Emulation of an RCT of dolutegravir vs. boosted-darunavir in advanced ART-naïve

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BACKGROUND

- Second generation integrase transcriptase inhibitors (INSTIs) currently represent the most highly recommended option for first-line ART
- HIV-infected individuals with advanced disease (e.g. CD4 count <200 cells/mm^3 or AIDS), are typically underrepresented or excluded from randomized controlled trials (RCTs)
- As a consequence, superiority of INSTIs-based regimens to boosted-PI regimens in the specific target population of people with advanced HIV disease, has not been demonstrated
- A single RCT is now ongoing comparing B/F/TAF to DRV/c/F/TAF in people with advanced HIV disease but first results are expected in late 2021 (**the LAPTOP trial** https://clinicaltrials.gov/ct2/show/NCT03696160)
- **Novel statistical methods** exist that allow the use of observational data to emulate RCTs when randomized comparisons are missing

METHODS

- We included ART-naïve patients with CD4 count <200 cells/mm3 or AIDS diagnosis in the Icona Foundation Cohort between 2014-2018 who started a dolutegravir [DTG] or boosted-darunavir [DRV/b (ritonavir or cobicistat)] based ART
- Outcome definition: **A composite endpoint (death, AIDS, serious non-AIDS events - SNAE - viral failure >200 copies/mL, anchor drug discontinuation not due to simplification and not followed by a restart of a drug in the same class)**
- Date of viral failure was estimated at the time of the first of 2 consecutive values >200 copies/mL
- We estimated the effect of the difference in risk between the two strategies using a marginal structural model.
- We accounted for differences in prognostic factors measured at time of ART initiation (time-fixed). We also accounted for differences in censoring by these same prognostic factors, and time-varying CD4, HIV-RNA and ALT.
- In the main analysis estimates were adjusted for the presence of any AIDS/SNAE at baseline (Model-1), while in an alternative analysis this covariate was replaced by one indicating the presence at baseline of a diagnosis of cancer or of toxoplasma encephalitis (Model-2)

RESULTS

- **Overall 1097 ART-naïve patients (DTG=700; DRV/b=397) were included.**
- **All characteristics were comparable between the two groups, except for higher proportion of HCV-Ab positive in DTG, higher proportion of previous AIDS in DRV/r, median viral load higher in DRV/r and median calendar year of baseline more recent in DTG. Higher proportion of pts used TDF and FTC as NRTI backbone (Tab. 1 and 2).**

Tab. 1 and 2 Main characteristics of 1,097 pts enrolled

Characteristics	Regimen started DRV/b N= 397	DTG N= 700	p-value
Age year, median (IQR)	44 (36, 52)	44 (36, 53)	0.827
Female gender	90 (22.7%)	141 (20.1%)	0.324
HIV Transmission, n (%)			0.224
IDU	19 (4.8%)	37 (5.3%)	
MSM	129 (32.5%)	269 (38.4%)	
Heterosexual	213 (53.7%)	337 (48.1%)	
Other/Unknown	36 (9.1%)	57 (8.1%)	
Not Italian nationality, n (%)	119 (30.0%)	204 (29.1%)	0.772
HCV-Ab positive, n (%)	14 (3.5%)	36 (5.1%)	0.008
Calendar year of baseline, median (IQR)	2016 (2014, 2018)	2017 (2016, 2018)	<.001
Follow-up time, months, median (IQR)	11 (2, 30)	11 (2, 25)	0.025
Time from HIV diagnosis to ART starting, months, median (IQR)	1 (0, 1)	1 (0, 1)	0.700
AIDS diagnosis, n (%)	159 (40.1%)	234 (33.4%)	0.028
Viral load, $\log_{10}$ copies/mL, median (IQR)	5.37 (4.74, 5.77)	5.11 (4.53, 5.61)	0.016
CD4 count, cells/mmc, median (IQR)	75 (29, 136)	76 (29, 140)	0.491
CD4 count <=200 cells/mmc, n (%)	362 (95.5%)	644 (95.5%)	0.979
CD8 count, cells/mmc, median (IQR)	559 (343, 870)	578 (347, 931)	0.713

