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EFFECTIVENESS OF DOLUTEGRAVIR AND BOOSTED-DARUNAVIR 3-DRUG REGIMENS IN ADVANCED ART NAÏVE: A TRIAL EMULATION

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on behalf of Icona Foundation Study Group

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Background

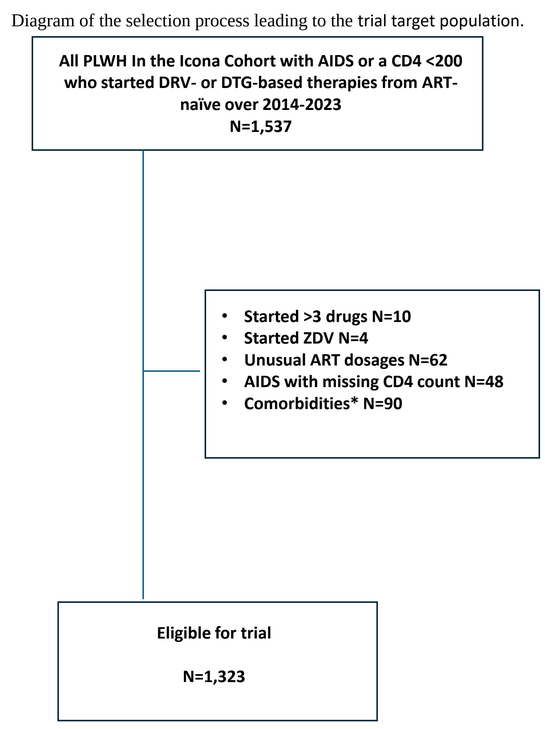
Rates of people with HIV (PWH) who present at diagnosis with advanced HIV infection (defined as CD4 cell count<200 cells/mm^3 or with an AIDS-defining condition) or with late presentation (defined as CD4 cell count<350 cells/mm^3 or with an AIDS-defining condition) are high in Europe. There are no available randomized comparisons between dolutegravir (DTG) and boosted-darunavir (DRV/b) -based regimens in PWH presenting with advanced disease. In this study we aimed to compare the effectiveness of dolutegravir to boosted darunavir in the context of advanced naïve PWH through an emulation trial.

Materials & Methods

Study population

- ART-naïve patients with CD4 count <200 cells/mm^3 or AIDS diagnosis, who started a DTG or DRV/b (ritonavir or cobicistat) based 3-drug regimen between 2014-2023, enrolled in the ICONA cohort.

Diagram of the selection process leading to the trial target population.



*Extrapulmonary cryptococcosis, cervix cancer, lymphoma, tuberculosis and other mycobacterial infection

Outcomes

Primary outcome:

- newly developed AIDS, newly developed serious non-AIDS events (SNAE), death, virological failure (VF, defined as confirmed HIV-RNA >200 cp/mL after >= 6 months from the initiation of ART) or treatment discontinuation of the anchor drug (DRV/b or DTG) due to failure, intolerance or toxicity.

Secondary outcomes:

- newly developed AIDS or death;
- newly developed SNAE or death;
- treatment failure (defined as VF or treatment discontinuation of the anchor drug due to failure, intolerance or toxicity).

Statistical analysis

- We emulated a parallel trial design, with 2 treatment strategies: starting a DTG-based 3-drug regimen or a DRV/b-based 3- drug regimen.
- We applied marginal structural Cox regression model to estimate hazard rate (HR) of the outcomes, weighted for age, gender, mode of HIV transmission, nationality, calendar year of starting ART, AIDS/SNAE at baseline, time from HIV diagnosis, NRTI (as time-fixed factors measured at BL, defined as starting ART). For the propensity score model for the censoring weights we also included current CD4 and current HIV-RNA (as time-varying factors).
- Results were also stratified for year of ART initiation (2014-2018 vs. 2019-2023).

Results

1,323 advanced ART-naïve PWH included: 895 (67.6%) started DTG+2NRTI; 428 (32.3%) started DRV/b+2NRTI.

Main characteristics of the study population

Characteristics	Regimen started: DRV/b	DTG	p-value
	N= 428	N= 895	
Age, year, median (IQR)	44 (36, 51)	45 (36, 53)	0.082
Female gender, n (%)	99 (23.1%)	179 (20.0%)	0.191
HIV Transmission, n (%)			
IDU	22 (5.1%)	45 (5.0%)	0.377
MSM	142 (33.2%)	341 (38.1%)	
Heterosexual	223 (52.1%)	428 (47.8%)	
Other/Unknown	41 (9.6%)	81 (9.1%)	
Not Italian nationality, n (%)	131 (30.6%)	260 (29.1%)	0.562
HCV-Ab positive, n (%)	18 (4.2%)	55 (6.1%)	0.059
Calendar year of baseline, median (IQR)	2018 (2015, 2019)	2018 (2017, 2019)	<0.001
AIDS diagnosis, n (%)	142 (33.2%)	291 (32.5%)	0.810
Viral load, log_{10} copies/mL, median (IQR)	5.33 (4.84, 5.79)	5.30 (4.71, 5.83)	0.548
CD4 count, cells/mm^3, median (IQR)	68 (23, 132)	71 (27, 130)	0.278
CD4 count <200 cells/mm^3 , n (%)	412 (96.3%)	859 (96.0%)	0.804
STR, n (%)	135 (31.5%)	194 (21.7%)	0.079
Follow-up time, months, median (IQR)	21 (4, 60)	40 (11, 66)	<0.001

