Dettaglio abstract

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Title: Associations between weight changes and plasmatic pro-inflammatory cytokines in PLWH following ART initiation: data from the ICONA cohort

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Abstract
Background: The mechanisms by which ART contributes to weight gain (WG) are unknown and larger WG has been observed in persons living with HIV (PLWH) treated with integrase inhibitors (INSTI) or protease inhibitors (PI) vs non-nucleoside reverse transcriptase inhibitors (NNRTI). Pro-inflammatory cytokines (IL-6, TNF-a) are affected by ART and are associated with cachexia. We aimed to estimate the impact of INSTI, IL-6 and TNF-a on WG and evaluate how much of the total effect of INSTI on WG might be mediated by IL-6 and TNF-a.
Material and methods: We studied PLWH enrolled in ICONA starting a first-line ART over 2014-2017. Inclusion criteria were: (i) having a stored plasma sample in the year before ART (T0) and at 11-18 months of ART (T1); (ii) weight measurements at T0-T1; (iii) no modifications in anchor class over T0-T1. We measured plasmatic IL-6 and TNF-a at T0-T1 (ELISA assays). Two linear regressions with T0-T1 WG as the outcome were fitted. The first to relate WG to T0-T1 changes in IL-6 and TNF-a, the second to compare mean WG by anchor class (INSTI vs NNRTI, PI vs NNRTI). Criteria for identification of confounders are described in Figure 1. A mediation analysis assuming no interactions was performed to estimate how much of the total effect associated with INSTI initiation (vs NNRTI) on WG might be mediated by changes in IL-6 and TNF-a.
Results: 151 PLWH started a first-line ART in the study period; median age was 50 (IQR 25-75) years, 18 (12%) were females. Baseline median CD4+ count was 358 cells/mmc (IQR 132-576), HIV-RNA was 4.77 log10 cp/mL (IQR 4.11-5.24). 76 PLWH (50.3%) started INSTI, 38 (15.2%) NNRTI and 37 (24.5%) PI; 21 (20.5%) started DGT, 114 (75.5%) TDF/FTC, 33 (21.8%) ABC/3TC, 4 (2.65%) TAF/FTC.
T0 weight was 72 (61-80) Kg in INSTI, 71 (60-78) in PI and 73 (65-82) in NNRTI (p=0.507).
PLWH who began INSTI and PI gained significantly more weight compared to NNRTI (INSTI: +3.4 Kg, 95%CI 1.7, 5.1; NNRTI: +0.9 Kg, 95%CI -1.5, +1.7; PI: +3.6 Kg, 95%CI 1.4, 5.8; p=.003). Higher WG in INSTI, but not in PI, was confirmed after controlling for HIV-RNA at T0 (Table 1A). Changes in TNF-a and IL-6 were inversely associated with WG in univariable analysis; after controlling for anchor class and HIV-RNA at T0, only IL-6 retained some independent association with WG (Table 1B-C). After decomposing the total difference in T0-T1 WG between patients initiating INSTI vs NNRTI, only 12.7% (95% CI:6.8-62.1) and 9.1% (95% CI:3.5-70.5) of this total effect could be explained by TNF-a and IL-6, respectively (Table 2).
Conclusions: By 1 year from starting ART, our analysis confirms a higher, although not clinically

significant, WG in patients who started INSTI instead of other anchor classes. IL-6 was an independent predictor of WG, but only part of the effect of INSTI on WG appeared to be mediated by peripheral inflammation pathways. Further studies are needed to investigate the role of IL-6/TNF-a as potential mediators of WG in PLWH receiving ART.

Figure 1 Directed acyclic graphs describing our assumptions behind the three linear regression models, according to the specific exposure

