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Discontinuation of DTG, EVG/c, and RAL due to toxicity in a prospective cohort

Josep M Llibre [1], Anna Esteve [2], Josep M Miro [3], Gracia Mateo [4], Adrià Curran [5], Daniel Podzamczer [6], Melcior Riera [7], Francesc Homar [8], Lluis Force [9] and the PISCIS Cohort Study Group.

1Univ Hosp Germans Trias, Badalona, Barcelona, Spain, 2Centre d'Estudis Epidemiològics sobre les ITS i Sida de Catalunya (CEEISCAT, CIBERESP), Badalona, Barcelona, Spain, 3Hospital Clinic - IDIBAPS. University of Barcelona, Barcelona, Spain, 4Hospital Sant Pau, Barcelona, Barcelona, 5Hospital Vall d'Hebró, Barcelona, Barcelona, Spain, 6Hospital Universitari de Bellvitge, Barcelona, Spain, 7Hospital Universitario Son Espases, Palma de Mallorca, Spain, 8Hospital Son Llàtzer, Palma de Mallorca, Palma de Mallorca, Spain, 9Hospital de Mataró, Mataró, Spain

Dr. Josep M. Llibre
jmllibre@flsida.org

PISCIS Cohort
www.pisciscohort.org

Background / Objective: The rates of discontinuation (D/C) due to adverse events (AEs) of the integrase strand transfer inhibitors (INSTI) dolutegravir (DTG), raltegravir (RAL) and cobicistat-boosted elvitegravir (EVG/c) have been very low in randomized clinical trials. However, some real-life retrospective series have reported unexpectedly high rates of D/C due to AEs, particularly with DTG. We aimed to compare the D/C rates due to AEs of the three INSTI inhibitors in a prospective multicenter cohort.

Methods: The PISCIS Cohort is an ongoing observational study that includes about 21000 HIV-infected patients aged ≥16 years from 10 hospitals in Catalonia and 2 in the Balearic Islands (Spain). All subjects having started one of these 5 regimens including DTG with abacavir/lamivudine (ABC/3TC) or tenofovir fumarate/emtricitabine (TDF/FTC), RAL with ABC/3TC or TDF/FTC, or the co-formulation EVG/c/TDF/FTC since July 2013 as their initial regimen or a switch with plasma HIV-1 RNA <50 c/mL were included. The incidence rate and 95% CI of D/C due to toxicity is estimated as the ratio of the number of discontinuations by 100 patients/year (p/y) of follow-up (FU). Adjusted hazard ratios (aHR) and their 95% CI were obtained from multivariate Cox models, adjusted for gender, age, transmission group, origin, treatment-naïve and hepatitis B/C co-infection.

Results. 2021 subjects were included, most of them (94,8%) starting the INSTI as a switch/simplification strategy. Neuropsychiatric AEs identified included: anxiety, depression, insomnia, dizziness, nightmares, paresthesia, somnolence, tremor and vertigo. The rates of D/C due to any toxicity (3.8-7.5 per 100 p/y of FU) or neuropsychiatric toxicity (0.0-3.1 per 100 p/y of FU) were low, without significant differences among the 5 regimens. Toxicities were rarely grade 3-4, had commonly been seen before the initiation of the INSTI, and resolution was common after drug withdrawal. All results shown in the Tables.

Table 1: Baseline characteristics of the patients.