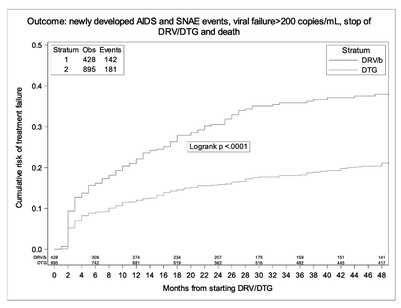
Events concurring to primary endpoint according to regimen started

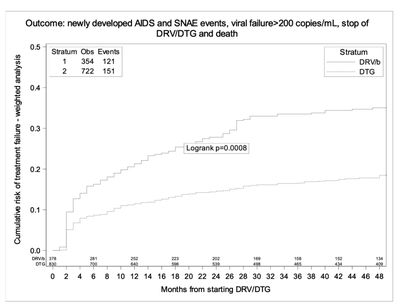
	DRV/b (N=428)	DTG (N=895)
AIDS	35 (24.7%)	52 (28.7%)
Death	16 (11.3%)	46 (25.4%)
SNAE	10 (7%)	22 (12.2%)
Treatment discontinuation	65 (45.6%)	41 (22.7%)
Virological failure	16 (11.3%)	20 (11.1%)
Total events	142 (100%)	181 (100%)

Notes: DRV/b, darunavir boosted; DTG, dolutegravir; IQR, interquartile range; IDU, intravenous drug users; MSM, men who have sex with men; STR, single tablet regimen.

Primary outcome

Unweighted and weighted Kaplan-Meier curves by anchor drug (DTG vs DRV/b) for the composite endpoint (newly developed AIDS or SNAE, death, VF or treatment discontinuation)





HR of the estimated causal effect from fitting Cox regression model – primary outcome

	Unweighted and weighted HR of the composite endpoint of newly developed AIDS or SNAE, death, VF or treatment discontinuation			
	Unweighted HR (95% CI)	p-value	Weighted* HR (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	0.51 (0.41-0.64)	<0.001	0.47 (0.35-0.64)	<0.001
Stratified by calendar period of ART initiation				
2014-2018				
DRV/b	1.00		1.00	
DTG	0.54 (0.41, 0.71)	<.001	0.55 (0.36, 0.85)	0.008
2019-2023				
DRV/b	1.00		1.00	
DTG	0.45 (0.30, 0.67)	<.001	0.37 (0.24, 0.59)	<.001

** for age, gender, mode of HIV transmission, nationality, calendar year of starting ART, AIDS/SNAE at baseline, time from HIV diagnosis, NRTI used, and current ALT, CD4 and HIV-RNA values.*

Secondary outcomes

HR of the estimated causal effect from fitting Cox regression model – secondary outcomes

	Unweighted and weighted HR of the composite endpoint of newly developed AIDS or death			
	Unweighted HR (95% CI)	p-value	Weighted* HR (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	0.74 (0.52, 1.06)	0.100	0.66 (0.41, 1.05)	0.079
Stratified by calendar period of ART initiation				
2014-2018				
DRV/b	1.00		1.00	
DTG	0.66 (0.43, 1.00)	0.049	0.67 (0.35, 1.28)	0.228
2019-2023				
DRV/b	1.00		1.00	
DTG	1.04 (0.52, 2.08)	0.917	0.50 (0.23, 1.08)	0.077

	Unweighted and weighted HR of the composite endpoint of newly developed SNAE or death			
	Unweighted HR (95% CI)	p-value	Weighted* HR (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	1.08 (0.68, 1.69)	0.750	0.99 (0.54, 1.82)	0.970
Stratified by calendar period of ART initiation				
2014-2018				
DRV/b	1.00		1.00	
DTG	0.94 (0.57, 1.56)	0.813	0.81 (0.36, 1.79)	0.595
2019-2023				
DRV/b	1.00		1.00	
DTG	1.87 (0.64, 5.47)	0.250	1.35 (0.52, 3.51)	0.540

	Unweighted and weighted HR of treatment failure			
	Unweighted HR (95% CI)	p-value	Weighted* HR (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	0.66 (0.51, 0.85)	0.001	0.63 (0.45, 0.90)	0.010
Stratified by calendar period of ART initiation				
2014-2018				
DRV/b	1.00		1.00	
DTG	0.80 (0.59, 1.09)	0.155	0.85 (0.51, 1.40)	0.519
2019-2023				
DRV/b	1.00		1.00	
DTG	0.40 (0.25, 0.65)	<.001	0.50 (0.29, 0.84)	0.009

** for age, gender, mode of HIV transmission, nationality, calendar year of starting ART, AIDS/SNAE at baseline, time from HIV diagnosis, NRTI used, and current ALT, CD4 and HIV-RNA values.*

Conclusions

Our analysis suggests that in ART-naïve PWH with CD4 count <200 or AIDS, initiating ART with DTG vs. DRV/b-based regimens led to a 50% reduction in the risk of new AIDS, new SNAE, death, VF or treatment discontinuation. The difference was mainly but not fully explained by anchor drug discontinuation.

Acknowledgements

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