Planned 24-week analysis of two dolutegravir (DTG)-based simplification strategies

José L Blanco[1], John F. Rojas[1], Eugenia Negredo[2], Roger Paredes[2], Elisa De Lazzari[1], Bonaventura Clotet[2], Jose M Gatell[1], Esteban Martinez[1], for the DOLAM Study Group

[1]Hospital Clínic-IDIBAPS, University of Barcelona, Barcelona, Spain,
[2]Hospital Universitari Germans Trias i Pujol, Badalona,Spain

Disclosures

- Research Grant / Principal investigator:

  Janssen, MSD, ViiV

- Consultant:

  Janssen, MSD, ViiV

- Honoraria:

  Janssen, MSD, ViiV

Background

•High potency and barrier to resistance, long half-life, low risk of interactions, convenience and tolerability make dolutegravir an appealing drug for «less-drugs regimens».

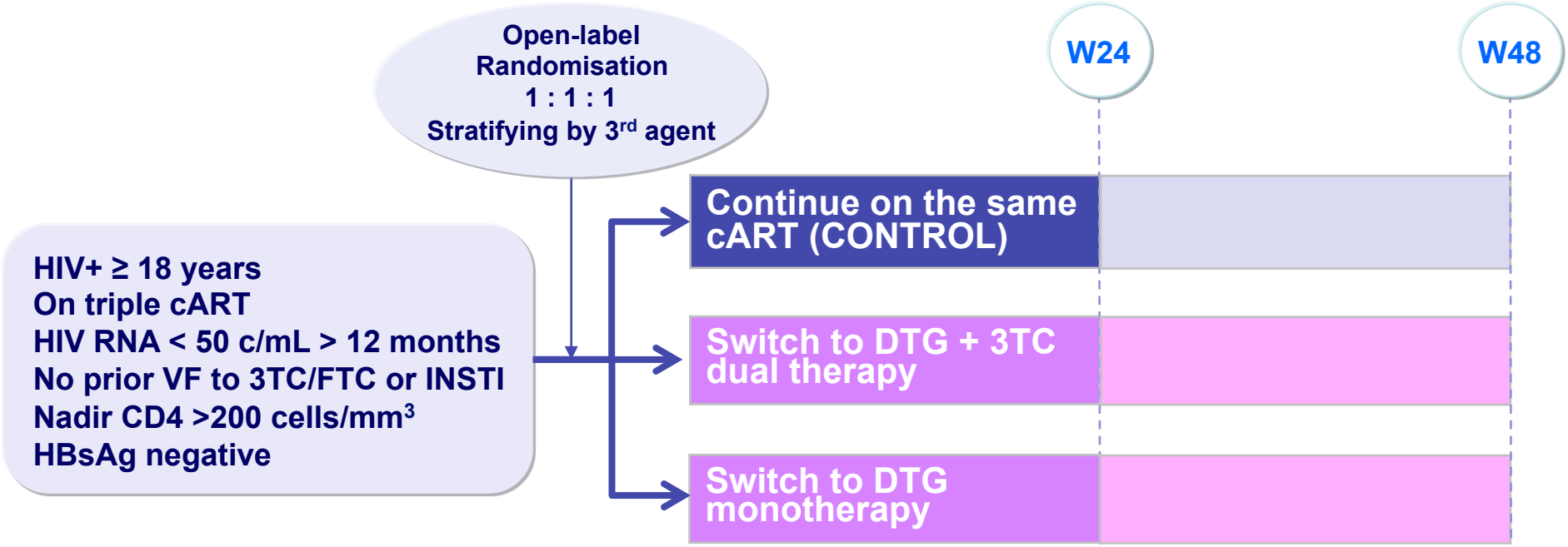
•To date, no controlled comparisons between DTG+3TC dual therapy or DTG monotherapy have been done.

•We hypothesized that DTG+3TC dual therapy or DTG monotherapy would be able to confer at least similar efficacy than triple regimens (CONTROL) in patients with sustained viral suppression.

