Dettaglio abstract

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Title: Effectiveness of lamivudine + dolutegravir (3TC+DTG) in persons living with HIV (PLWH) starting their first antiretroviral treatment

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Abstract
Background: The GEMINI RCTs have shown in person living with HIV (PLWH) starting their first line ART, the non-inferiority of 3TC+DTG compared to FTC/TDF+DTG up to 96 weeks. Despite these results, due to the inclusion criteria of the trials, it is unclear whether the same efficacy will be seen in subsets of the ART-naïve who are at higher risk of treatment failure (TF) e.g. those with low CD4 count/AIDS, high HIV-RNA and hepatitis co-infection.
Material and Methods: We included PLWH enrolled in ICONA starting a first-line ART based on 3TC+DTG. TF was defined as having experienced a single HIV-RNA>50 copies/mL or a treatment change regardless of the reason in the window 6-12 months from ART initiation (baseline). Characteristics of PLWH who experienced TF and of those who remained free from TF were compared using chi-square test for categorical and the Mann-Whitney test for numerical variables. A logistic regression analysis was used to estimate unadjusted odds ratios (OR) of TF. Adjusted estimates were obtained after controlling for calendar year of baseline.
Results: We included 142 PLWH of the Icona Foundation Study cohort who started 3TC+DTG as their first-line regimen. Overall, 9% were females, 61% acquired HIV through MSM contacts, 25% were of foreign nationality and had a median age of 38 years (IQR:29-47, Table 1). Risk of TF by 1 year was low at 8.5% (12/142, of whom only 4 due to HIV-RNA>50). Most were pro-active switches but 2 which were due to intolerance/toxicity. The prevalence of baseline characteristics identified as potential risk factors for failing 3TC+DTG was low: 5% (n=7) with a CD4 count ≤200 cells/mm3, 500,000 copies/mL, most likely present in PLWH who experienced TF. Other factors associated with the risk of TF were a delay in ART initiation (higher risk for longer delay, p=0.02) and calendar year of baseline (lower risk in more recent years, p=0.004, Table 1). PLWH with HIV-RNA>500,000 copies/mL (aOR=36.5 vs. 0-100,000, 95% CI: 1.70-781.8, p=0.02) showed the greatest difference in risk (Table 2). After controlling for calendar year of treatment initiation, among the key risk factors (CD4 count, HIV-RNA, delay in ART initiation, and HCV coinfection) only the association with the latter was considerably attenuated (Table 2).
Conclusions: In our cohort, the risk of failing first line with 3TC+DTG by 1 year was low and mainly driven by pro-active treatment changes. The data show a reluctance by clinicians in real world to start first-line with 3TC-DTG in advanced patients, which resembles the inclusion criteria of the RCTs. Lower risk of TF was seen in PLWH initiating in more recent years. Larger sample size or longer follow-up is needed to re-evaluate the risk of failure in PLWH with CD4 count ≤200 cells/mm3 and/or HIV-RNA>500,000 copies/mL starting ART with 3TC+DTG.
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Table 1. Main characteristics at baseline

Characteristics	Enrolment			
	TF	No TF	p-value*	Total
	N= 12	N= 130		N= 142
Gender, n(%)			0.918	
Female	1 (8.3%)	12 (9.2%)		13 (9.2%)
Mode of HIV Transmission, n(%)			0.083	
IDU	2 (16.7%)	5 (3.8%)		7 (4.9%)
Homosexual contacts	9 (75.0%)	77 (59.2%)		86 (60.6%)
Heterosexual contacts	1 (8.3%)	47 (36.2%)		48 (33.8%)
Other/Unknown	0 (0.0%)	1 (0.8%)		1 (0.7%)
Nationality, n(%)			0.976	
Not Italian	3 (25.0%)	33 (25.4%)		36 (25.4%)
AIDS diagnosis, n(%)			0.761	
Yes	0 (0.0%)	1 (0.8%)		1 (0.7%)
HCVAb, n(%)			0.039	
Negative	7 (58.3%)	112 (86.2%)		119 (83.8%)
Positive	1 (8.3%)	5 (3.8%)		6 (4.2%)
Not tested	4 (33.3%)	13 (10.0%)		17 (12.0%)
Calendar year of baseline*			0.004	
Median (IQR)	2018 (2017, 2019)	2019 (2019, 2020)		2019 (2019, 2020)
2014-2015	1 (8.3%)	0 (0.0%)		1 (0.7%)
2016-2017	5 (41.7%)	14 (10.8%)		19 (13.4%)
2018-2019	4 (33.3%)	76 (58.5%)		80 (56.3%)
2020-2021	2 (16.7%)	40 (30.8%)		42 (29.6%)
Age, years			0.403	
Median (IQR)	42 (31, 51)	38 (29, 47)		38 (29, 47)
CD4 count, cells/mmc			0.618	
Median (IQR)	565 (377, 792)	487 (352, 664)		492 (352, 664)
<=200 cells/mmc	2 (16.7%)	5 (3.9%)	0.052	7 (5.0%)
CD4 count nadir, cells/mmc			0.778	
Median (IQR)	488 (287, 650)	477 (344, 662)		477 (344, 662)
Viral load, log10 copies/mL			0.271	
Median (IQR)	4.72 (4.05, 5.08)	4.45 (3.93, 4.82)		4.46 (3.96, 4.84)
<=50 copies/mL, n(%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
>100,000 copies/mL, n(%)	3 (25.0%)	23 (18.0%)	0.551	26 (18.6%)
egfr (CKD_Epi formula), ml/min/1.73m²			0.208	
Median (IQR)	84.71 (73.39, 117.9)	106.7 (94.33, 117.6)		106.5 (92.14, 117.6)
Below 60, n(%)	1 (11.1%)	3 (2.3%)	0.132	4 (2.9%)
Smoking, n(%)			0.673	
No	6 (50.0%)	48 (36.9%)		54 (38.0%)
Yes	4 (33.3%)	54 (41.5%)		58 (40.8%)
Unknown	2 (16.7%)	28 (21.5%)		30 (21.1%)
Total cholesterol, mg/dL			0.070	
Median (IQR)	183 (179, 197)	162 (142, 192)		164 (144, 192)
HDL cholesterol, mg/dL			0.616	
Median (IQR)	43 (34, 45)	43 (36, 48)		43 (36, 48)
Time from HIV diagnosis to date of starting cART, months			0.016	
Median (IQR)	3 (2, 9)	1 (1, 3)		1 (1, 3)

*Chi-square or Mann-Whitney test as appropriate

Table 2. Odds ratios from fitting a logistic regression model

Factor	Unadjusted		Adjusted*	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
CD4 count, cells/mm³				
<=200 vs >200	4.96 (0.85, 28.88)	0.075	4.71 (0.69, 32.31)	0.115
HIV-RNA, copies/mL				
100k-500k vs. <=100k	1.06 (0.21, 5.25)	0.943	1.47 (0.25, 8.55)	0.666
>500k vs. <=100k	11.67 (0.67, 202.5)	0.092	36.47 (1.70, 781.8)	0.021
Hepatitis B/C				
Positive vs . Negative	2.27 (0.24, 21.22)	0.471	1.17 (0.08, 18.19)	0.910
Time from HIV diagnosis to ART initiation, months				
per 6 months longer	1.04 (1.01, 1.08)	0.025	1.03 (0.98, 1.07)	0.245
Year of ART initiation, months				
per more recent	0.45 (0.29, 0.72)	<.001		

*adjusted for year of ART initiation