A Healthy Brain in People Living with HIV

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Title: **Comparative neuropsychiatric toxicity profile of dolutegravir (DTG)-based versus efavirenz (EFV)-based versus other recommend first-line antiretroviral therapies (ART): data from Icona Foundation Study Cohort**

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Abstract body
Background: Both EFV and DTG have been associated with a higher risk of neuropsychiatric adverse events (NPAEs) compared to other antiretrovirals. Despite this, comparison of NPAEs risk between this two drugs in observational cohorts are lacking. The aim of the study was to compare the risk of neuropsychiatric toxicity among DTG-based, EFV-based regimens as well as other currently recommended first-line ART over a period in which all these treatment strategies have been used.
Materials and Methods: We included all ART-naive patients (pts), enrolled in the Icona cohort, who started a first-line recommended (as main or alternative) ART, according to EACS guidelines 2018, over the period January 2006-December 2018. Probabilities of both experiencing NPAEs (defined as occurrence of neuropsychiatric symptoms or start new treatment for neuropsychiatric disorders) either leading or not to treatment discontinuation (TD) and discontinuing third drug due to NPAEs (ignoring changes in the backbone) were estimated by Kaplan Meier analysis comparing pts starting EVF-based, DTG-based or other regimens. Predictors of TD due to NPAEs were identified by Cox regression analysis. A sensitivity analysis in pts starting ART from 2011 (year in which DTG was firstly available) was also performed.
Results: Overall, 7854 pts were included, of whom 1322 (17%) initiating a DTG-based regimen, 1542 (20%) an EFV-based regimen and 4990 (63%) a non-DTG non-EFV based ART. Compared to the other treatment groups, pts starting DTG were more likely to be non-Italian, MSM, class CDC C and to have abacavir/lamivudine as backbone [Table 1]. At univariable survival analysis, pts on an EFV-based ART, were more likely both to experience NPAEs (8.5% vs 5.2% for DTG and 3.2% for other at 2 year, log rank p<.001) and to stop third drug due to NPAEs (6.9% vs 2.4% for DTG and 0.3% for other at 2 year, log rank p<.001) [Fig. 1a,1b]. At multivariable analysis, after adjusting for key confounders, the third drug started was the only predictor of TD due to NPAEs and, particularly, starting DTG was associated with a lower risk of discontinuing treatment due to NPAEs compared to EFV (adjusted relative hazard [aRH] 6.84, p<.001) but with a higher risk compared to other ART (aRH 0.10, p<.001). This result was also confirmed restricting the analysis to pts starting ART after 2011 [Table 2]
Conclusions: In our analysis, we found a 2% risk of stopping DTG due to NPAEs by 2 year from initiating first-line DTG-based cART regimens. This estimated risk is lower than that observed in similar

observational studies in Europe although higher than that recorded in the DTG-arm of phase-III randomized clinical trials. Our comparison also shows that this risk is higher than that experienced by people starting other EACS recommended first-line regimens but significantly lower than that seen for people starting EFV. Residual confounding by calendar year or other unmeasured factors cannot be ruled out.

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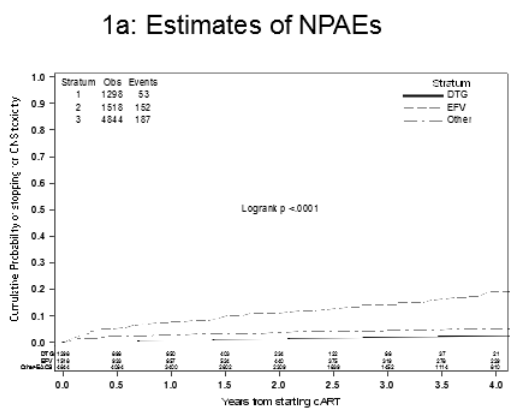
Table 1: Baseline characteristics of 7,854 patients enrolled, according to the third drug

