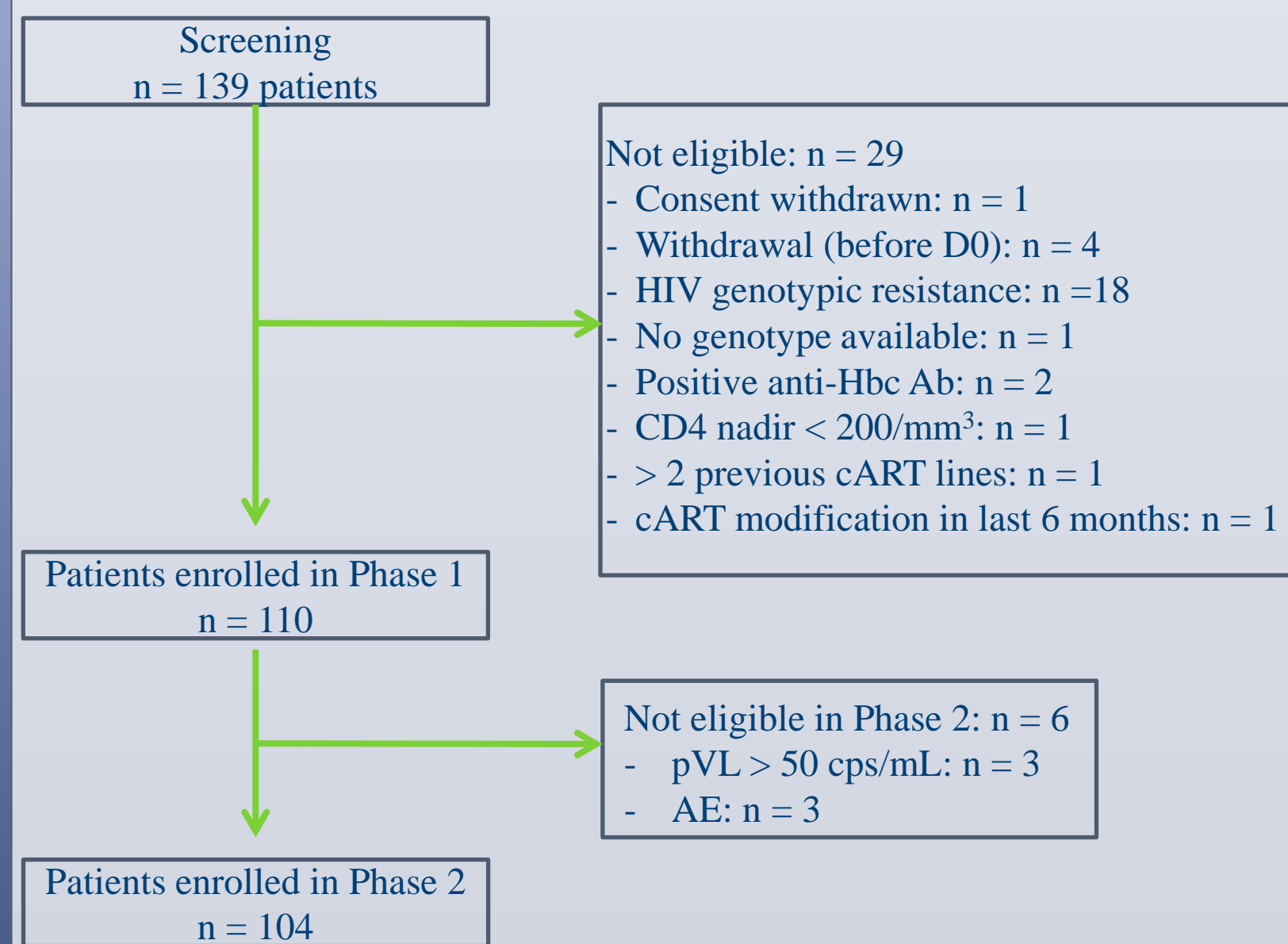


Table 1: Phase 2 Patients Baseline Characteristics

	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 <sup>3</sup>	399 [203 – 1155]
CD4 cell count per mm <sup>3</sup>	743 [373 – 1571]
Third agent in the current cART,	
- NNRTI	58 (55.8%)
- PI	24 (23.1%)
- INSTI (RAL, EVG, DTG): (n)	22 (21.2%) (8, 7, 7)
CDC stage A	91 (87.5%)

