Serum Metabolomic Signatures Associated with INSTI-related Weight Gain in Women with HIV

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Introduction

- Starting or switching to integrase strand-transfer inhibitors (INSTIs) for HIV is linked to weight gain, especially in women, with unclear mechanisms.
- We performed serial high-throughput untargeted metabolomics to determine metabolic signatures associated with INSTI-related weight gain in women with HIV (WWH).

Methods

MACS/WIHS COMBINED COHORT STUDY

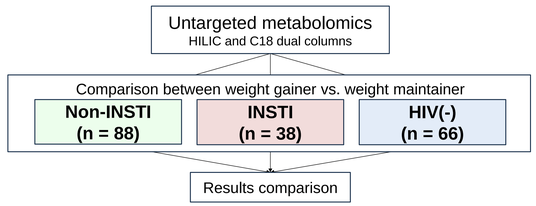


Figure 1. The analytical workflow

- One hundred and ninety-two virologically suppressed WWH (CD4 <200 cells/mL) from the Women's Interagency HIV Study (WIHS), on antiretroviral therapy, were categorized by INSTI use and weight change (gain, as ≥5% from baseline, maintenance, as <5% change).
- Serum was obtained at three time points: 6-12 months before switching to or adding INSTI (baseline), 1-6 months post switch/add, and 1-2 years post switch/add, with corresponding times in the non-INSTI& HIV seronegative controls.
- Untargeted high-resolution metabolomics (HRM) assessed using liquid chromatography-mass spectrometry (LC-MS) with Hydrophilic Interaction Chromatography (HILIC) in positive mode and C18 in negative mode.
- Group differences analyzed with linear mixed-effect models, controlling for age and BMI at baseline.
- Pathway enrichment analysis was performed using *mummichog*.

Results

Table 1. Baseline demographic and clinical characteristics for WWH who added/switched to INSTI in WIHS

	Overall (N=38)	Weight maintain (N=22)	Weight gain (N=16)	*p*-value weight change groups
Baseline Age				
Mean (SD)	46.24 (9.23)	44.95 (9.46)	48.00 (8.90)	0.318
Baseline BMI, kg/m²				
Mean (SD)	32.81 (7.83)	34.34 (7.31)	30.81 (8.27)	0.186
Race				
White NH	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Black NH	28 (73.7%)	16 (72.7%)	12 (75.0%)	*NAN*
Else	10 (26.3%)	6 (27.3%)	4 (25.0%)	
Current smoker				
No	24 (63.2%)	16 (72.7%)	8 (50.0%)	0.274
Yes	14 (36.8%)	6 (27.3%)	8 (50.0%)	
Heavy alcohol use				
No	35 (92.1%)	22 (100.0%)	13 (81.2%)	0.132
Yes	3 (7.9%)	0 (0.0%)	3 (18.8%)	
Diabetes				
No	31 (81.6%)	18 (81.8%)	13 (81.2%)	1
Yes	7 (18.4%)	4 (18.2%)	3 (18.8%)	
Hyperlipidemia				
No	25 (65.8%)	13 (59.1%)	12 (75.0%)	0.500
Yes	13 (34.2%)	9 (40.9%)	4 (25.0%)	
TAF use				
No	36 (94.7%)	21 (95.5%)	15 (93.8%)	1
Yes	2 (5.3%)	1 (4.5%)	1 (6.2%)	
TDF use				
No	8 (21.1%)	4 (18.2%)	4 (25.0%)	0.698
Yes	30 (78.9%)	18 (81.8%)	12 (75.0%)	
NNRTI use				
No	18 (47.4%)	12 (54.5%)	6 (37.5%)	0.477
Yes	20 (52.6%)	10 (45.5%)	10 (62.5%)	
PI use				
No	20 (52.6%)	10 (45.5%)	10 (62.5%)	0.477
Yes	18 (47.4%)	12 (54.5%)	6 (37.5%)	

- Regression and pathway enrichment analyses revealed association between polyunsaturated fatty acid (PUFA)-related pathways and INST-related weight gain.
- Linoleic acid (LA) and arachidonic acid (AA) metabolisms were found uniquely in the INSTI group.
- Eicosapentaenoic (EPA) metabolism was found uniquely in the non-INSTI control.
- Besides PUFA-related pathways, this study also identified associations between INSTI-related weight gain and pathways such as histidine metabolism, pentose phosphate pathway, and fat-soluble vitamin metabolisms.