	DTG/ABC/3TC		DTG/TDF/FTC		RAL/ABC/3TC		RAL/TDF/FTC		EVG/c/TDF/FTC		
	N	%	N	%	N	%	N	%	N	%	p
N	792	39,19	81	4,01	226	11,18	340	16,82	582	28,8	<,0001
Age, median IQR	37,1	30,8 - 44,3	40,6	34,2 - 46,8	40	34,2 - 47,1	38,5	32,5 - 44,4	35,1	29,9 - 40,7	
Male, n (%)	645	81,4	68	84,0	174	77,0	267	78,5	500	85,9	0,0118
HIV exposure group, n %											<,0001
MSM	444	56,1	44	54,3	84	37,2	148	43,53	359	61,68	
IDU	99	12,5	14	17,3	48	21,2	109	32,06	53	9,11	
Heterosexual	204	25,8	18	22,2	77	34,1	68	20,00	138	23,71	
Other/Unknown	45	5,7	5	6,2	17	7,5	15	4,41	32	5,50	
Migrant, n %	228	28,8	29	35,8	51	22,6	87	25,59	195	33,51	0,0043
Years of HIV Dx, median IQR	8,3	4,3 - 12,7	8,4	3,5 - 13	7,7	3,9 - 11,5	6,8	1,7 - 11	6	2,1 - 10,1	
Prior AIDS, n %	135	17,1	18	22,22	48	21,24	60	17,65	88	15,12	0,2125
INSTI is the initial ART, n %	24	3,0	7	8,64	5	2,21	30	8,82	39	6,70	<,0001
Hepatitis C status (Ac), n %	217	27,4	20	24,69	76	33,63	127	37,35	94	16,15	<,0001
Hepatitis B status (HbsAg +), n %	83	10,5	10	12,35	15	6,64	24	7,06	58	9,97	0,0935
CD4 count, median IQR	689	519 - 886	605	455- 834,5	546	351 - 814	547,5	351 - 750	643	466 - 832	
CD4 count <200, n %	53	7	7	8,6	31	13,72	46	13,53	45	7,73	0,0003
VL <50 c/mL, n %	768	97	74	91,4	221	97,8	310	91,2	543	93,3	<,0001
Exitus, n %	0	0	2	2,5	10	4,42	10	2,94	0	0,00	<,0001
D/C after February 2016	676	85	49	60,5	46	20,35	66	19,41	363	62,37	<,0001

Table 2: Prior ART regimens in subjects switching to an INSTI regimen.

	DTG/ABC/3TC		DTG/TDF/FTC		RAL/ABC/3TC		RAL/TDF/FTC		EVG/c/TDF/FTC	
	N	%	N	%	N	%	N	%	N	%
N	768	100,0	74	100,0	221	100,0	310	100,0	543	100,0
Previous ART regimen, n %										
PI based	288	40,2	50	69,4	118	54,1	141	46,2	198	37,2
NNRTI based	370	51,7	11	15,3	79	36,2	138	45,3	323	60,7
NRTI based	14	2,0	1	1,4	4	1,8	2	0,7	7	1,3
INSTI based	37	5,2	6	8,3	15	6,9	21	6,9	0	0,0
Others	7	1,0	4	5,6	2	0,9	3	1,0	4	0,8
Was the 1st ART regimen?	192	25,0	27	36,5	32	14,5	88	28,4	193	35,5
CD4 count, median (IQR)	691	527 - 889	632	494 - 840	546	351 - 821	552	360 - 747	647	464 - 834

Table 3: Incidence of D/C due to any toxicity per 100 p/y of follow-up.

	n	D/C	%	PYFU	IR	95% CI
DTG/ABC/3TC	792	23	2,9	555,1	4,1	2,6 - 6,0
DTG/TDF/FTC	81	2	2,5	53,1	3,8	0,5 - 10,5
RAL/ABC/3TC	226	13	5,8	172,3	7,5	4,0 - 12,2
RAL/TDF/FTC	340	16	4,7	240,4	6,7	3,8 - 10,3
EVG/c/TDF/FTC	582	20	3,4	453,4	4,4	2,7 - 6,5

Table 4: Incidence of D/C due to neuro-psychiatric toxicity per 100 p/y of FU.

	n	D/C	%	PYFU	IR	95% CI
DTG/ABC/3TC	792	17	2,1	555,1	3,1	1,8 4,9
DTG/TDF/FTC	81	0	0,0	53,1	0,0	0,0 7,0
RAL/ABC/3TC	226	2	0,9	172,3	1,2	0,1 4,2
RAL/TDF/FTC	340	7	2,1	240,4	2,9	1,2 6,0
EVG/c/TDF/FTC	582	4	0,7	453,4	0,9	0,2 2,3

Table 5: Clinician evaluation of every toxicity associated to D/C.