	DTG-based N= 1,322	EFV-based N= 1,542	Other N= 4,990	p*	Total N= 7854
Gender, n(%)				**<.001**	
Female	223 (16.9%)	230 (14.9%)	1016 (20.4%)		1469 (18.7%)
Age, years				0.051	
Median (IQR)	40 (31, 49)	39 (32, 46)	39 (31, 47)		39 (31, 47)
Mode of HIV Transmission, n(%)				**<.001**	
IDU	62 (4.7%)	121 (7.9%)	381 (7.7%)		564 (7.2%)
Homosexual contacts	703 (53.7%)	701 (45.9%)	2293 (46.4%)		3697 (47.5%)
Heterosexual contacts	442 (33.4%)	599 (38.8%)	1948 (39.0%)		2989 (38.1%)
Other/Unknown	102 (7.8%)	107 (7.0%)	322 (6.5%)		531 (6.8%)
Nationality, n(%)				**<.001**	
Not Italian	556 (42.1%)	289 (18.7%)	1351 (27.1%)		2196 (28.0%)
AIDS diagnosis, n(%)				**0.005**	
Yes	163 (12.3%)	136 (8.8%)	486 (9.7%)		785 (10.0%)
HCVAb, n(%)				**<.001**	
Positive	69 (5.2%)	151 (9.8%)	416 (8.3%)		636 (8.1%)
CD4 count, cells/mmc				**<.001**	
Median (IQR)	349 (139, 562)	324 (226, 420)	351 (199, 503)		344 (195, 491)
CD4 count nadir, cells/mmc				**<.001**	
Median (IQR)	333 (129, 526)	307 (213, 399)	337 (191, 480)		328 (187, 467)
Viral load, log10 copies/mL				**<.001**	
Median (IQR)	4.62 (4.10, 5.24)	4.75 (4.23, 5.14)	4.57 (4.00, 5.04)		4.61 (4.07, 5.08)
Calendar year of baseline				**<.001**	
Median (IQR)	2016 (2016, 2017)	2011 (2009, 2012)	2014 (2012, 2016)		2014 (2012, 2016)
Backbone n(%)				**<.001**	
TDF/FTC	625 (47.3%)	1409 (91.4%)	4595 (92.1%)		6629 (84.4%)
3TC/ABC	697 (52.7%)	115 (7.5%)	381 (7.6%)		1193 (15.2%)
Other	0 (0.0%)	18 (1.2%)	14 (0.3%)		32 (0.4%)
Third drug, n(%)					
DTG	1322 (100.0%)	-	-		
EFV	-	1542 (100.0%)	-		
ATV			1131 (22.6%)		
DRV			1271 (25.5%)		
EVG/c			889 (17.8%)		
RAL			469 (9.5%)		
RPV			1230 (24.6%)		
Time from HIV diagnosis to ART, months				**<.001**	
Median (IQR)	1 (1, 3)	11 (2, 39)	3 (1, 24)		3 (1, 24)
Education, n(%)				**<.001**	
Primary school	35 (2.6%)	88 (5.7%)	226 (4.5%)		349 (4.4%)
Secondary school	162 (12.3%)	319 (20.7%)	810 (16.2%)		1291 (16.4%)
College	356 (26.9%)	522 (33.9%)	1482 (29.7%)		2360 (30.0%)
University	176 (13.3%)	179 (11.6%)	615 (12.3%)		970 (12.4%)

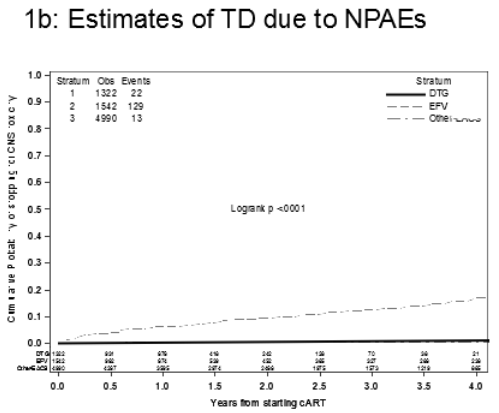
Other/Unknown	593 (44.9%)	434 (28.1%)	1857 (37.2%)	2884 (36.7%)
Employment, n(%)				
Unemployed	143 (16.0%)	194 (14.8%)	661 (16.7%)	998 (16.2%)
Employed	446 (49.9%)	702 (53.5%)	1910 (48.2%)	3058 (49.6%)
Self-employed	156 (17.5%)	225 (17.1%)	667 (16.8%)	1048 (17.0%)
Occasional	19 (2.1%)	44 (3.4%)	172 (4.3%)	235 (3.8%)
Student	47 (5.3%)	52 (4.0%)	163 (4.1%)	262 (4.2%)
Retired	21 (2.4%)	31 (2.4%)	124 (3.1%)	176 (2.9%)
Invalid	3 (0.3%)	2 (0.2%)	10 (0.3%)	15 (0.2%)
Housewife	12 (1.3%)	33 (2.5%)	86 (2.2%)	131 (2.1%)
Other/unknown	46 (5.2%)	29 (2.2%)	169 (4.3%)	244 (4.0%)
Follow-up time, months			**<.001**	
Median (IQR)	11 (4, 19)	8 (3, 27)	21 (9, 38)	16 (6, 33)

*Chi-square or Kruskal-Wallis test as appropriate

Figure 1: Probability of experiencing NPAEs (1a) and discontinuing third drug due to NPAEs (1b) according to treatment group.



Estimates (95% CI)			
	DTG	EFV	Other
1-year	3.9% (2.8-5.1)	6.9% (5.4-8.3)	2.7% (2.2-3.2)
2-year	5.2% (3.7-6.6)	8.5% (6.8-10.2)	3.2% (2.7-3.7)
3-year	5.2% (3.7-6.6)	12.4% (10.1-14.8)	4.1% (3.5-4.7)



Estimates (95% CI)			
	DTG	EFV	Other
1-year	1.6% (0.9-2.4)	5.3% (4.0-6.6)	0.3% (0.1- 0.4)
2-year	2.4% (1.4-3.4)	6.9% (5.4, 8.5)	0.3% (0.1-0.4)
3-year	2.4% (1.4-3.4)	10.7% (8.5-12.9)	0.3% (0.1-0.4)

Table 2: Relative hazards (RH) of discontinuation of third drug for neuropsychiatric toxicity from fitting Cox regression models according to treatment group.

	aRH* (95% CI) of TD due to NPAES	p-value	aRH *(95% CI) of TD due to NPAES#	p-value
DTG-based regimens	1.00		1.00	
EFV-based regimens	6.84 (2.91-16.04)	**<.001**	6.01 (2.21-16.38)	**<.001**
Other regimens	0.10 (0.03-0.31)	**<.001**	0.08 (0.03-0.28)	**<.001**
* Adjusted for: gender, age, mode of HIV transmission, nationality, calendar year of starting ART, AIDS diagnosis, BMI, STR (yes vs no), backbone, CD4 count nadir, highest level of education and employment # sensitivity analysis on pts starting ART from 2011.				