Methods

- Open-label non-inferiority randomized controlled trial (DOLAM study, EudraCT number: 201500027435) designed in two phases, A and B:
  - Phase A (90 patients, 24-week follow-up completed) was established to test that experimental arms did not have an unacceptable failure rate (≥5%).
  - Phase B would include the full number of patients (150 per arm) followed for 48 weeks.
- Premature discontinuation was considered if viral failure or therapy interruption due to adverse events (AE's), concurrent illness, protocol deviation or patient's wish. Blips were registered. The study is ongoing and planned phase A results at 24 weeks are presented here.
- Data Safety Monitoring Board (DSMB) would review the data if the proportion of confirmed virological failure in any of the experimental arms reached ≥ 5%.

Design



DOLAM study, EudraCT number: 201500027435

Baseline characteristics

	CONTROL (n=31)	DTG+3TC (n=29)	DTG (n=31)	TOTAL
Age, years	46 (12)	44 (9)	47 (13)	46 (12)
Men	27 (87%)	23 (79%)	28 (90)	78 (86)
MSM	22 (76%)	21 (75%)	24 (77%)	67 (76%)
CD4/mm^3	675 (265)	753 (214)	791 (393)	739 (303)
CD4 cells (%)	33 (6)	33 (7)	33 (7)	33 (7)
CD8/mm^3	711 (269)	861 (269)	902 (416)	824 (334)
CD8 cells (%)	35 (7)	37 (7)	38 (9)	37 (8)
CD4/CD8 ratio	1.01 (0.36)	0.95 (0.36)	0.95 (0.35)	0.97 (0.35)
Prior ART				
NNRTI	22 (71%)	21 (72%)	21 (68%)	64 (70)
PI	3 (10%)	4 (14%)	5 (16%)	12 (13%)
INSTI	6 (19%)	4 (14%)	5 (16%)	15 (17%)

Data are mean (SD) unless otherwise stated

Patients' disposition at 24 weeks

•Three patients (none previously exposed to INSTI) prematurely discontinued due to viral failure:

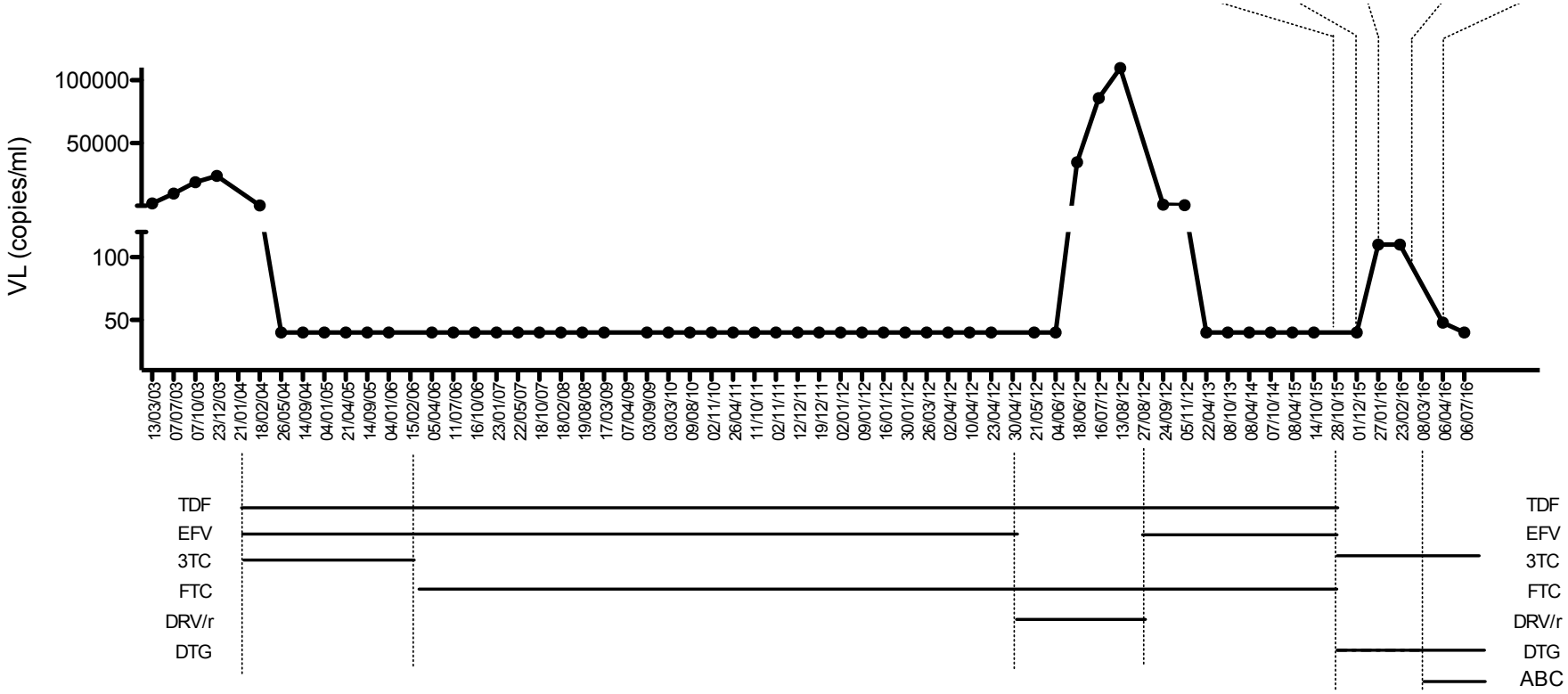
Patient	Arm	Week
HUGTiP 1	DTG + 3TC	12 weeks
HUGTiP 2	DTG	24 weeks
HCB	DTG	24 weeks

