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Durability of lopinavir/ritonavir dual-therapies in individuals with viral load <50 copies/mL in the observational setting

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Background

- The study of strategies aimed at increasing the use of both TDF- and ABC-sparing regimens (especially in elderly individuals) remains a priority in HIV treatment research.
- Maintenance monotherapies with a boosted-protease inhibitor (PI/r) might reduce or even prevent NRTIs toxicity, but the risk of virological failure with these regimens is perceived by some patients and clinicians as unacceptably high, even in selected populations.
- Dual NRTI-sparing regimens have been initially studied in patients starting their first-line regimen as a possible strategy to avoid NRTI toxicity and are necessarily based on a PI/r (to include at least one high-genetic barrier drug).
- Also a dual regimen including a single NRTI and a PI/r has been studied recently in a large RCT of ART-naive patients starting cART.
- The results of the aforementioned studies support the use of LPV/r-based dual regimens also as a maintenance therapy aimed at limiting NRTI toxicity, but clinical data are scarce and the strategy is not currently recommended in treatment guidelines for use outside selected populations.

Aim

- To evaluate the efficacy and durability of LPV/r-based dual regimens in virologically-controlled, HIV-infected individuals seen for HIV care in Italian clinical sites.

Study Design

- Retrospective study.
- Patients in the Icona Foundation Study cohort or seen at clinical sites contributing patients to the cohort who have initiated for the first time a LPV/r-based dual regimen with HIV-RNA <50 copies/mL were included in this analysis.
- The second drug could be either a NRTI, NNRTI, raltegravir or maraviroc.

Methods

- The main end-points were:
  - time to virological rebound [VR=time of first of two consecutive viral loads (VL) >50 copies/mL]
  - time to experience either a single VL >200 copies/mL or discontinuation/intensification (=treatment failure, TF).
- Individuals' follow-up accrued from the date of starting the LPV/r-based dual regimen (baseline, BL) to event or last available VL.
- Kaplan-Meier curves and Cox regression analysis were used.
- Descriptive results are presented as median (Q1, Q3) or frequency (%), as appropriate.
- T-test was used to compare mean change of biomarkers (e.g. CD4 count) at the a priori chosen time point of 36 months from baseline.
- Laboratory markers measured after the discontinuation of dual-therapy are not included in the plots and the t-test analysis.

Results

- 114 individuals were included in the analysis; BL characteristics are detailed in table 1.
- 96/114 (84%) were already receiving LPV/r at BL; at BL, 53/114 (46%) were receiving TDF, 19 (17%) a thymidine analogue, 4 (3%) ABC.
- Median follow-up = 18 (IQR: 7, 30) months
- By 36 months from switching to the LPV/r-DR, the proportion of individuals with VR and TF was 10% (95% CI:3-17%, Figure 1) and 36% (95% CI:22-50%, Figure 2), respectively.
- Older age [ARH = 0.49 (95% CI: 0.30, 0.78) per 10 years older; p=0.003] was found to be protective from TF. There was no evidence for an association with the risk of TF for any of the other factors evaluated (Table 3).
- Mean (SE) CD4+ cells/µL increase from BL to month 36 resulted significant: 195 (40.1) cells/µL (p= 0.003), Figure 3.
- Overall, we did not observe significant changes in AST, ALT, eGFR (MDRD formula), triglycerides and both total and HDL-cholesterol.