	DTG/ABC/3TC		DTG/TDF/FTC		RAL/ABC/3TC		RAL/TDF/FTC		EVG/c/TDF/FTC	
	N	%	N	%	N	%	N	%	N	%
N	24	32,0	2	2,7	13	17,3	16	21,3	20	26,7
Grade										
1	15	62,5	1	50,0	6	46,2	9	56,3	10	50,0
2	4	16,7	0	0,0	6	46,2	5	31,3	7	35,0
3	2	8,3	0	0,0	1	7,7	2	12,5	0	0,0
4	1	4,2	0	0,0	0	0,0	0	0,0	0	0,0
Unknown	2	8,3	1	50,0	0	0,0	0	0,0	3	15,0
Presented previously?										
Yes	18	81,8	0	0,0	8	61,5	6	37,5	11	55,0
No	3	13,6	2	100,0	2	15,4	8	50,0	6	30,0
Unknown	1	4,6	0	0,0	3	23,1	2	12,5	3	15,0
Resolution after D/C?										
Yes	20	87,0	0	0,0	9	69,2	12	75,0	17	85,0
Partially	2	8,7	1	50,0	4	30,8	2	12,5	1	5,0
No	1	4,4	1	50,0	0	0,0	2	12,5	1	5,0
Unknown	0	0,0	0	0,0	0	0,0	0	0,0	1	5,0
Time of resolution										
<1 week	2	8,7	0	0,0	3	23,1	1	6,3	4	20,0
1-3 weeks	9	39,1	0	0,0	2	15,4	4	25,0	5	25,0
>3 weeks	11	47,8	1	50,0	8	61,5	8	50,0	9	45,0
Physician considers finally drug-related										
Yes	17	73,9	2	100,0	9	69,2	7	43,8	12	60,0
No	6	26,1	0	0,0	3	23,1	6	37,5	7	35,0
Unknown	0	0,0	0	0,0	1	7,7	3	18,8	1	5,0

Table 6: Analysis of risk factors for D/C due to any (A), or neuropsychiatric (B) toxicity.

A)

	Adjusted HR	95% CI		p
DTG vs RAL	1,69	0,84	- 3,39	0,1382
Age >60 years	2,16	0,29	- 16,09	0,454
Gender (female vs male)	2,48	1,09	- 5,66	0,0308
ABC vs TDF	1,39	0,73	- 2,64	0,3165
On ART > Feb 2016 vs	0,13	0,06	- 0,27	<,0001

	Adjusted HR	95% CI		p
DTG vs EVG/c	1,79	0,94	- 3,41	0,0766
Age >60 years	0,42	0,10	- 1,86	0,2547
Gender (female vs male)	1,87	0,70	- 4,94	0,2095
On ART > Feb 2016 vs	0,16	0,08	- 0,30	<,0001

	Adjusted HR	95% CI		p
EVG/c vs RAL	1,28	0,69	- 2,39	0,4288
Age >60 years	1,54	0,20	- 11,60	0,6752
Gender (female vs male)	2,80	1,27	- 3,27	0,0109
On ART > Feb 2016 vs	0,11	0,04	- 0,33	<,0001

B)

	Adjusted HR	95% CI		p
DTG vs RAL	3,18	1,12	- 9,04	0,0303
Gender (female vs male)	1,67	0,50	- 5,66	0,407
ABC vs TDF	1,22	0,44	- 3,36	0,6985
On ART > Feb 2016 vs not	0,19	0,07	- 0,48	0,0185

	Adjusted HR	95% CI		p
DTG vs EVG/c	4,93	1,57	- 15,50	0,0063
Age >60 years	0,33	0,04	- 2,60	0,2934
Gender (female vs male)	1,35	0,34	- 5,25	0,67
On ART > Feb 2016 vs not	0,23	0,09	- 0,57	0,0015

	Adjusted HR	95% CI		p
EVG/c vs RAL	1,02	0,28	- 3,75	0,9709
Gender (female vs male)	1,75	0,42	- 7,31	0,4452
On ART > Feb 2016 vs not	0,11	0,01	- 0,90	0,04

* Analysis was adjusted additionally for origin, HIV transmission group, hepatitis B and C status, switch, year of first visit

Limitations and strengths

1. The prospective cohort is subject to biases inherent to non-randomized treatment choice.
2. We had a low number of treatment-naïve subjects, and a short follow-up after February 2016.
3. Marginal structural models adjusted for baseline and time-varying confounding variables will be run in further analysis to reduce prescription bias effect.
4. All D/C reviewed by the treating physician to confirm any toxicity, grade and resolution.
5. The cohort includes most (approx 75%) HIV-infected subjects on ART in the Region.

