Lipidome composition and weight changes at 48week 3TC-DTG and FTC/TAF/BIC: data of the ICONA cohort 813

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BACKGROUND

3TC/DTG (2DR) and FTC/TAF/BIC (3DR) are effective therapeutic options recommended as first-line cART. However, their association with weight gain (WG), lipids, lipidomic profile, gut-barrier dysfunction and microbial translocation (MT), which eventually associate with increased atherosclerotic cardiovascular disease risk, remain to be evaluated.

METHODS

Cohort: PLWH starting first-line 2DR or 3DR (2016-2023), before therapy (T0) and 48w after (T1). Lipidome: ultra performance liquid chromatography-mass spectrometry. iFABP, eCAD, LBP: ELISA. Statistics: Student T, Mann-Whitney, Wilcoxon, and Chi-squared tests; controlled linear regression models; orthogonal partial least squares discriminant analysis (OPLS-DA).

RESULTS

Table 1. Study population

	2DR (n = 164)	3DR (n = 308)	*p-value*
Age (mean, SD)	38.51 (11.1)	42.81 (12.7)	**<0.001**
Males (n, %)	148 (90.2)	263 (85.4)	0.176
Non-Italian (n, %)	36 (22.0)	66 (21.4)	0.989
Mode of HIV transmission (n, %)			
Heterosexual	47 (28.7)	117 (38.0)	
IDU	9 (5.5)	16 (5.2)	0.233
MSM	100 (61.0)	160 (51.9)	
Other/Unknown	8 (4.9)	15 (4.9)	
Baseline log HIV-RNA cp/mL (mean, SD)	4.14 (1.03)	4.84 (1.14)	**<0.001**
Baseline CD4 count cell/mm³ (median, IQR)	489.5 (344.7-684.7)	316.5 (115.7-512.7)	**<0.001**
Baseline CD4/CD8 (median, IQR)	0.62 (0.4-0.8)	0.34 (0.15-0.6)	**<0.001**
AIDS events (n, %)	1 (0.6)	37 (12.0)	**<0.001**
Baseline weight Kg (mean, SD)	74.2 (11.7)	70.9 (12.6)	**0.019**
Total cholesterol mg/dL (mean, SD)	171.3 (34.4)	163.1 (38.3)	**0.025**
HDL mg/dL (mean, SD)	43.8 (11.6)	41.9 (14.0)	0.157
LDL mg/dL (mean, SD)	110.6 (29.9)	103.5 (33.2)	**0.035**
Triglycerides mg/dL (median, IQR)	87.5 (66-130.7)	97.5 (69.2-134.7)	0.324

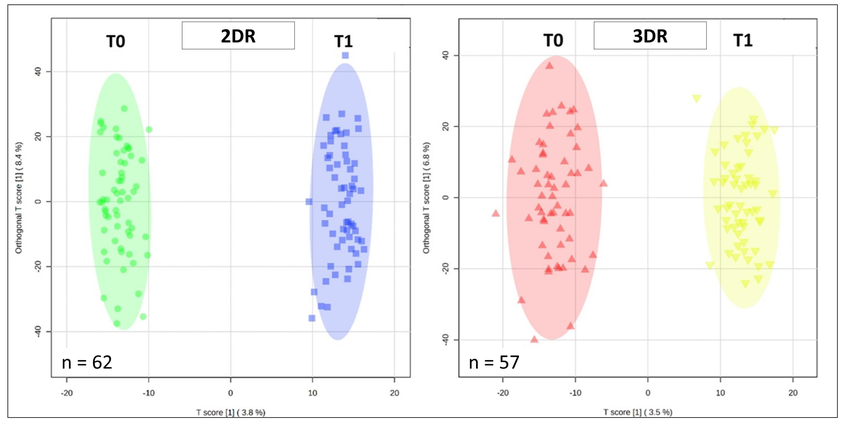
HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 2. Despite similar WG, PLWH starting 2DR display a trend to lower LDL increase vs 3DR-receiving PLWH.

	2DR mean (SD)	3DR mean (SD)	*p-value#*	*p-value§*	*p-value**
Weight gain (T1-T0)	2.6 (9.8) (n=54)	5.3 (6.7) (n=104)	0.056	0.914	0.590
Triglycerides (T1-T0)	9.1 (70.3) (n=152)	7.5 (73.8) (n=263)	0.816	0.594	0.459
Total cholesterol (T1-T0)	8.52 (24.9) (n=152)	20.91 (36.3) (n=271)	0.002	0.108	0.086
HDL (T1-T0)	2.9 (9.9) (n=139)	7.7 (14.23) (n=244)	0.002	0.244	0.282
LDL (T1-T0)	3.2 (20.9) (n=127)	11.3 (29.56) (n=196)	0.050	0.055	**0.052**
Ratio total cholesterol/HDL (T1-T0)	-0.05 (0.9) (n=138)	-0.28 (1.3) (n=239)	0.087	0.462	0.432

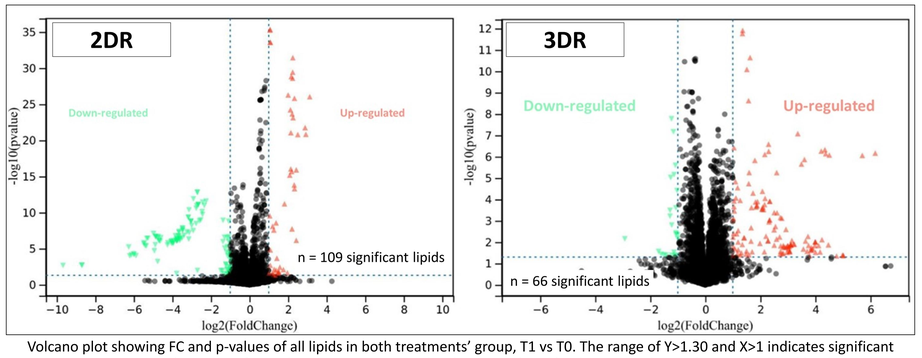
Statistical analyses: linear regression model controlling for #baseline values; §baseline values, age, sex, mode of HIV transmission, baseline CD4 count, HIV-RNA, glycemia, hemoglobin, ALT, AST, hypertension; *baseline values, propensity score.