Table 1. Baseline characteristics

	Other drug class				Total	p-value
	NRTI	NNRTI	INSTI	CCR5 antagonist		
	N= 53	N= 10	N= 31	N= 20	N= 114	
Gender, Female, ***n (%)***	19 (35.8%)	3 (30.0%)	10 (32.3%)	2 (10.0%)	34 (29.8%)	
Mode of HIV Transmission, n (%)						<.001
IDU	15 (28.3%)	5 (50.0%)	11 (35.5%)	1 (5.0%)	32 (28.1%)	
Homosexual contacts	6 (11.3%)	1 (10.0%)	5 (16.1%)	14 (70.0%)	26 (22.8%)	
Heterosexual contacts	18 (34.0%)	3 (30.0%)	14 (45.2%)	4 (20.0%)	39 (34.2%)	
Other/Unknown	14 (26.4%)	1 (10.0%)	1 (3.2%)	1 (5.0%)	17 (14.9%)	
Hepatitis co-infection (HCVAb+ or HBsAg+), ***n (%)***						0.170
No	20 (37.7%)	5 (50.0%)	7 (22.6%)	9 (45.0%)	41 (36.0%)	
Yes	15 (28.3%)	3 (30.0%)	11 (35.5%)	1 (5.0%)	30 (26.3%)	
Not tested	18 (34.0%)	2 (20.0%)	13 (41.9%)	10 (50.0%)	43 (37.7%)	
Calendar year of starting dual, Median (IQR)	2011 (2009, 2012)	2011 (2004, 2011)	2012 (2010, 2012)	2012 (2011, 2012)	2011 (2010, 2012)	
Age, years, Median (IQR)	47 (41, 56)	42 (39, 48)	50 (46, 54)	44 (36, 50)	47 (41, 53)	
CD4 count at starting dual , cells/µL, Median (IQR)	420 (294, 650)	712 (306, 884)	455 (282, 678)	610 (530, 640)	486 (305, 701)	
ALT at starting dual, UI/L, Median (IQR)	24 (18, 39)	43 (29, 56)	29 (17, 45)	18 (12, 21)	24 (17, 39)	
AST at starting dual, UI/L, Median (IQR)	24 (15, 51)	41 (28, 83)	28 (21, 53)	23 (19, 29)	27 (19, 46)	
Viral load at initiation of first ART, log_{10} copies/mL						0.062
≤100,000	11 (20.8%)	4 (40.0%)	8 (25.8%)	3 (15.0%)	26 (22.8%)	
>100,000	6 (11.3%)	4 (40.0%)	2 (6.5%)	3 (15.0%)	15 (13.2%)	
Unknown	36 (67.9%)	2 (20.0%)	21 (67.7%)	14 (70.0%)	73 (64.0%)	
Previously virologically failed a PI, Yes, ***n (%)***	6 (11.3%)	2 (20.0%)	1 (3.2%)	0 (0.0%)	9 (7.9%)	
Time with VL ≤50 before switch to dual, months, Median (IQR)	6 (2, 49)	38 (14, 60)	5 (2, 14)	7 (3, 16)	7 (2, 25)	
CD4 nadir, cells/µL, Median (IQR)	302 (162, 527)	216 (92, 405)	356 (238, 642)	472 (348, 603)	347 (189, 544)	
CD4 nadir, cells/µL						0.324
≤200	14 (26.4%)	5 (50.0%)	7 (22.6%)	2 (10.0%)	28 (24.6%)	
>200	37 (69.8%)	5 (50.0%)	22 (71.0%)	16 (80.0%)	80 (70.2%)	
Unknown	2 (3.8%)	0 (0.0%)	2 (6.5%)	2 (10.0%)	6 (5.3%)	
eGFR at starting dual , mL/min/1.73m², Median (IQR)	82 (68, 109)	94 (59, 113)	81 (54, 102)	104 (93, 113)	86 (66, 110)	
Cholesterol at starting dual , mg/dL, Median (IQR)	200 (157, 231)	226 (170, 275)	172 (126, 231)	236 (188, 265)	200 (154, 236)	
HDL at starting dual , mg/dL, Median (IQR)	44 (39, 53)	54 (47, 80)	48 (37, 60)	44 (37, 50)	46 (38, 58)	
Triglycerides at starting dual , mg/dL, Median (IQR)	150 (99, 200)	154 (107, 232)	158 (113, 200)	186 (100, 206)	155 (102, 201)	

Table 2. Treatement during follow-up

	Other drug class				Total	p-value
	NRTI	NNRTI	INSTI	CCR5 antagonist		
	N= 53	N= 10	N= 31	N= 20	N= 114	
Follow-up for composite outcome (VL>200 or stop/intensification), ***months***, Median (IQR)	18 (5, 30)	25 (9, 28)	11 (7, 33)	22 (10, 26)	18 (7, 30)	
Second drug in the LPV/r-based dual regimen, n (%)						
Lamivudine	44 (83.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	44 (38.6%)	<.001
Emtricitabine	3 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.6%)	0.319
Tenofovir	6 (11.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.3%)	0.065
Efavirenz	0 (0.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	3 (2.6%)	<.001
Nevirapine	0 (0.0%)	6 (60.0%)	0 (0.0%)	0 (0.0%)	6 (5.3%)	<.001
Etravirine	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0.015
Raltegravir	0 (0.0%)	0 (0.0%)	31 (100.0%)	0 (0.0%)	31 (27.2%)	<.001
Maraviroc	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (100.0%)	20 (17.5%)	<.001

