Lipidomic, metabolomic and immunological profiles preceding cardiovascular events in people living with HIV

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BACKGROUND

People with HIV (PWH) have an increased risk of cardiovascular disease (CVD), driven by persistent immune activation and metabolic disturbances, despite successful antiretroviral therapy (ART). Alterations in some immune parameters and metabolites have been associated with the CVD onset. However, specific lipidomic, metabolomic, and immunological biomarkers preceding CVD in PWH are still unknown.

METHODS

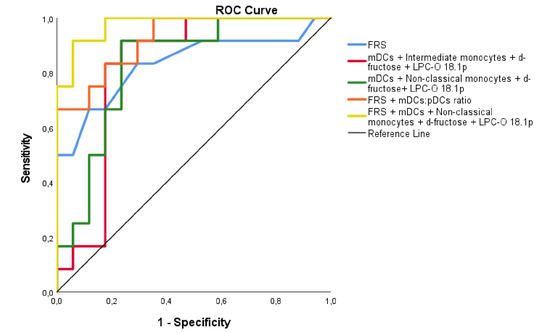
Participants: 35 PWH on ART 3-18 months **before suffering** acute myocardial infarction or acute coronary syndrome (CVD) and 35 PWH who did not suffer any non-AIDS event (CTRL), matched by sex, age, active HCV infection, nadir and CD4+ T-cell levels, time since HIV diagnosis, and Framingham Risk Score.

Methods:

- Mass spectrometry: LC-QTOF (236 lipids) and GC-qTOF (102 metabolites).
- Flow cytometry: T cell, monocyte and dendritic cell (DC) phenotype.
- Analysis: Mann-Whitney test (two group statistic), Random Forest and ROC curves (predictive potential), Enrichment and Pathway analysis (MetaboAnalyst 5.0).

Significant alterations in **lipidomic, metabolomic** and **immune** profiles precede **cardiovascular disease** in people with **HIV**.

The integration of these parameters increase the predictive accuracy of a common risk score for cardiovascular disease in these people.



Combinations	AUC	CI 95%	PPV	NPV
FRS	0.742	0.573-0.910	1.000	0.630
mDCs + Intermediate monocytes + d-fructose + LPC-O 18.1p	0.812	0.669-0.954	0.773	0.875
mDCs + Non-classical monocytes + d-fructose + LPC-O 18.1p	0.831	0.703-0.959	0.762	0.824
FRS + mDCs:pDCs ratio	0.910	0.827-1.000	0.919	0.738
FRS + mDCs + Non-classical monocytes + d-fructose + LPC-O 18.1p	0.975	0.930-1.000	0.940	0.919

Figure 4. Integrative analysis by ROC Curves. Each line represents the predictive value of different lipid, metabolite or immune parameter combinations. Abbreviations: lysophosphatidylcholines (LPC), myeloid dendritic cells (mDCs), Framingham Risk Score (FRS), Area Under the Curve (AUC), Confidence Intervals (CI) 95%, Positive Predictive Value (PPV), and Negative Predictive Value (NPV). (CTRL, n = 19; CVD, n = 19).

RESULTS

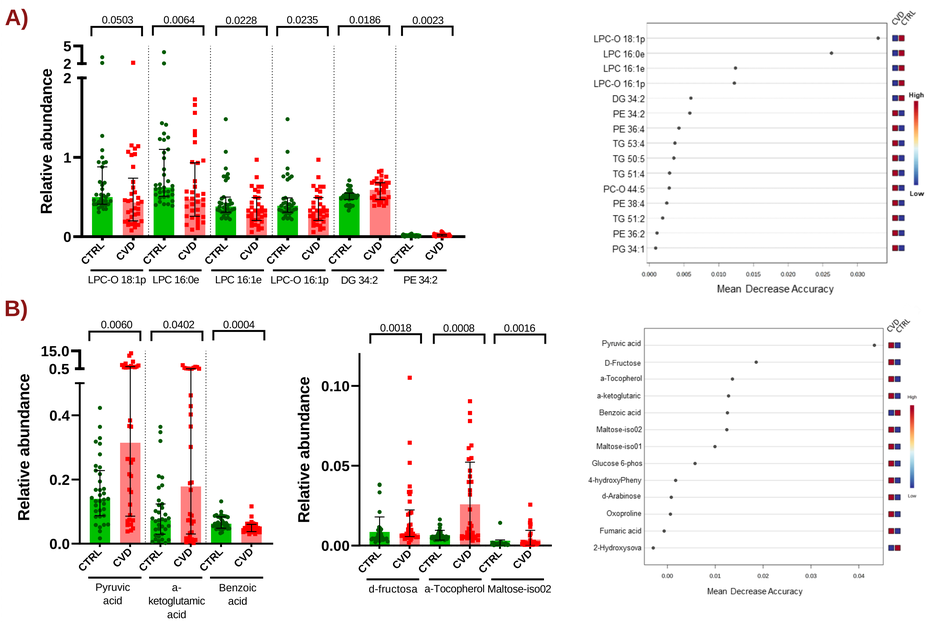
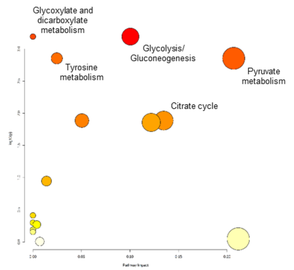


