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OC 7 **Effectiveness of dolutegravir (DTG)-based regimens as either first line or switch antiretroviral therapy (ART): data from the Icona cohort**

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Abstract:

Background: Conflicting results about DTG safety have risen by recent observational reports, mainly conducted in treatment-experienced (TE) patients (pts). It is important to accurately estimate the long-term risk of failure and safety profile of DTG-based regimens especially in ART-naïve subjects.

Material and Method: Both ART-naïve and virologically-suppressed TE pts from Icona cohort initiating, for the first time, a DTG-based regimen from January 2015 to December 2017 were included. Probabilities of DTG-treatment discontinuation (TD) for any reason, DTG-TD for toxicity and virological failure (VF) [2 consecutive HIVRNA>50 copies/mL; after 6 months from DTG-start for ART-naïve pts] were estimated by Kaplan-Meier analysis. Predictors of DTG-TD for any reason were identified by Cox regression model.

Results: 1,717 pts (997 ART-naïve and 720 TE) were included. 94% ART-naïve pts started a DTG standard triple therapy (TT) (52% abacavir [ABC]-based); in TE group, 69% pts started a standard TT (81%ABC-based) and 28% pts a dual regimen.

In the ART-naïve group, the estimated probabilities of DTG-TD for any reason and for toxicity were 6.4% (95%CI:4.7-8.1) and 3.6% (95%CI:2.3-4.9) by 1 year and 10.4% (95%CI:7.7-13.0) and 5.3% (95%CI:3.4 -7.1) by 2 years, respectively [Fig 1a,1c]. Neuropsychiatric (NP) symptoms were the most reported adverse events (AEs) leading to TD (n=15, 1.5%). At multivariable analysis, pts diagnosed with an AIDS defining event (aHR=2.83 vs AIDS free,p=0.006) and pts starting DTG more recently (aHR=1.99 per more recent year, p=0.004) were at higher risk of stopping DTG for any reason [Table1a].

In the TE group, the cumulative probabilities of DTG-TD for any reason and for toxicity were 5.6% (95% CI:3.7-7.6) and 2.2% (95%CI:1.0-3.3) by 1 year and 7.0% (95%CI:4.8-9.3) and 3.6% (95%CI:2.0-5.2) by 2 years, respectively [Fig 1b,1d]. NP AEs were the main reason of DTG-TD for toxicity (n=11, 1.5%). At multivariable analysis, TE patients starting DTG in a dual regimen compared to standard TT were at lower risk of DTG-TD regardless of the reason (aHR=0.35,p=0.023) [Table1b]. After stratifying DTG-based TT according to the backbone, starting a dual therapy was again associated with lower risk than ABC-based TT (aHR=0.39, p=0.047) whereas no difference was observed between ABC-based and tenofovir-based TT [Table1c]. VF occurred in 20 ART-naïve (2%) and 10 TE (1%) pts with a 2-year probability of 3.9% (95% CI:2.1-5.6) and 2.0% (95%CI:0.7-3.2), respectively.

Conclusions: In our study, DTG showed excellent efficacy and tolerability both in ART-naïve and TE pts with a low rate AEs, mostly NP, leading to TD. This is, to our knowledge, the largest cohort of HIV positive pts starting DTG from ART-naïve and results are key for calibrating models on the potential long-term effect of this strategy. ART-naïve pts starting DTG more recently appeared to be at higher risk of DTG-TD, however this is possibly related to the increasing concerns on DTG safety.

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Table 1: Predictors of DTG-TD for any reason in ART-naïve (1A) and TE (1B and 1C) groups (Cox regression analysis)

(A) NAIVE-GROUP				
	HR (95% CI)	**p-value**	**aRH* (95% CI)**	**p-value**
Gender				
Female	1.66 (0.94-2.95)	0.082	1.66 (0.73-3.74)	0.226
AIDS diagnosis				
Yes vs. No	2.53 (1.43-4.47)	**0.001**	2.83 (1.35-5.95)	**0.006**
Baseline CD4 count, cells/mm3				
per 100 higher	0.88 (0.79-0.98)	**0.023**	0.94 (0.83-1.06)	0.328
Calendar year of baseline				
per more recent year	1.79 (1.22-2.62)	**0.003**	1.99 (1.24-3.18)	**0.004**
Baseline viral load, log10 copies/mL				
per log higher	1.26 (0.97-1.65)	0.087	1.16 (0.85-1.56)	0.348

(B) TE-GROUP [Model 1]				
	HR (95% CI)	**p-value**	**aRH** (95% CI)**	**p-value**
Gender				
Female	1.17 (0.57-2.40)	0.669	0.99 (0.42-2.35)	0.989
Age, years				
per 10 older	1.11 (0.84-1.46)	0.454	1.25 (0.91-1.73)	0.167
DTG-based treatment#				
Standard triple regimen	1.00		1.00	
Dual regimen	0.36 (0.15-0.86)	**0.022**	0.35 (0.14-0.87)	**0.023**

(C) TE-Group [Model 2: DTG-based treatments stratified according to the backbone**]**				
	HR (95% CI)	**p-value**	**aRH** (95% CI)**	**p-value**
Gender				
Female	1.18 (0.57-2.41)	0.660	0.93 (0.39-2.23)	0.876
Age, years				
per 10 older	1.11 (0.84-1.46)	0.474	1.19 (0.87-1.63)	0.275
DTG-based treatment				
Triple with ABC	1.00		1.00	
Triple without ABC	1.13 (0.53-2.42)	0.749	1.31 (0.56-3.04)	0.531
Dual	0.38 (0.15-0.94)	**0.037**	0.39 (0.15-.99)	**0.047**

(Notes: HR= unadjusted hazard ratio; HR= adjusted hazard ratio; CI= confidence intervals)
**after adjusting for age, mode of HIV transmission, nationality, backbone (Tenofovir/FTC versus ABC/3TC)*
*** after adjusting for mode of HIV transmission, nationality, AIDS diagnosis, hepatitis co-infection, calendar year of baseline, baseline CD4 cell count, reasons for stopping previous regimen, previous virological failure, duration of ART, duration of virological suppression.*
 # other therapies group not shown because no events occurred in the group.

Fig 1 Kaplan-Meier curves estimating cumulative probability of DTG-discontinuation for any reason and for toxicity in ART-naïve (1A, 1C) and TE (1B, 1D) groups.