Table 3. RH from fitting a Cox regression model

	Crude and adjusted relative hazards of single VL>200 or stop/intensification			
	Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Gender, n(%)				
Female vs. male	0.46 (0.19, 1.12)	0.088	0.44 (0.12, 1.57)	0.207
Mode of HIV Transmission, n (%)				
IDU	1.00		1.00	
Homosexual contacts	0.69 (0.27, 1.78)	0.449	0.25 (0.04, 1.64)	0.149
Heterosexual contacts	0.52 (0.21, 1.28)	0.153	0.36 (0.07, 1.90)	0.231
Other/Unknown	1.87 (0.72, 4.84)	0.197	3.23 (0.58, 18.03)	0.181
Hepatitis co-infection, n (%)				
No	1.00		1.00	
Yes	1.15 (0.51, 2.58)	0.743	0.86 (0.19, 3.81)	0.843
Not tested	0.77 (0.34, 1.74)	0.530	0.43 (0.14, 1.29)	0.131
Calendar year of starting dual				
per more recent year	0.96 (0.85, 1.08)	0.487	1.01 (0.85, 1.21)	0.885
Age				
per 10 years older	0.58 (0.41, 0.81)	0.002	**0.49 (0.30, 0.78)**	**0.003**
CD4 count at starting dual				
per 100 cells/µL higher	1.03 (0.92, 1.16)	0.596	1.08 (0.88, 1.34)	0.461
Viral load at initiation of first ART, log_{10} copies/mL				
≤100,000	1.00		1.00	
>100,000	2.32 (0.86, 6.25)	0.096	2.47 (0.71, 8.61)	0.156
Unknown	1.10 (0.48, 2.52)	0.822	0.97 (0.32, 2.96)	0.960
Other class, n(%)				
NRTI	1.00		1.00	
NNRTI	1.32 (0.46, 3.74)	0.606	0.71 (0.18, 2.88)	0.635
Raltegravir	0.76 (0.29, 1.97)	0.574	2.17 (0.51, 9.32)	0.297
Maraviroc	1.66 (0.72, 3.83)	0.238	4.19 (0.99, 17.83)	0.052
Previously virologically failed a PI				
Yes	1.38 (0.48, 3.93)	0.552	2.18 (0.51, 9.29)	0.292
Time with VL ≤50 before switch to dual				
per 6 months longer	0.99 (0.91, 1.08)	0.849	1.00 (0.85, 1.16)	0.954
CD4 count nadir, cells/µL				
≤200	1.00		1.00	
>200	0.88 (0.43, 1.81)	0.733	1.20 (0.30, 4.70)	0.797

Table 4. Trend of mean (±SE) CD4 change from baseline after initiation of dual therapy-patients switching to LPV/r and a second drug (according to second drug type).

	12 months	p-value (vs. BL)	24 months	p-value (vs. BL)	36 months	p-value (vs. BL)
NRTI	93 (±35)	0.0156	135 (±24)	0.0001	202 (±56)	0.0151
NNRTI	69 (±34)	0.1352	31 (±79)	0.7221	NC	NC
InSTI	96 (±83)	0.2872	81 (±76)	0.3489	213 (±133)	0.2502
CCR5-antagonist	100 (±70)	0.1772	64 (±89)	0.4925	NC	NC

Table 5. Trend of mean (±SE) change from baseline after initiation of dual therapy in selected laboratory values

	12 months	p-value (vs. BL)	24 months	p-value (vs. BL)	36 months	p-value (vs. BL)
Triglycerides (mg/dL)	7.6 (±19.6)	0.7018	1.8 (±14.6)	0.9033	36.5 (±23.9)	0.1572
HDL-cholesterol (mg/dL)	-1.4 (±3.4)	0.6971	-2.8 (±7.2)	0.7090	-1.7 (±9.1)	0.8568
Total cholesterol (mg/dL)	3.4 (±7.7)	0.6653	3.5 (±9.2)	0.7069	17.6 (±19.9)	0.3962
eGFR (mL/min/1.73m²)	2.5 (±2.8)	0.3628	6.9 (±3.4)	0.0532	4.7 (±5.5)	0.4103
ALT (U/L)	-12.2 (±8.0)	0.1349	-14.6 (±10.7)	0.1840	-39.1 (±22.9)	0.1162
AST (U/L)	-6.8 (±5.8)	0.2470	-8.1 (±5.4)	0.1460	-19.4 (±11.9)	0.1334

Table 6. Trend of mean (±SE) change from baseline after initiation of dual therapy in eGFR and cholesterol among 53 patients switched away from TDF

	12 months	p-value (vs. BL)	24 months	p-value (vs. BL)	36 months	p-value (vs. BL)
Total cholesterol (mg/dL)	3.2 (±9.1)	0.7286	-9.0 (±10.4)	0.3982	18.1 (±10.5)	0.1289
eGFR (mL/min/1.73m²)	-4.1 (±5.8)	0.4909	-1.2 (±6.8)	0.8584	-9.3 (±6.7)	0.2192

Figure 1 and 2. Probability of VR and of TF.

