METABOLOMIC PROFILING SHOWS MORE LIPID ABNORMALITIES IN NNRTI COMPARED TO INSTI USERS

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BACKGROUND

Integrase strand transfer inhibitor (INSTI) use is linked to weight gain, metabolic syndrome and potentially cardiovascular disease, in contrast to non-nucleoside reverse transcriptase inhibitors (NNRTI). Metabolomic and lipoproteomic analysis may reveal mechanisms underlying these comorbidities.

METHODS

Design

The 2000HIV study is a prospective longitudinal cohort of people living with HIV (PLHIV), see Vos et al Front Immunol 2022 Dec 20; 13:982746. Findings in the discovery cohort were tested in the validation cohort.

Participants

PLHIV, >18yo, >6mo cART, viral load<200 copies/ml. Plasma samples collected after >4h of fasting. INSTI and NNRTI users were compared. The discovery cohort encompassed 730 INSTI and 617 NNRTI users, the validation cohort 209 INSTI and 90 NNRTI users.

Instruments

- Untargeted metabolomics with liquid chromatography-mass spectrometry, using serum metabolites only (n=500 ion m/z ratios).
- Targeted lipoproteomic with nuclear magnetic resonance spectroscopy (n= 141 lipoproteins).

Statistical analysis

Differential expression analysis by linear regression. Strong intercorrelated lipoproteins (r>0.7) were analyzed per cluster.

RESULTS

Table 1: Baseline characteristics discovery cohort

Discovery cohort	INSTI; n = 730	NNRTI; n = 617
Age	51 [41-58]	53 [46-60]
Male sex at birth	619 [84.8%]	533 [86.4%]
BMI	25.0 [22.7-27.7]	25.2 [22.2-27.4]
Time since HIV diagn.	10.8 [5.7-16.5]	14.6 [9.9-20.4]
Time on cART	9.7 [4.7-13.4]	11.5 [8.4-1.9]
CD4 Nadir	314 [160-423]	270 [150-350]
Most recent CD4	740 [550-940]	699 [550-918]
Lipid lowering drug	141 [19.3%]	112 [18.2%]

- INSTI users have lower levels of atherogenic lipids than NNRTI users
- INSTI associated weight gain appears not to be driven by lipids

