Long-term efficacy and safety of Dolutegravir/Lamivudine in virologically suppressed persons with HIV and history of resistance to lamivudine: Week 96 results of VOLVER clinical trial - GESIDA 11820

P-043

M. De Lagarde[1,3,11], R. De Miguel[2,3], J.L. Blanco[4], A. Pinto-Martinez[1,3], R. Montejano[2,3], A. Gutiérrez Liarte[5], R. Navarro-Soler[1,3], E. Cañas-Ruano [6], A. Inciarte [4], L. Martin-Carbonero[2,3], A. Imaz [7], C. Hernández Gutiérrez [8], A. Ocampo[9], M. de Miguel[10], R. Delgado[1,3,11], F. Pulido [1,3,11], J.R. Arribas[2,3], VOLVER GESIDA 11820 study group.

[1]University Hospital 12 de Octubre, imas12, Madrid, Spain; [2]University Hospital La Paz -IdiPAZ, Madrid, Spain; [3]CIBER of Infectious Diseases (CIBERINFEC), Madrid, Spain; [4]Hospital Clínic, Barcelona, Spain; [5]University Hospital La Princesa, Madrid, Spain; [6]Hospital del Mar, Barcelona, Spain; [7] Bellvitge University Hospital, Barcelona, Spain; [8]Hospital Universitario Príncipe de Asturias de Alcalá de Henares, Madrid, Spain; [9] Hospital Alvaro Cunqueiro, Vigo, Spain; [10] Fundación SEIMC-GESIDA, Madrid, Spain, University; [11] Universidad Complutense Madrid, Spain.

Background

The VOLVER Trial investigated the efficacy of dolutegravir/lamivudine (DTG/3TC) as a maintenance treatment for people with HIV and historical confirmed or suspected lamivudine resistance, after excluding lamivudine mutations in proviral DNA Sanger genotyping.

The results at week 48 (primary endpoint) showed high efficacy of DTG/3TC in maintaining viral suppression with no emergence of new resistance mutations.
This analysis presents the results after **96 weeks of follow-up.**

Methods

Open-label, single arm, multicentric clinical trial of a switch to DTG/3TC. NCT04880785.

Primary endpoint: proportion of participants with HIV-1 RNA viral load (VL) ≥50 copies/mL at 48 weeks in the intention-to-treat-exposed (ITT-e) population using the US Food and Drug Administration (FDA) snapshot algorithm.

Key inclusion criteria

- Virologically suppressed
- Past 3TC resistance: confirmed by genotypic testing or suspected based on prior virological failure while receiving emtricitabine or lamivudine
- No prior integrase resistance or virological failure under integrase inhibitors (INSTI)
- CD4+ >200 cells/mm^3
- Sanger proviral DNA sequencing at screening without 3TC resistance mutations

Virologic withdrawal criteria:

- Confirmed Virologic Withdrawal (CVW): VL ≥ 50 copies/mL followed by a VL≥ 200 copies/mL in re-test 2-4 weeks apart.
- Precautionary Virologic Withdrawal (PVW): Three consecutive VL 50-200 copies/mL (each VL separated 2-4 weeks).