Compared to non-INSTI and HIV-seronegative controls, PUFA-related pathways—including LA, AA, and EPA metabolisms—were uniquely associated with weight gain over time in the INSTI group.

Inflammatory PUFAs and downstream oxylipins were enriched within these pathways.

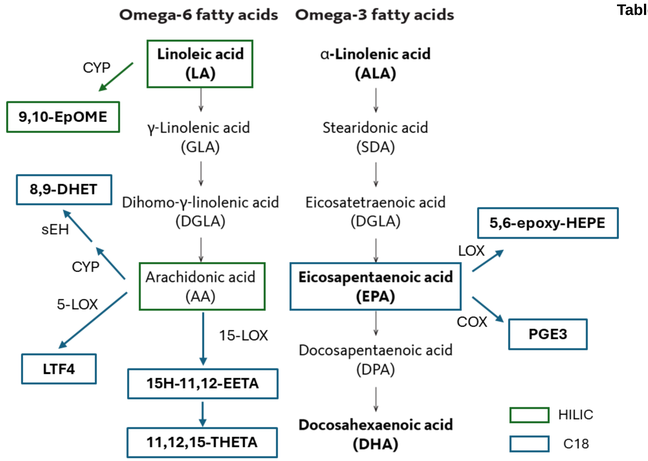


Figure 2. Significant PUFA-related pathways and enriched oxylipins

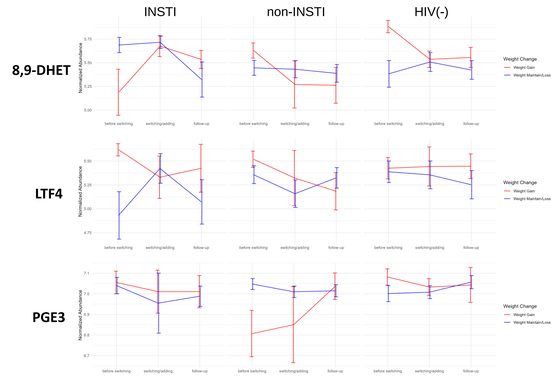


Figure 3. Abundance of specific oxylipins over time

Table 2. Significant PUFA-related pathway and directionality of enriched oxylipins

Metabolic Pathway	*p*-value	Key Metabolite	Directionality (abundance in weight gainers vs. maintainers)
HILIC			
WWH who added/switched to INSTI			
Linoleic acid (LA) metabolism	0.015	Linoleic acid (LA)	↑
		9,10-Epoxyoctadecenoic acid (9(10)-EpOME)	↓
Arachidonic acid (AA) metabolism	0.050	Arachidonic acid (AA)	↓
		8,9-Dihydroxyeicosatrienoic acid (8,9-DHET)	↑
C18			
WWH who added/switched to INSTI			
Arachidonic acid (AA) metabolism	0.004	15-Hydroxy-11,12-epoxyeicosatrienoic acid (15H-11,12-EETA)	↑
		11,12,15-Trihydroxyicosatrienoic acid (11,12,15-THETA)	↑
		8,9-Dihydroxyeicosatrienoic acid (8,9-DHET)	↓
		Leukotriene F4 (LTF4)	↑
WWH who didn't add/switch to INSTI			
Eicosapentaenoic acid (EPA) oxylipin metabolism	0.039	Prostaglandin E3 (PGE3)	↓
		5,6-epoxy,18R-hydroxyeicosapentaenoic acid (5,6-epoxy,18R-HEPE)	↓

- In AA metabolism, the potential anti-inflammatory metabolite 8,9-dihydroxyeicosatrienoic acid (8,9-DHET) was lower in weight gainers within the INSTI group, while the potential pro-inflammatory leukotriene F4 (LTF4) was higher.
- In EPA metabolism, the potential anti-inflammatory prostaglandin E3 (PGE3) was lower in weight gainers within the non-INSTI control.

Conclusions

- Lipid-related pathways, including LA, AA, and EPA metabolism, have been linked to INSTI-related weight gain over time.
- PUFAs and their downstream oxylipins were enriched within these three pathways. Additionally, PUFAs and oxylipins exhibited inflammatory properties associated with weight gain and chronic diseases.
- Further research is needed to explore the role of key pathways and metabolites in the underlying biological mechanisms of INSTI-related weight gain.

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