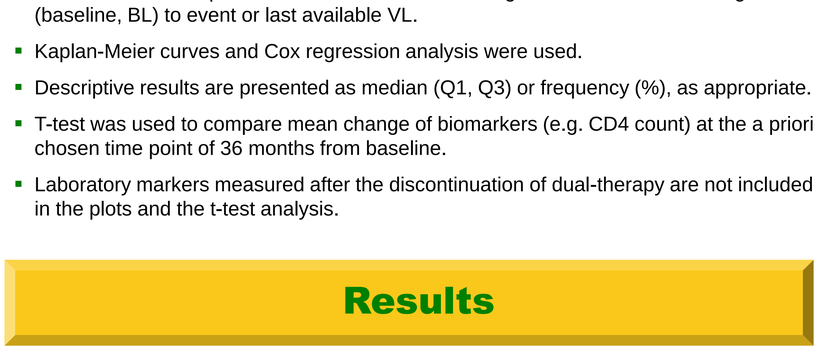
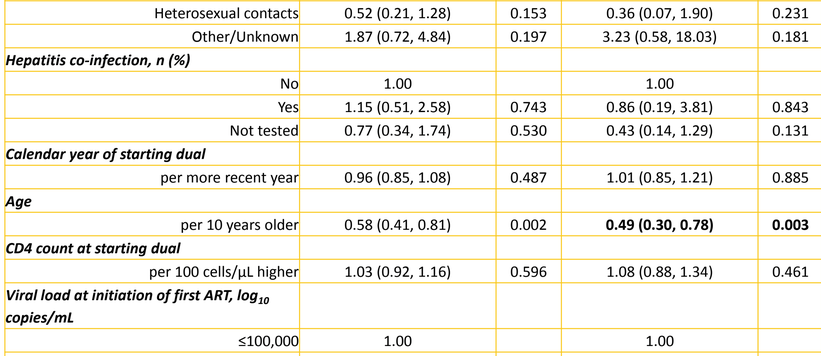


Figure 3 and 4. Probability of TF according to drug classes started together with LPV/r and changes in CD4+ cell counts from baseline levels.



Discussion

- The results of this study are consistent with those observed in RCT of ART-naive patients starting a dual PI/r-based regimen and of virologically suppressed pts switching to dual, PI/r-based regimens[1-5]. Virological failures (but not treatment failures) seem slightly higher than those reported in RCT of virologically suppressed patients continuing a PI/r-based cART.
- Age was inversely associated with TF, independently of a number of potential confounders: we hypothesize that elderly patients were those who had a major benefit (in terms of side effects and quality of life) from the removal of NRTIs and thus were those more adherent and less prone to change the dual regimen.
- A characteristic not independently associated with the risk of VF or TF was the CD4+ nadir: this seems to suggest that these dual regimens could be prescribed also to patients that are not eligible for PI/r monotherapy, due to a nadir CD4+ count <200 cells/µL.
- As reported in similar studies, LPV/r-based dual regimens were not associated with a reduction in CD4+ cell counts; indeed we observed an increase of these cells during follow-up in pts receiving LPV/r + 1 NRTI (3TC in 83% and FTC in 11% of cases) and maintaining HIV-RNA <50 copies/mL. An increase in CD4+ cell counts was observed also in patients randomized to maintaining PI/r monotherapy: altogether, these findings suggest that removing one or two NRTIs does not hamper CD4+ recovery, as long as viral load remains suppressed below 50 copies/mL.
- An increase in plasma lipids has been reported in patients stopping TDF; the lipid profile of our patients did not change significantly during follow-up even in pts switching away from TDF.
- Limitations.
  - The lack of a control group forces comparisons with historical groups to determine whether "results are good enough" to support this strategy rather than other strategies.
  - Patients included in this analysis are potentially a selected group of individuals deemed to benefit from this strategy.
  - The impact of this strategy on other clinically relevant outcomes such as bone metabolism and mineralization was not evaluated because these data are not collected in our patients.

(1) Negredo E, et al. J AIDS 2005;38:47-52. (2) Ofotokun I, et al. AIDS Res Hum Retroviruses. 2012 Apr 20. (3) Perez-Molina JA, et al. 14th European AIDs Conference (EACS 2013). Brussels. October 16-19, 2013. Abstract PE7/1. (4) Cahn P, et al. Lancet Infect Dis. 2014 Jul;14(7):572-80. (5) Raffi F, et al. Lancet. 2014 Aug 4. pii: S0140-6736(14)61170-3.

Conclusions

- A LPV/r-DR can be considered a option in patients with HIV-RNA <50 copies/mL and ongoing toxicity from the third drug of the regimen, although up to 17% of patients showed viral rebound by 3 years.
- Older patients are at lower risk of failure with this strategy, but larger sample size and randomised controlled studies are needed to identify. appropriate selection criteria for this strategy.

ICONA Foundation Study Group