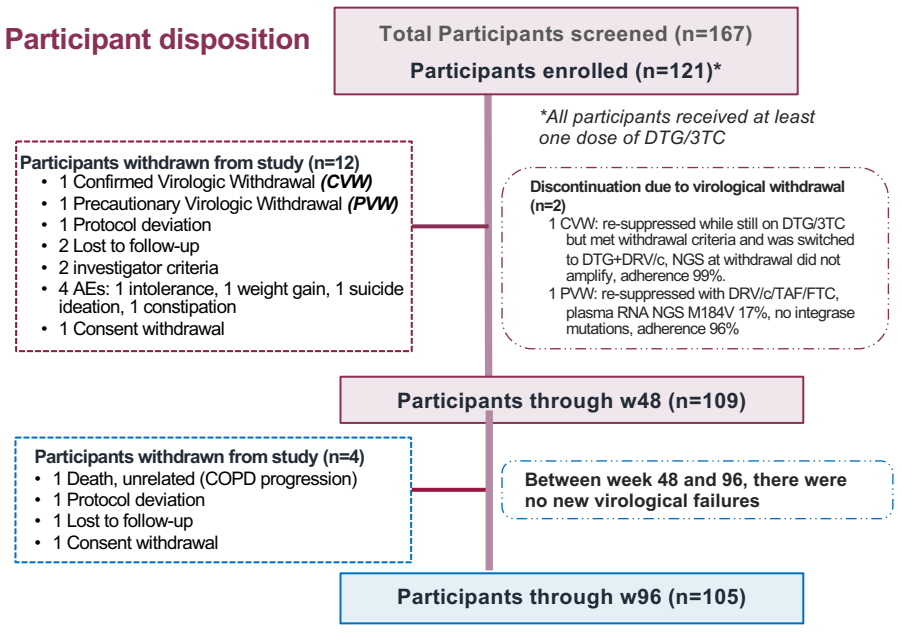
Results

Baseline data

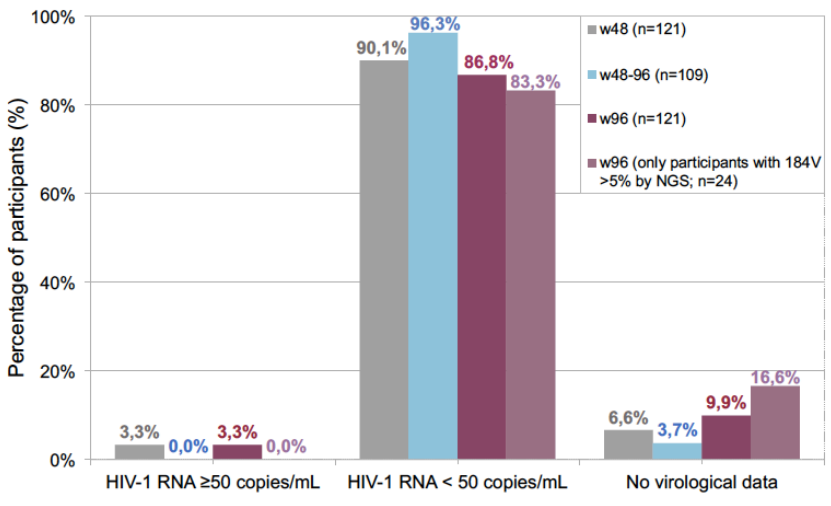
	All (n=121)
Sex at birth, Male (%)	86 (71.1%)
Age, median (IQR)	56.2 (51.8, 59.8)
Years since HIV diagnosis, median (IQR)	26.9 (20.7, 30.7)
ART duration (years), median (IQR)	23.4 (17.5, 27.1)
Number of previous ART regimens, median (IQR)	8 (6, 12)
Suppressed plasma HIV RNA (years), median (IQR)	9.2 (3.7, 14.4)
Baseline CD4+ count (cells/mm^3), median (IQR)	675 (516, 819)
Confirmed prior 3TC resistance (%)	**114 (94.2%)**
M184V mutation (%)	107 (88.4%)
M184I/undefined (%)	7 (5.8%)
Prior K65R mutation (%)	5 (4.1%)
Suspected prior 3TC resistance (%)	**7 (5.8%)**
Years since genotype with 3TC resistance, median (IQR)	15.2 (14.9, 15.3)
M184V/I > 5% in baseline proviral DNA by NGS	24 (19.8%)

NGS = next generation sequencing

Participant disposition



Efficacy FDA- Snapshot ITT-e



	All (n=121)
HIV-1 RNA < 50 copies/mL	**105 (86.8%)**
HIV-1 RNA ≥50 copies/mL	**4 (3.3%)**
HIV-1 RNA ≥50 copies/mL in week 96 window	0 (0)
Discontinuation due to lack of efficacy	2 (1.7%)
Discontinuation for other reasons and last available HIV-1 RNA ≥50 copies/mL	2 (1.7%) [1]
No virologic data at week 96	**12 (9.9%)**
Discontinuation due to an adverse event (AE)	3 (2.5%)
Discontinuation for other reasons and last available HIV-1 RNA <50 copies/mL	9 (7.4%) [2]

[1] **Discontinuation for other reasons and last VL ≥50 copies/mL:**
- 1 Lost to follow-up
- 1 adverse event (and VL at study withdrawal 90 copies/mL)

[2] **Discontinuation for other reasons and last VL<50 copies/mL:**
- 2 Lost to follow-up
- 2 protocol deviation (M184V in proviral DNA at screening; chronic Hepatitis B with HBAgs +)
- 2 investigator criteria (1 lung cancer, 1 M184V detected in plasma population genotyping at transient rebound, suppressed while still on DTG/3TC not fulfilling criteria for PVW/CVW but switched to DTG+DRV/c)
- 1 death, unrelated (COPD progression)
- 2 consent withdrawal

None of the 24 participants with baseline M184V/I >5% by NGS discontinued due to lack of efficacy:
- 20 participants with VL <50 copies/mL.
- 4 discontinuations (last VL <50 copies/mL): 1 protocol deviation and 2 discontinuations due to AEs (w48); 1 death, unrelated (w96)

Adverse Events

	Day 1- w48		w48-w96	
	Participants (n=121)	Adverse events	Participants (n=109)	Adverse Events
Drug-related AEs	19 (15.7%)	27	3 (2.8%)	3
Drug-related SAEs	1 (0.8%)	1	0	0
Drug-related grade 3-4 AEs	2 (1.7%)	3	0	0
Discontinuation due to AEs*	4 (3.3%)	6	0	0
Death	0	-	1 (0.9%)	-

* 1 constipation, 1 intolerance (gastrointestinal, neuropsychiatric), 1 suicide ideation, 1 weight gain (with VL ≥ 50 copies/mL at study withdrawal)

After excluding lamivudine mutations in proviral DNA by population sequencing, **DTG/3TC effectively maintained virological suppression after two years of follow-up in participants with HIV and prior history of 3TC resistance.**

No treatment-emergent resistance was observed.

Virological efficacy was not affected by detection of M184V/I in proviral DNA using Next Generation Sequencing

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