Characteristics	Regimen started DRV/b N= 397	DTG N= 700	p-value
Site geographical position, n (%)			
North	154 (38.8%)	386 (55.1%)	<0.001
Center	163 (41.1%)	272 (38.9%)	
South	80 (20.2%)	42 (6.0%)	
NRTI backbone, n(%)			
Emtricitabine	366 (92.2%)	452 (64.6%)	<.001
Lamivudine	31 (7.8%)	248 (35.4%)	<.001
TDF	244 (61.5%)	262 (37.4%)	<.001
TAF	123 (31.0%)	190 (27.1%)	0.176
Abacavir	30 (7.6%)	248 (35.4%)	<.001
Boost, n (%)			
Ritonavir	255 (64.2%)	0 (0.0%)	
Cobicistat	142 (35.8%)	0 (0.0%)	
STR	38 (9.6%)	194 (27.7%)	<.001

- **103 (15%) patients receiving DTG and 120 (30%) receiving DRV/b experienced the composite endpoint (Tab 4).**
- **Main reasons for stopping therapy are reported in fig. 2, the most prevalent cause was toxicity both for DRV and DTG**

Tab. 3 Main infectious and non-infectious (SNAE) comorbidities at baseline

Characteristics	Patients with baseline comorbidities by regimen started DRV/b N= 174	DTG N= 279	Total N=453
AIDS defining event, n (%)*	132* (75.9%)	198* (71%)	330* (72.8%)
Non-AIDS defining event, n (%)*	42* (24.1%)	81* (29%)	123* (27.2%)
- CVD	33 (19%)	50 (18%)	83 (18.3%)
- Cancer	6 (3.4%)	17 (6%)	23 (4.2%)
- CKD	0	6 (2.1%)	6 (1.3%)
- Severe infections	1 (0.6%)	8 (2.9%)	9 (2.0%)
- Other	2 (1.1%)	0	2 (0.4%)

*Patients having both AIDS and non-AIDS events (27 in DRV/b and 36 in DTG arm) were considered as SNAEs

Tab. 4 Absolute number of patients who experienced the composite end-point (by different events)

		DRV/b (N=397)	DTG (N=700)
AIDS	N (% enrolled)	31 (8%)	31 (4%)
Death	N (% enrolled)	11 (3%)	12 (2%)
SNAE	N (% enrolled)	13 (3%)	11 (2%)
Discontinuation	N (% enrolled)	40 (10%)	31 (4%)
VF	N (% enrolled)	25 (6%)	18 (3%)
Total events	N (% enrolled)	120 (30%)	103 (15%)

Fig. 1 Proportion of different events among total events

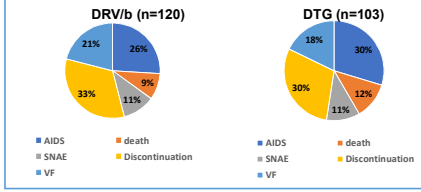


Fig. 2 Reasons for stopping boosted-DRV or DTG

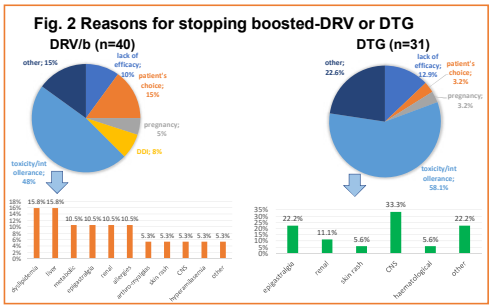
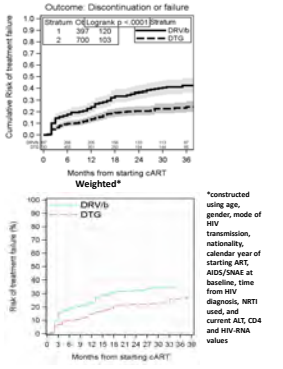