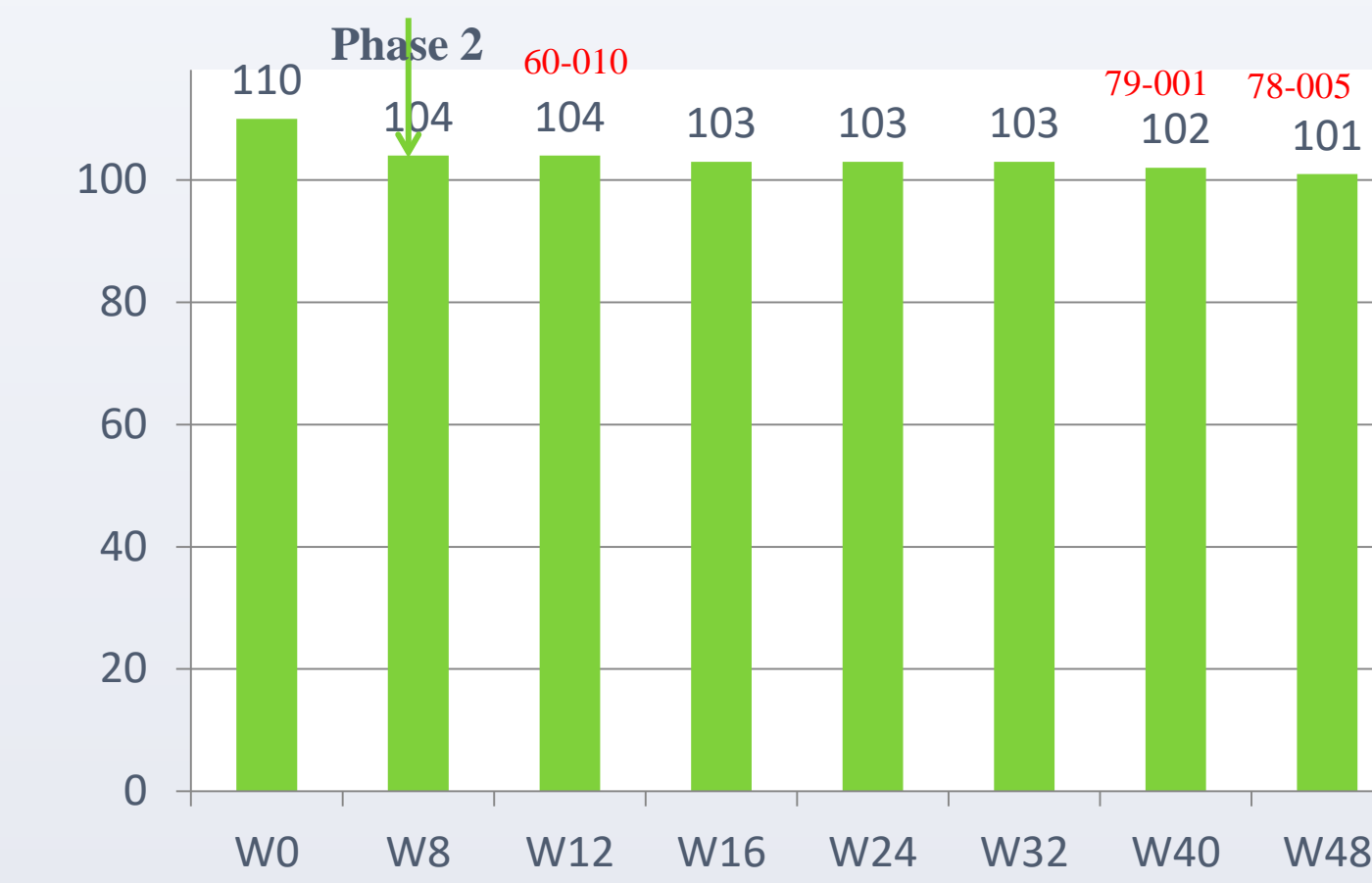
RAL: raltegravir, EVG: elvitegravir,

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+APV 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, APV: 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
<b>Phase 1</b>			
1	Suicide ideation	1/1	Yes
<b>Phase 2</b>			
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

## ACKNOWLEDGMENTS

Thanks to investigators, research staff and subjects

Participating Centers :Jean-Roussillon (Perpignan),Necker (Paris) Avicenne (Bobigny),Geroges Pompidou (Paris) ,Pitié-salpêtrière (Paris),St Antoine (Paris),Saint Louis (Paris) La Meynard (Fort de France), St André (Bordeaux), Bichat (Paris),Gui de Chauliac (Montpellier),Hotel Dieu (Nantes),Archet (Nice),Pontchaillou (Rennes), Bretonneau (Tours), Purpan (Toulouse), François-Mitterand (Dijon),Gustave Dron (Tourcoing)

DSMB : F,Bani-Sadr ,S Yerly, D Costagliola, JC Alvarez, M Korzec

We are indebted to Julie Le Boulicault and François Montestruc for data management.

This trial was conducted with the support de ViiV Healthcare