Fig 1: Annotated metabolites discovery cohort

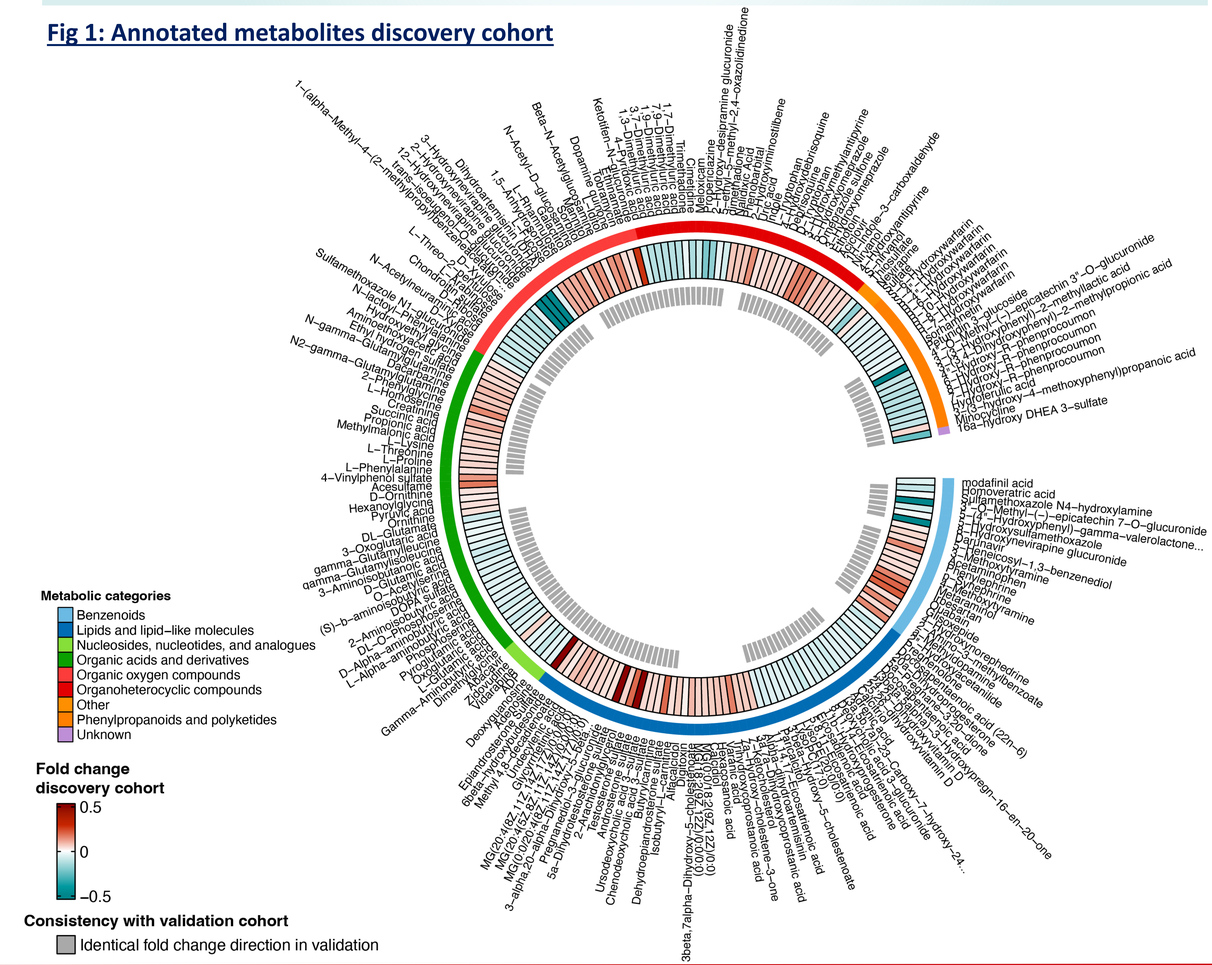
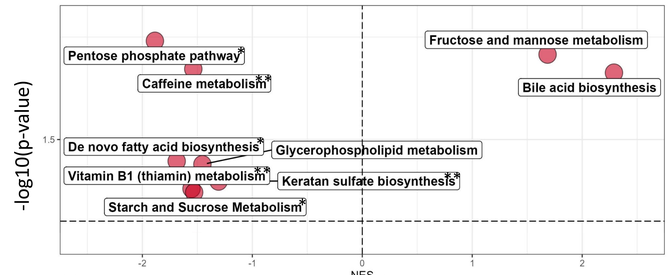
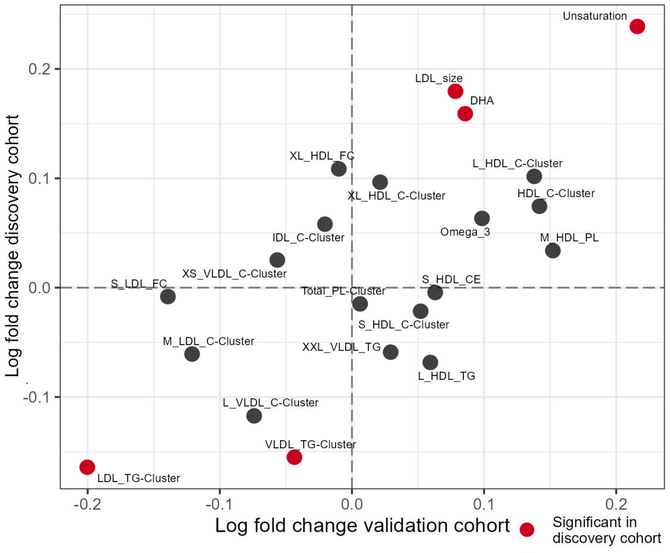


Fig 2: Metabolite pathway analysis discovery cohort



**Also significant in validation * Equal directionality in validation

Fig 3 Differential expression analysis lipoproteins



CONCLUSIONS

- Lipids are among the most common differentially expressed metabolites in INSTI compared to NNRTI users.
- 'De novo fatty acid biosynthesis' is lower in INSTI users.
- VLDL-TG and LDL-TG are lower in INSTI users, and LDL-size, DHA and unsaturation are higher in INSTI users.

ADDITIONAL KEY INFORMATION

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Vos et al. Front Immunol 2022 Dec 20; 13:982746

www.2000HIV.com