Fig. 3 Unweighted and weighted Kaplan-Meier curves by anchor drug



*constructed using 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

- **Patients who initiated DTG were at lower risk of experiencing the composite endpoint compared to those who started DRV/b both in model I and model II.**
- **Calendar year of starting cART was a key factor but results were consistent across periods of initiation.**

Tab. 5 HR ratio of the estimated causal effect from fitting a weighted Cox regression model - I and - II

model - I	Unadjusted and adjusted relative hazards of treatment failure^ Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	0.50 (0.39, 0.66)	<.001	0.60 (0.40, 0.91)	0.015
Stratified by calendar period of cART initiation				
2014-2015				
DRV/b	1.00		1.00	
DTG	0.28 (0.14, 0.56)	<.001	0.40 (0.16, 1.01)	0.053
2016-2017				
DRV/b	1.00		1.00	
DTG	0.59 (0.38, 0.90)	0.015	0.71 (0.39, 1.26)	0.239
2018-2019				
DRV/b	1.00		1.00	
DTG	0.64 (0.33, 1.23)	0.181	0.59 (0.27, 1.31)	0.198

^adjusted 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

*newly developed AIDS and SNAE events, viral failure>200 copies/mL, stop of DRV/DTG without starting a drug within the same class of anchor and death

model - II	Unadjusted and adjusted relative hazards of treatment failure^ Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
All years				
DRV/b	1.00		1.00	
DTG	0.50 (0.39, 0.66)	<.001	0.56 (0.37, 0.84)	0.005
Stratified by calendar period of cART initiation				
2014-2015				
DRV/b	1.00		1.00	
DTG	0.28 (0.14, 0.56)	<.001	0.39 (0.16, 0.94)	0.037
2016-2017				
DRV/b	1.00		1.00	
DTG	0.59 (0.38, 0.90)	0.015	0.67 (0.37, 1.21)	0.180
2018-2019				
DRV/b	1.00		1.00	
DTG	0.64 (0.33, 1.23)	0.181	0.50 (0.22, 1.11)	0.087

^adjusted for age, gender, mode of HIV transmission, nationality, calendar year of starting ART, ***cancer and Toxoplasma encephalitis at baseline***, time from HIV diagnosis, NRTI used, and current ALT, CD4 and HIV-RNA values

*newly developed AIDS and SNAE events, viral failure>200 copies/mL, stop of DRV/DTG without starting a drug within the same class of anchor and death

LIMITATIONS

- Reason for discontinuations are those reported as the main reason for stopping the anchor drug by treating clinicians and these can be misreported/highly subjective
- Discontinuations due to patients' choice and those not reported were counted as events as potentially linked to issues related to intolerance/toxicity
- In contrast, those reported as simplifications/change in formulation/participation in RCT were not counted as events
- The difference in risks shown can be interpreted as causal under the assumptions of a correctly specified model and no unmeasured confounding
- Patients' adherence to treatment and other unreported symptoms which can affect initial therapy choice are potential unaccounted sources of unmeasured confounding

CONCLUSIONS

- Under the assumptions of no unmeasured confounding and correct model specification, our results suggests that a RCT conducted in a comparable target population is likely to show a 40% reduction in risk of treatment failure in people initiating DTG vs. DRV/b based therapies
- Calendar year was a potential effect-modifier with some evidence that this difference in risk was attenuated in people initiating the two strategies in more recent years, in which people starting DTG had a significant worse prognosis at baseline
- Discontinuation of DTG/DRVb was the most incident outcome but results did not seem to be triggered by a specific component of the composite endpoint used
- A similar RCT should be conducted to exclude with more certainty that confounding has not played a role and better inform treatment guidelines for the important subset of PLWH with advanced disease who are about to start their first-line cART

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