•There were no discontinuations for other reasons.

•Only 1 patient (DTG+3TC) had a blip 4 weeks

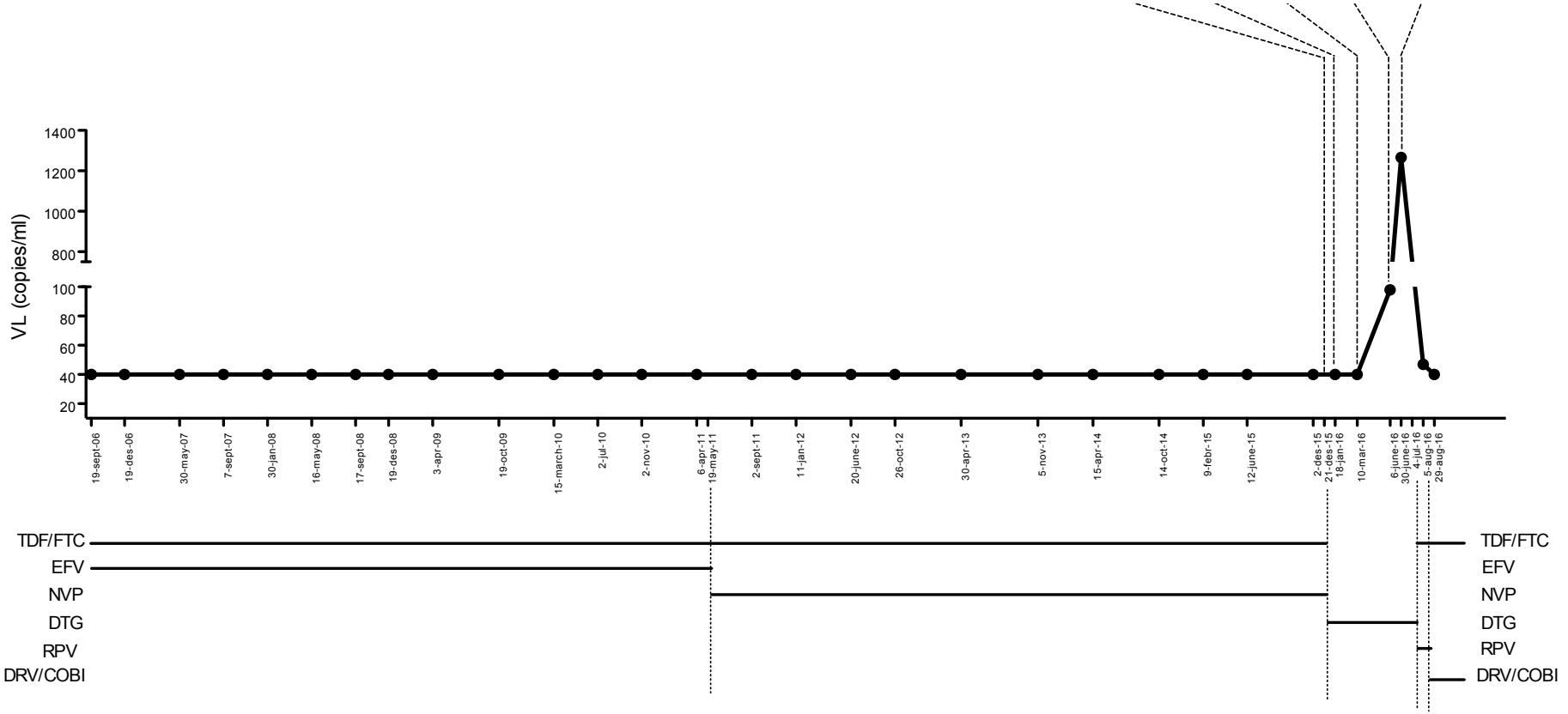
Patient HUGTiP 1 (DTG + 3TC)