Figure 1. 48w cART substantially changed the circulating lipidomic profile in both 2DR- and 3DR-receiving PLWH



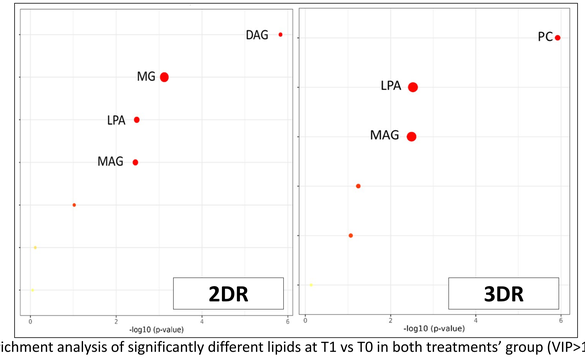
Scores scatter plot from OPLS-DA model showing group separation at T1 compared to T0 based on the entire lipidomic profile in both treatments groups. Each dot represents an individual.

Figure 2. 3DR-receiving PLWH display a higher proportion of up-regulated lipids at 48w cART, while 2DR-receiving PLWH showed similar distribution of up- and down-regulated lipids.



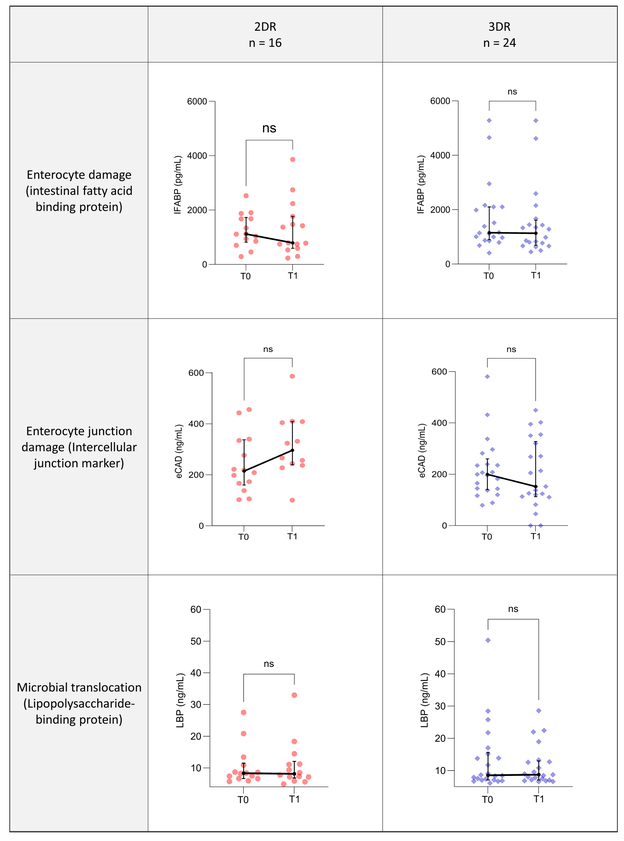
Volcano plot showing FC and p-values of all lipids in both treatments' group, T1 vs T0. The range of Y>1.30 and X>1 indicates significant increase, Y>1.30 and X<-1 significant decrease, green triangles down-regulated lipids at T1, red triangles up-regulated lipids at T1.

Figure 3. Pathway enrichment analysis resulted in a predominant involvement of glycerolipids in 2DR-receiving PLWH, and glycerophospholipids in 3DR-receiving PLWH.



Pathway enrichment analysis of significantly different lipids at T1 vs T0 in both treatments' group (VIP>1.5, FC>2, and p-value<0.05). Each dot represents a pathway, colours p-value, size enrichment ratio. DAG: Diacylcerols; MG: Monoacylglycerols; MAG: Monoradylglycerols; PC: Phosphatidylcholines; LPA: Lysophosphatidic acids.

Figure 4. Stable gut-barrier dysfunction and MT markers in PLWH starting a 2DR or 3DR first-line cART.



CONCLUSIONS

While not showing a substantial WG rise, 2DR-receiving PLWH, succeed in containing the increase of LDL cholesterol as compared to 3DR-receiving PLWH. Most interestingly, such changes in circulating LDL according to cART regimen, is accompanied by a lipidomic profile skewed towards glycerophospholipids metabolism only in 3DR, known major component of LDL (Dashti M. et al 2011, Hu C. et al 2008) that is not seen in 2DR. The lack of differences in leaky gut markers according to cART regimen, might suggest a possible effect of antiviral drug/combination in dyslipidaemia which is not linked to microbiome alterations. The fine understanding of pathogenetic pathways and clinical risks of dyslipidaemia in cART-receiving PLWH needs further investigation.

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