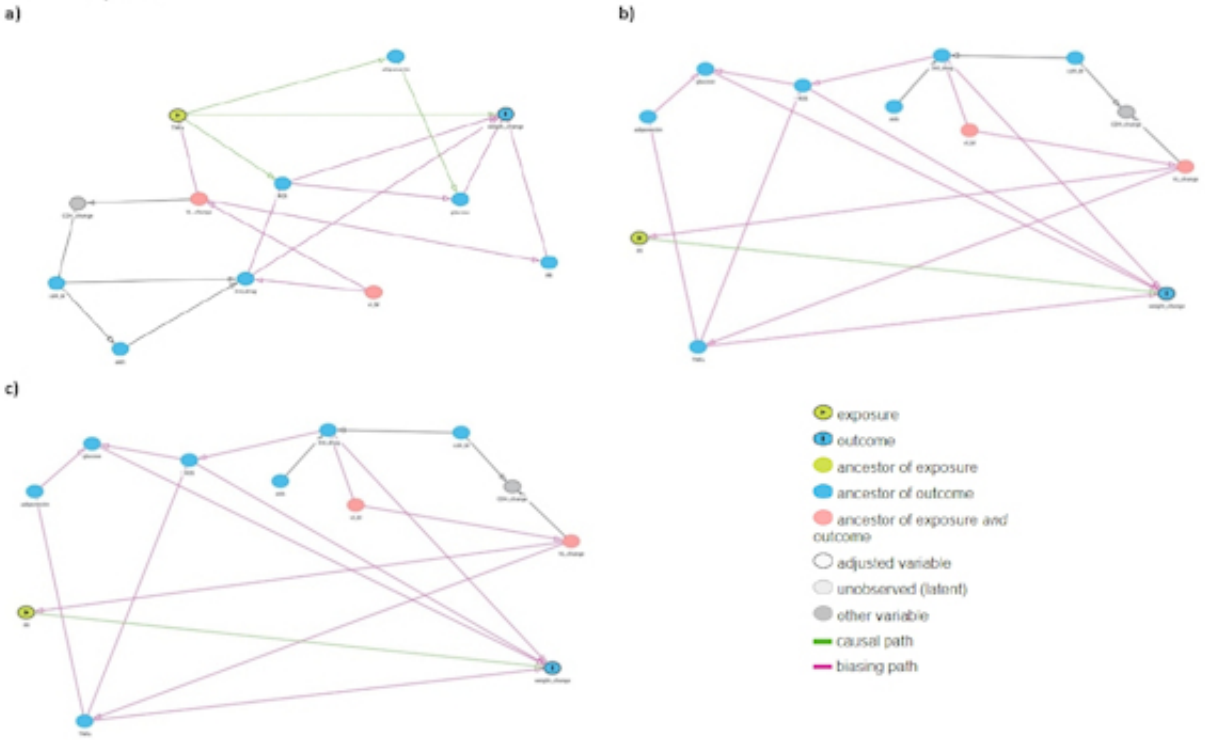

Table 1 Association between changes in pro-inflammatory cytokines, 3rd drug class and weight gain by fitting linear regressions

a)	Mean weight change after 1-year (kg)		Difference in weight change at 1-year (Kg)								
			Unadjusted model			Adjusted model 1			Adjusted model 2		
	mean	95%CI	Mean	95%CI	p value	Mean	95%CI	p value	Mean	95%CI	p value
3rd drug:											
NNRTI	+0.9	-1.5; +1.7	1.000			1.000			1.000		
INSTI	+3.4	+1.7; +5.1	3.333	0.722; 5.943	0.013	3.195	0.443; 5.948	0.023	2.796	0.074; 5.519	0.044
PI	+3.6	+1.4; +5.8	3.532	0.498; 6.567	0.023	3.420	0.270; 6.570	0.034	2.800	-0.405; 6.005	0.086

b)	Difference in weight change at 1-year (Kg)											
	Unadjusted model			Adjusted model 1			Adjusted model 2			Adjusted model 3		
	Mean	95%CI	p value	Mean	95%CI	p value	Mean	95%CI	p value	Mean	95%CI	p value
1 year change in TNF-a, per 1 ng/dL higher	-2.749	-5.54; 0.043	0.054	-0.882	-4.375; 2.612	0.618	-2.780	-5.61; 0.048	0.054	-1.392	-4.778; 1.994	0.417

c)	Difference in weight change at 1-year (Kg)											
	Unadjusted model			Adjusted model 1			Adjusted model 2			Adjusted model 3		
	Mean	95% CI	p value	Mean	95%CI	p value	Mean	95%CI	p value	Mean	95%CI	p value
1 year change in IL6, per 1 ng/dL higher	-3.300	-5.66; 0.93	0.007	1.986	-4.765; 0.793	0.159	-3.271	-5.701; -0.833	0.009	-1.916	-4.702; 0.871	0.176

LEGEND: a) Model 1 adjusted for 1-year HIV-RNA change, Model 2 adjusted for T0 HIV-RNA; b-c) Model 1 adjusted for 3rd drug class and 1 year IL-6 change and 1 year TNF-a change; Model 2 adjusted for 1 year HIV-RNA change; Model 3 adjusted for T0 HIV-RNA and 1 year IL-6 change and 1 year TNF-a change

Table 2 Effect of INSTI on weight change: mediation through TNF-a and IL-6 (analysis including only patients on INSTI and NNRTI)

Effect of INSTI on 1 year weight change (Kg)						
	Direct effect of INSTI vs NNRTI		Total effect of INSTI vs NNRTI		% of total effect mediated through the biomarker	
	mean*	95%CI	mean*	95%CI	%	95%CI
TNF-a	3.16	0.30; 6.16	3.62	0.65; 6.63	12.7	6.8; 62.1
IL-6	2.65	-0.17; 5.59	2.92	0.01; 5.90	9.1	3.5; 70.5

*Adjusted for HIV-RNA change (log10 copies/ml)