		28/10/2015	1/12/2015	27/01/2016	02/03/2016	06/04/2016
Sample Information	Study week	0	4	12	17 (VF confirmation)	24
	ART	EFV/FTC/TDF → DTG+3TC	DTG+3TC	DTG+3TC	DTG+3TC	ABC/3TC/DTG
	HIV-1 RNA	40	40	110	110	48
	Drug levels (ng/mL)					
	DTG	<LLQ	1776.000	-	-	-
	RAL	<LLQ	<LLQ	-	-	-
	ELV	<LLQ	<LLQ	-	-	-
	DRM by Sanger	-	**Plasma** • RT: No mutations • Integrase: No mutations	**Plasma** • RT: No mutations • Integrase: No mutations	-	-
	DRM by MiSeq	-	-	-	**Plasma** • RT: No mutations • Integrase: No mutations	**PBMC** • *NRTI*: K70E (1.5%), K219E (1.2%) • *NNRTI*: G190R, M230I



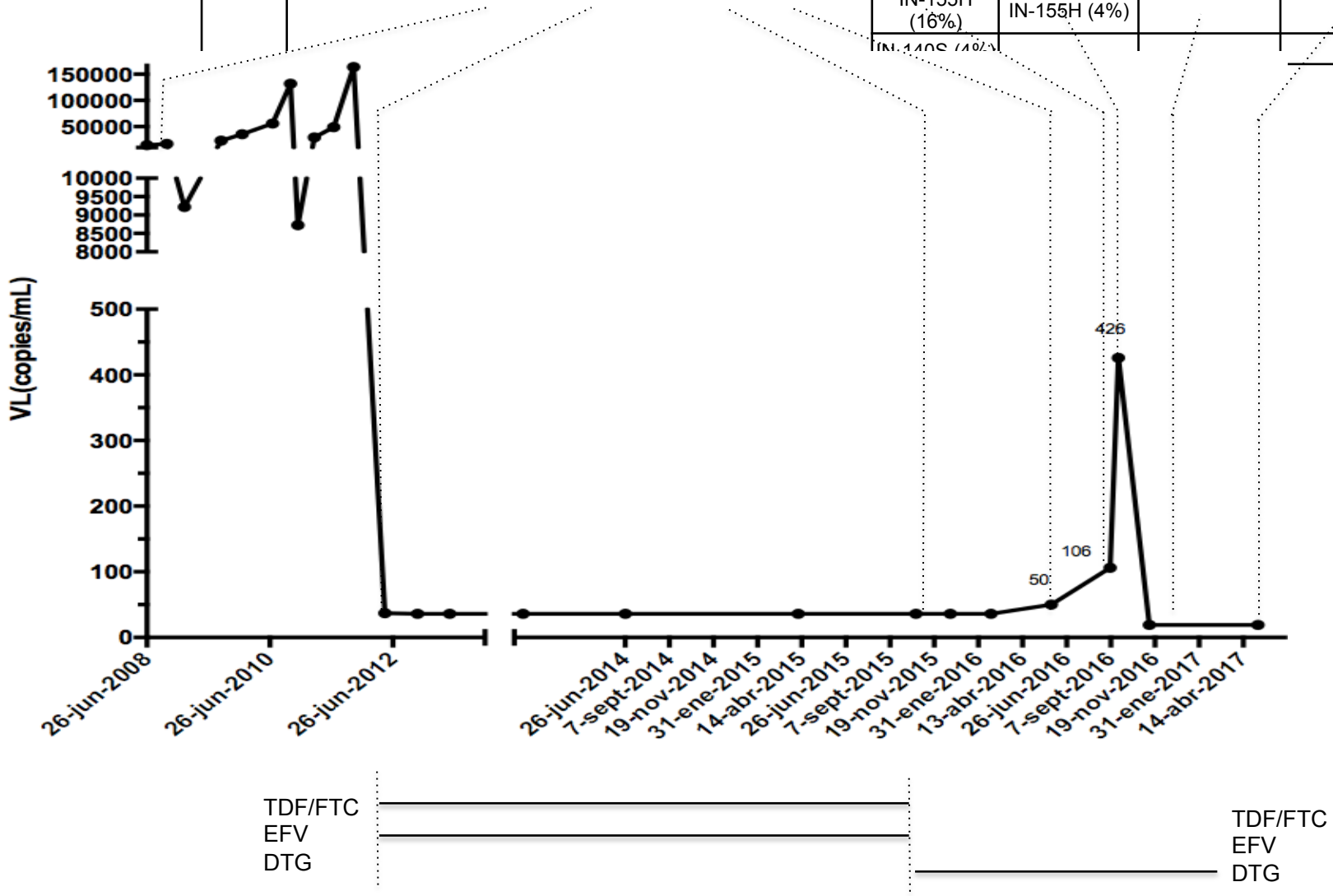
Patient HUGTiP 2 (DTG)

		21/12/2015	18/01/2016	10/03/2016	06/06/2016	30/06/2016
Sample Information	Study week	0	4	12	24	24 (VF confirmation)
	ART	TDF/FTC+NVP	DTG	DTG	DTG	DTG
	HIV-1 RNA	<40	<40	<40	98	1266
