Dettaglio abstract

N. pgm: OC 18

Title: Effectiveness of first-line lamivudine-dolutegravir (3TC-DTG) antiretroviral therapy (ART) in persons living with HIV (PLWH): real-life data from the ICONA Foundation cohort

Presentation type: Oral Communication

Session/Topic
Outcome in first-line regimens

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Abstract
Background: Week 96 data of the GEMINI-1 and GEMINI-2 trials showed that the efficacy of the 2-drug regimen (2DR) including 3TC-DTG is non-inferior to triple DTG-containing regimens as first-line therapy. However, concerns were expressed on the regimen efficacy in PLWH starting with CD4 counts <200/mm3. More in general, real-life long-term estimates of the effectiveness of first line treatment with 3TC-DTG are sparse.
Methods: We included PLWH enrolled in ICONA cohort who started first-line ART with 3TC-DTG. Primary endpoint: time to treatment failure (TF, i.e. time of the first of 2 consecutive viral load-VL>50 copies/mL after 6 months, or discontinuation of the regimen regardless of the reason). A sensitivity analysis was conducted in which only discontinuations due to toxicity/failure were counted as events. Main exposure of interest was CD4 count at ART initiation. We identified geographical location of attending site, age and HIV-RNA at ART initiation as time-fixed confounders. Participants' characteristics were compared according to CD4 count at ART initiation using non-parametric tests. Standard survival analysis by Kaplan-Meier curves and Cox regression model was used.
Results: A total of 281 PLWH started 3TC-DTG as first-line: 10.6% females, 27% born outside Italy, median CD4 458/mm3, 6% with CD4<200/mm3, 20.6% with HIV-RNA >100,000 copies/mL, only 2.0% with HIV-RNA >=500,000 copies/mL. PLWH with CD4<200/mm3 were more frequently males, older and with higher HIV-RNA copies (Table 1). Over a median follow-up of 19 months (IQR:3-30), 21 PLWH experienced TF (3 viral load>50 -of which 2 discontinuations- and other 18 discontinuations). Reported reasons for the latter were: allergic reactions (n=2), CNS toxicity (n=2), liver toxicity (n=1), switch to Long-acting regimens (n=2), patient's choice/simplification (n=5), other/unknown (n=4), lack of virological control (n=4). In the main analysis, the 2-year probability of TF was of 23% (00-46) in PLWH with CD4 <200/ mm3and 7.8% (3.7-11.9) in CD4>=200/mm3 (log-rank test p=0.04). This difference was attenuated after adjusting for age, HIV-RNA and geographical region (aRH=1.65 95% CI:0.42-6.48, p=0.47, Table2). In the sensitivity analysis including 12 true failure events, the 2 years estimate of the risk of TF was 4.0% (95% CI:1.4-6.7%). The results from the multivariable analysis showed an even larger aHR of TF according to CD4 count strata (>2-fold difference), although still with large uncertainty around the estimates (Table 2).
Conclusions: In our real-life setting, rate of TF of first line 3TC-DTG was even lower than that observed

in randomized studies (<10% of individuals by 2 years, 4% in analysis excluding discontinuations for simplification). Also, after adjusting for potential confounders including HIV-RNA, we found little evidence that a CD4 count<200 cells/mm3 at ART initiation was associated with increased risk of TF, but longer follow-up is needed to obtain robust estimates.
This study was funded by ViiV Healthcare. The authors are solely responsible for final content and interpretation.

Table 1- Main characteristics of the study population according to CD4 strata (cut-off 200/mm^3)

	CD4 count ≤200 (n= 17)	CD4 count>200 (n=264)	p-value*	Total (n=281)
Female, n(%)	5 (29.4%)	25 (9.5%)	0.010	30 (10.7%)
Mode of HIV Transmission, n(%)			0.035	
IDU	2 (11.8%)	10 (3.8%)		12 (4.3%)
Homosexual contacts	6 (35.3%)	166 (62.9%)		172 (61.2%)
Heterosexual contacts	9 (52.9%)	74 (28.0%)		83 (29.5%)
Other/Unknown	0 (0.0%)	14 (5.3%)		14 (5.0%)
Foreign, n(%)	2 (11.8%)	75 (28.4%)	0.137	77 (27.4%)
Previous AIDS diagnosis, n(%)	2 (11.8%)	1 (0.4%)	<.001	3 (1.1%)
HCVAb, n(%)			0.534	
Negative	13 (76.5%)	214 (81.1%)		227 (80.8%)
Positive	0 (0.0%)	9 (3.4%)		9 (3.2%)
Not tested	4 (23.5%)	41 (15.5%)		45 (16.0%)
Calendar year of baseline			0.898	
Median (IQR)	2020 (2019, 2021)	2020 (2019, 2021)		2020 (2019, 2021)
2015-2018	4 (23.5%)	30 (11.4%)		34 (12.1%)
2019-2020	7 (41.2%)	146 (55.3%)		153 (54.4%)
2021-2022	6 (35.3%)	88 (33.3%)		94 (33.5%)
Age, years			0.002	
Median (IQR)	47 (41, 58)	36 (28, 46)		37 (29, 47)
CD4 count, cells/mmc			<.001	
Median (IQR)	147 (55, 169)	483 (352, 679)		458 (331, 662)
Viral load, log10 copies/mL				
Median (IQR)	4.81 (4.22, 5.45)	4.44 (3.90, 4.87)	0.033	4.45 (3.91, 4.91)
>100,000 copies/mL, n(%)	7 (41.2%)	51 (19.3%)	0.031	58 (20.6%)
>500,000 copies/mL, n(%)	2 (11.8%)	3 (1.1%)	0.001	5 (1.8%)

Table 2-Hazard ratio (HR) of treatment failure of first-line 3TC/DTG by Cox regression analysis

	Unadjsuted HR(95% CI)	p-value	Adjusted[1] HR (95% CI)	p-value	Adjusted[2] HR (95% CI)	p-value
All stops counted as failures						
CD4 count, cells/mm^3						
<=200 vs >200	3.32 (0.97, 11.35)	0.055	3.27 (0.95, 11.21)	0.060	1.65 (0.42, 6.48)	0.474
Only stops due to toxicity/intolerance/failure counted as failures						
CD4 count, cells/mm^3						
<=200 vs >200	6.55 (1.76, 24.43)	0.005	6.62 (1.75, 25.00)	0.005	2.41 (0.49, 11.89)	0.278

[1]adjusted for year of ART initiation, [2]adjusted for geographical location of attending site, age and HIV-RNA