Figure 1. Lipidomic and Metabolomic analysis. Bar graphs and Random Forest showing most important lipids (A) and metabolites (B) which differed between Controls (CTRL, in green) and PLWH who suffered a cardiovascular event (CVD) (in red). Abbreviations: triacylglycerols (TG), diacylglycerols (DG), lysophosphatidylcholines (LPC), phosphatidylcholines (PC) and phospatidylethanolamines (PE). (CTRL, n = 35; CVD, n = 35).



Pathway Name	Match status	P value	Impact
Glycolisis /Gluconeogenesis	1/26	6.4458·10^{-4}	0.10044
Glycine. serine and threonine metabolism	1/33	6.4458·10^{-4}	0.0
Cysteine and methionine metabolism	1/33	6.4458·10^{-4}	0.0
Arginine and proline metabolism	1/38	6.4458·10^{-4}	0.0
Glyoxylate and dicarboxylate metabolism	1/32	6.4458·10^{-4}	0.0
Pyruvate metabolism	2/22	0.0014024	0.20684
Tyrosine metabolism	2/42	0.0014024	0.02463
Alanine. aspartate and glutamate metabolism	3/28	0.012994	0.05048
Citrate cycle (TCA cycle)	3/20	0.012994	0.13471
Glycerolphospholipid metabolism	2/26	0.013882	0.12185

Figure 2. Enrichment analysis of significant metabolic pathways. The size of the bubbles shows the pathway impact value and the color denote the level of significance (high in red and low in yellow) by mean of p-values. (CTRL, n = 19; CVD, n = 19)

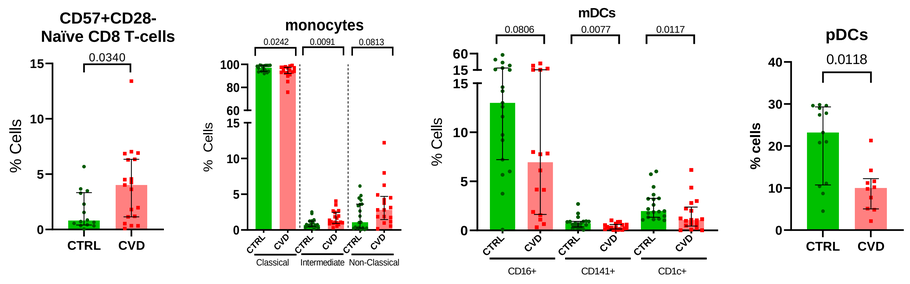


Figure 3. T cell, monocyte and DC phenoptype. Bar graphs showing different percentages of exhausted CD8+ T cells (CD57+CD28-), monocyte subsets and DC subsets (myeloid (mDCs) and plasmacytoid (pDCs) DCs) between Controls (CTRL, in green) and PLWH who suffered a cardiovascular event (CVD) (in red). (CTRL, n = 19; CVD, n = 19).

CONCLUSIONS

- Several lipids and metabolites were altered in PWH before CVD; Lysophosphatidylcholine LPC-O18:1p and pyruvic acid were the most important ones.
- Pyruvic metabolism was the pathway with major impact.
- PWH before suffering CVD showed higher percentages of regulatory and senescent T cells, more differentiated monocyte subsets and lower percentages mDCs and pDCs.
- An integrative predictive model combining LPC-O 18:1p, d-fructose, myeloid DCs, and non-classical monocytes achieved the highest predictive accuracy and the introduction of this combination increased the predictive accuracy of Framingham Risk Score.

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