	Drug levels (ng/mL)					
	DTG	<LLQ	3503.916	1052.520	2899.466	-
	RAL	<LLQ	<LLQ	<LLQ	<LLQ	-
	ELV	<LLQ	<LLQ	<LLQ	<LLQ	-
	DRM by Sanger	-	-	**Plasma** RT: E138A	**Plasma** RT: E138A	**Plasma** RT: E138A
				Integrase: WT	Integrase: S147G N155H	Integrase: S147G N155H
	DRM by MiSeq	**PBMC** Pending	-	**Plasma** RT: E138A	**Plasma** RT: E138A	**Plasma** RT: E138A
				Integrase: WT	Integrase: S147G N155H	Integrase: S147G Q148R (3%) N155H



Patient HCB 1 (DTG)

Sample	Data	22/05/2008	10/05/2012	18/11/15	01/06/2016	06/09/2016	20/09/16	10/11/2016	09/05/2017
	ART	No	TDF/FTC/ EFC	DTG	DTG	DTG	DTG	DRV/c	DRV/c
	HIV-1 RNA	14700	<37	<37	50	106	426	<20	<20
	DRM-PS	V245E-RT					ND		
	DRM-454					Plasma	Plasma:		
						IN-138K(82%)	**IN-138K (87%)**		
						IN-155H (16%)	IN-155H (4%)		
						IN-140S (4%)			