Conclusions

- **In this prospective cohort study, we did not find significant differences in the rate of D/C due to any toxicity (neither related with all the regimen nor specifically with the INI) among the 5 regimens studied with DTG, RAL or EVG/c, either in naives or in switch.**
- **There was a significantly higher rate of D/C due to neuropsychiatric AEs with DTG *vs* either RAL or EVG/c. EVG/c/TDF/FTC and DTG + TDF/FTC showed the lower rates of D/C due to neurosychiatric AEs.**
- **Rates of D/C due the AEs were low, but most subjects discontinuing DTG/ABC/3TC did so due to neuropsychiatric AEs. Why this was not seen with DTG + TDF/FTC merits further investigation.**
- **We did not find a higher rate of D/C for subjects with >60 y.o., those receiving ABC (*vs* TDF) or those D/C beyond February 2016 (limited sample). We found a higher risk of D/C in females with DTG or EVG/c (vs RAL) for any AE but not for neuropsychiatric AEs.**
- **Toxicities were rarely grade 3-4, had commonly been seen also before the initiation of the INSTI, and resolution was frequent after drug withdrawal.**

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Generalitat de Catalunya Departament de Salut

Coordination: J. Casabona (Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya: [CEEISCAT]-CIBERESP), Jose M. Miró (Hospital Clínic-IDIBAPS, Universitat de Barcelona). Field coordinator: Juan Ignacio García (CEEISCAT). Steering committee: J. Casabona, A. Esteve (CEEISCAT-CIBERESP), Juan Ignacio García (CEEISCAT), Jose M. Miró (Hospital Clínic-IDIBAPS, Universitat de Barcelona), D. Podzamczer (Hospital Universitari de Bellvitge-IDIBELL), J. Murillas (Hospital Son Espases de Mallorca). Scientific committee: JM Gatell, C. Manzardo (Hospital Clínic-Idibaps, Universitat de Barcelona), JM. Llibre, B. Clotet (Fundació Lluita contra la Sida, Fundacio irsicaixa, Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona), E. Ferrer (Hospital Universitari de Bellvitge-IDIBELL), M. Riera (Hospital Son Espases de Mallorca), F. Segura, G. Navarro (Corporació Sanitària i Universitària Parc Taulí, Universitat Autónoma de Barcelona), L. Force (Hospital de Mataró, Consorci Sanitari del Maresme), J. Vilaró (Hospital General de Vic), A. Masabeu (Hospital de Palamós), E. Leon (Hospital General d'Hospitalet), C. Cifuentes, F Homar (Hospital Son Llàtzer), D. Dalmau, À. Jaen (Hospital Universitari Mútua de Terrassa), Mª. Gracia Mateo, Mª del Mar Gutierrez, (Hospital de la Santa Creu i Sant Pau), V. Falcó, A. Curran (Hospital Universitari Vall d'Hebron), P. Domingo, T. Puig (Hospital de Santa Maria) C. Agusti (CEEISCAT). Data Management and statistical analysis: A. Esteve (CEEISCAT-CIBERESP), A. Montoliu (CEEISCAT), E. De Lazzari (Hospital Clínic- Idibaps, Universitat de Barcelona), Dolors Giralt (Hospital Universitari de Bellvitge-IDIBELL). Informatics: E. Loureiro (CEEISCAT), F. Gargoulas, (Hospital Son Espases y Hospital Son Llàtzer), JC Rubia (Hospital General d'Hospitalet). Participating physicians and centers: J. Ambrosioni, L. Zamora, J.L. Blanco, F. Garcia- Alcaide, E. Martinez, J. Mallolas, (Hospital Clínic- Idibaps, Universitat de Barcelona), G. Sirera, J. Romeu, A. Jou, E. Negredo, (Fundació Lluita contra la Sida, Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona), M. Saumoy, A Imaz, F. Bolao, J. Tiraboschi, A. Silva (Hospital Universitari de Bellvitge-IDIBELL), M. Sala, M. Cervantes, M.J. Amengual, M. Navarro, V. Segura (Corporació Sanitària i Universitària Parc Taulí, Universitat Autónoma de Barcelona,) P. Barrufet, (Hospital de Mataró, Consorci Sanitari del Maresme), T. Payeras (Hospital Son Llàtzer), M. Gurgui, (Hospital de la Santa Creu i Sant Pau), L. Utrillo, (Hospital de Santa Maria).
Civil society representatives: Sebastián Meyer (Comitè 1er de Desembre).

CEEIS Cat Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya