

DOLUTEGRAVIR INDUCED NEUROTOXICITY

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INTRODUCTION



DTG presents an excellent safety/tolerability profile in clinical trial setting, although some SE in relation with CNS has been described after commercialization.

In our country, [in the unique series published to date (Llibre JM et al. CROI 2017. P651)] they have become the main cause of its discontinuation.



CROI 2017, Seattle, WA February 13-16, 2017 Poster 651

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

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On ART > Feb 2016 ws not 0,11 0,01 - 0,90 0,04

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 natients.

% 30,19 30,8 - 64,3 81,4 56,1 12,5 25,8 5,7	81 40,6 68 68 14 18 5	4,82 24,2 - 46,8 84,0 54,3 17,3 22,2	84 48 77	% 11,18 24,2 - 47,1 77,0 37,2 21,2	N 340 36,5 267 348 109	% 16,82 22,5 - 64,4 78,5 43,53 32,06	N 582 35,1 500 350 53	% 28,8 29,9 - 40,7 85,9 61,68 9,11	0,0116
30,8 - 64,3 81,4 56,1 12,5 25,8 5,7	40,6 68 44 14 18	34,2 - 46,8 84,0 54,3 17,3 22,2	40 176 84 48	34,2 - 47,1 77,0 37,2 21,2	38,5 267 148 109	32,5-64,4 78,5 43,53 32,06	35,1 500 359	29,9 - 40,7 85,9 61,68	
81,4 56,1 12,5 25,8 5,7	68 44 14 18	84,0 54,3 17,3 22,2	176 84 48	77,0 37,2 21,2	267 248 309	78,5 43,53 32,06	500 359	85,9 61,68	
56,1 12,5 25,8 5,7	44 14 18	54,3 17,3 22,2	84 48	37,2 21,2	14E 100	43,53 32,06	350	61,68	<,0001
12,5 25,8 5,7	14 18	17,3 22,2	48	21,2	109	32,06			<,0001
12,5 25,8 5,7	14 18	17,3 22,2	48	21,2	109	32,06			
25,8 5,7	18	22,2					53	9.11	
5,7			77						
	5.			34,1	68	20,00	138	23,71	
		6,2	17	7,5	15	4,41	32	5,50	
28,8	29	35,8	51	22,6	87	25,59	195	33,51	0,0043
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	
17,1	18	22,22	41	21,26	60	17,65	98	15,12	0.2125
3,0	7	8.64	5	2,21	30	8,92	39	6.70	<.0001
27,4	20	24,69	76	33,63	127	37,35	94	16,15	<,0001
10.5	10	12.35	15	6.64	24	7.06	58	9.97	0.0935
519 - 886	605	455-834.5	546	351 - 814	547.5	351-750	643	466 - 832	
7	7	8,6	31	13,72	46	13,53	45	7,73	0,0003
9.7	74	91.4	221	97.8	310	91.2	543	93.3	<.0001
0	2	2.5	10	4,42	10	2,94	0	0.00	<.0001
85	49	60.5	46	30,35	66	19,41	363	62,37	<.0001
	17,1 3,0 27,4 10,5 519 - 886 7 97 0 85	17,1 18 2,0 7 27,4 20 20,5 10 519 - 886 655 7 7 97 74 0 2 85 49	17,1 18 22,22 2,0 7 8,64 27,4 20 24,69 20,5 10 12,35 519 886 626 455 824,5 7 7 8,6 0 2 2,5 85 49 60,5	17,1 18 22,22 48 2,0 7 8,44 5 22,4 20 24,6 3 7 8,4 5 5 519 886 6 45 84,5 5 66 6 45 84,5 5 66 6 45 84,5 5 66 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	17,1 18 22,22 48 21,38 30 7 8,46 5 2,21 22,A 20 34,48 78 33,63 519-105 101,235 5 6,44 519-106 655 455-884,5 566 255-884 76 7 76 8,5 21 13,72 97 74 91,4 221 97,8 90 2 2,5 00 4,42 85 69 66,5 48 20,35	17.1 18 22.22 48 21.38 60 3.0 7 8,64 5 2.21 20 22.A 20 34,64 78 33,63 127 105.5 10 12.38 5 6,64 24 1319-106 655 455-884,5 566 255-884 50-25 77 7 8,6 21 11.72 45 107 24 91,4 221 97,8 310 10 2 2,5 0 4,42 10 165 40 62,5 44 20,55 64	17.1 18 22.22 48 31.38 60 17.58 3.0 7 8.64 5 2.21 30 80 80 2 2.58 22.4 20 24.68 78 18.63 13.7 27.38 10.5 10 12.38 15 6.64 24 7.66 139 86 65 455 88.45 56 26.1 18.5 57.5 581.7 20 7 7 8.6 13 13.72 48 13.13 59.2 10 2 2.5 10 4.42 20 7.8 13.0 59.2 85 40 60.5 44 20.25 64 10.41	17.1 18 22.22 48 31.38 60 17.65 68 30 7 8.64 5 2.21 30 802 30 27.4 20 24.68 78 31.81 31.9 27.35 68 30.5 10 12.38 5 5 6.64 34 7.66 88 139 60 65 415 418.5 566 361 418 54.75 531 702 7 7 8,6 11 13.72 41 13.12 54 10 2 2,5 0 4,2 20 2,98 0 10 2 2,5 0 4,2 20 2,98 0 15 40 60.5 44 20.25 64 10.41 343 16 17 18 18 18 18 18 17 18 18 18 18 18 18 18	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$

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	76	
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	298	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	3.7	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	293	35.5	
CD4 count, median (IOR)	691	527 - 889	632	494 - 840	546	351 - 821	552	360 - 747	647	464 - 83	

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

	-	U/L	76	PIIO	116	******
DTG/ABC/STC	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/STC	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 neuropsychiatric toxicity per 100 p/y of FU.

	n	Dyc	76	PYFU	-	951	s CI
DTG/ABC/STC	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/STC	DTG/TDF/FTC		RAL/ABC/STC		RAL/TDF/FTC		EVG/c/TDF/FTC	
	24	76			13		16		20	76
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
1	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	11,3	1	50,0	0	0,0	0	0,0	3	15,0
Presented previously?										
Yes	18	81,8	Ω	0,0	9	61,5	6	37,5	11	55,0
No	3	13,6	2	100,0	2	15,4		50,0	6	30,0
Unknown	1	4,6	0	0,0	3	23,1	2	12,5	3	15,0
Resolution after D/C7										
Yes	20	87,D	0	0,0	9	69,2	12	75,0	17	85,0
Partially	2	8,7	1	50,0	4	20,8	2	12,5	1	5,0
No	1	4,4	1	50, D	0	0,0	2	12,5	1	5,0
Unknown	0	0,0	Ω	0,0	Ω	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		50,0	9	45,D
Physician considers finally drug-related										
Yes	17	73,9	2	100,0	9	69,2	7	43,8	12	0,00
No	6	26,1	Ω	0,0	2	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.

		Adjusted HR	9	SN	a	р			Adjusted HR	1	95%	CI	р
A)	DTG ws RAL	1,69	0.84	-	3,29	0.1392		DTG vs RAL	3,18	1,12		9,04	0,0303
~,	Age >60 years	2,16	0,29	-	16,09	0,454	B)	Gender (female vs male)	1,67	0,50		5,66	0,407
	Gender (Female vs male)	2,48	1,09	-	5,66	0,0308		ABC vs TDF	1,22	0,44	-	1,16	0,6985
	On ART > Feb 2016 vs	0,13	0.73		0,27	<.0001		On ART > Feb 2016 vs not	0,19	0,07	-	0,48	0,0185
		Adjusted HR	9	sx.		р			Adjusted HR	1	95%	cı	р
	DTG vs EVG/c	1.79	0.94	-	3.41	0.0766		DTG vs EVG/c	4,93	1,57		15,50	0,0063
	Age >60 years	0,42	0.10		1,86	0.2547		Age >60 years	0.33	0,04		2,60	0.2934
	Gender (Fersale vs male)	1,87	0,70		4,94	0,2095		Gender (female vs male)	1.35	0.34	-	5.25	0.67
	On ART > Feb 2016 vs	0,16	0,06	-	0,30	<.0001		On ART > Feb 2016 vs nat	0,23	0,09		0,57	0,0015
)-		Adjusted HR	9	SN:	a	р			Adjusted HR	,	95%	а	р
	EVG/c vs RAL	1,28	93,0	-	2,29	0,4298		EVG/c vs RAL	1,02	0.28	_	1,75	0.9709
_	Age >60 years	1,54	0,20		11,60	0,6752		Gender (female vs male)	1,75	0.42		7,31	0,4452
31	Gender (Fersale vs male)	2,80	1,27		3,27	60100		anner penias trinas,	4,73	4,42		-,	4/4425

On ART > Feb 2016 vs 0,11 Limitations and strengths

The prospective cohort is subject to biases inherent to non-randomized treatment choice.

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

- 2. We had a low number of treatment-naïve subjects, and a short follow-up after February 2016.
- 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.

- 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.



Controlled 1. Co



Neurological side effects with integrase inhibitors cause low rates of discontinuation in clinical practice

1 October 2016. Related: Conference reports, Side effects, Lipodystrophy Workshop (IWADRH) 18 New York 2016.



An analysis from use of integrase inhibitors in clinical practice reported significantly higher rates of discontinuations related to side effects than seen in clinical studies and includes neurological complications with dolutegravir.

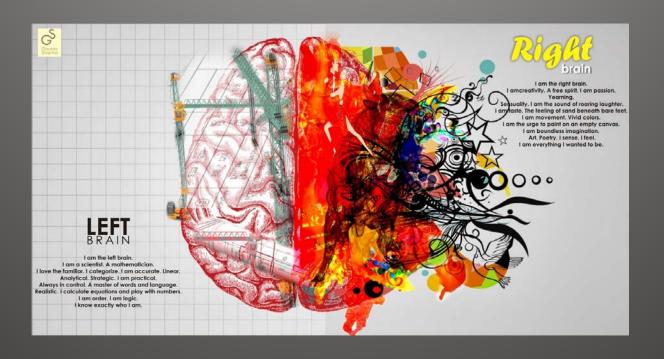
This was a retrospective analysis presented in an oral presentation at the 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV by Esteban Martinez from University of Barcelona. [1]

18th International Workshop on Comorbidities & Adverse Drug Reactions in HIV 12-13 September 2016, New York Neurological side effects with integrase inhibitors cause low rates of discontinuation in clinical practice

This was a retrospective analysis presented in an oral presentation at the 18th International Workshop on Comorbidities and Adverse Drug Reactions in HIV 2016 by Esteban Martinez from University of Barcelona

OBJECTIVE

To study and describe the SE of DTG on the CNS.



PATIENTS AND METHODS:

- Retrospective study (December 2014 until April- 2018) collecting patients receiving DTG and they presented SE in the CNS.
- During this period 300 patients were enrolled and demographic/epidemiological, clinical, psychiatric, immunovirological data were registered, as well as the type and characteristics of SE on the CNS.



RESULTS

- 7 (16,6%) over 42 patients that received DTG presented CNS toxicity.
- The average time of use of the drug until the onset of symptoms was 10 months and in all cases led to drug discontinuation with complete clinical resolution the next 4 weeks.



Sex	Age	Neurotoxicity	PSQ	CV/CD4 Start DTG	CV/CD4 without DTG	New ART
Man	47	Dysthymia	NO	CV<40 CD4: 1728	CV<40 CD4: 2065	ABC/3TC + RAL
Man	35	Suicide attempt	YES	CV<40 CD4: 762	CV < 40 CD4: 824	DRV/COBI+(TAF/FTC)
Woman	49	Depression	YES	CV<40 CD4: 189	CV 154 CD4: 223	TAF/FTC/COBI/EVG
Man	57	Psychosis	YES	CV<40 CD4: 594	CV<40 CD4: 425	TAF/FTC/COBI/EVG
Man	33	Headache	NO	CV<40 CD4: 642	CV<40 CD4: 703	TAF/FTC/COBI/EVG
Man	48	Mania	YES	CV<40 CD4: 802	CV<40 CD4: 910	TAF/FTC/COBI/EVG
Man	75	Suicide attempt	YES	CV <u>124</u> CD4: 806	Pending result.	(TAF/FTC) + RAL

CONCLUSIONS:

- In our series, a 16,6% of patients presented SE in the CNS with the use of DTG.
- Predominantly male with a PSYCHIATRIC history.
- In patients with psychiatric comorbidity is was more severe when compared to patients not affected.
- In the absence of confirmation in larger series, treatment with DTG in patients with psychiatric background need to be checked.











Thanks a lot.

EFAVIRENZ

DOLUTEGRAVIR

RALTEGRAVIR

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