Adverse events at 24 weeks

	CONTROL (n=31)	DTG+3TC (n=29)	DTG (n=31)	TOTAL
Group				
Infection	2	4	12	18
Neuropsychiatric	0	5	8	13
Genitourinary	2	4	1	7
Muscular	1	0	5	6
Gastrointestinal	2	0	3	5
Laboratory	2	1	2	5
Ocular/visual	0	1	1	2
Respiratory	0	1	1	2
Endocrine	1	0	0	1
Systemic	0	1	0	1
Grade				
1	8	17	28	53
2	2	0	6	8

DSMB recommendation

•Data Safety Monitoring Board recommended stopping DTG monotherapy arm and continuing the study with CONTROL and DTG+3TC arms.

Dr. JOSE ANTONIO MARTINEZ MARTINEZ, acting as the Secretary of the DOLAM Study DSMB (AN OPEN-LABEL, RANDOMIZED, CONTROLLED CLINICAL TRIAL TO ASSESS THE SAFETY, TOLERABILITY AND EFFICACY OF TWO DOLUTEGRAVIR-BASED SIMPLIFICATION STRATEGIES IN HIV-INFECTED PATIENTS WITH PROLONGED VIROLOGICAL SUPPRESSION: DOLAM STUDY; EudraCT number: 2015-000274-35) and met ad hoc upon the call of the Coordinator Investigator, Dr. Esteban Martinez, due to concern about the detection of virologic failures in three study patients included and follow up during the first 24 weeks of the study, declares the following:

After the revision of the available data, it is manifest that none of 31 control arm patients, 1 of 29 DTG+3TC arm patients and 2 of 31 DTG arm patients have presented virologic failure, of which that observed in the two patients of the monotherapy DTG arm was associated with resistance mutations. This Board considers that the rate of virologic failure in the DTG monotherapy arm of the study surpasses the tolerability criteria and is clinically relevant enough as to recommend the immediate interruption of the DTG monotherapy arm of the DOLAM study. The occurrence of a single virologic failure not associated with mutations in the DTG+3TC arm is not considered by this Committee relevant enough as to recommend the interruption of this study arm.

The decision expressed in this document has been taken unanimously by the three clinical member of the DOLAM study DSMB (Dr. Frascesc Vidal Marsal, Dr. Xavier Carné y Dr. José A. Martínez).

Barcelona, November 2, 2016.

José Antonio Martínez Martínez

Secretary of DSMB of the DOLAM Study.

Conclusion

- In contrast with DTG+3TC dual therapy, DTG monotherapy in patients with sustained viral suppression led to an unacceptable risk of viral failure with development of resistance mutations.

DOLAM study: Amendments and current status

- To continue the study with two arms only: DTG+3TC vs. CONTROL

- To re-calculate sample size according to the fact that there are two arms only (non-inferiority margin of 8%, 80% power, alpha 0.05, 10% patients lost-to-follow-up): 129 patients per arm (258 in total)

- To invite other investigators and centres with experience in similar studies (in addition to Hospital Clínic and Hospital Germans Trías i Pujol):

  Dr Daniel Podzamczer (Hospital de Bellvitge)

  Dr Esteve Ribera (Hospital Vall d'Hebron)

  Dr Gracia Mateo y Dr Mar Gutiérrez (Hospital de Sant Pau)

  Dr Pere Domingo (Hospital Arnau de Vilanova)

Acknowledgements

•All the patients participating in the study

•Hospital Clínic:

Dr José L. Blanco, Dr Jhon Rojas, Dr José Gatell, Dr Esteban Martinez

•Hospital Germans Trías i Pujol:

Dr Roger Paredes, Dr Eugènia Negredo, Dr Bonaventura Clotet

•Clinical Trial Unit:

Fundació Lluita contra la Sida (Crsitina Herrero, Myriam Solé)

•Statistician:

Elisa de Lazari