Network analysis highlights differential clinical and omics profiles in HIV infection

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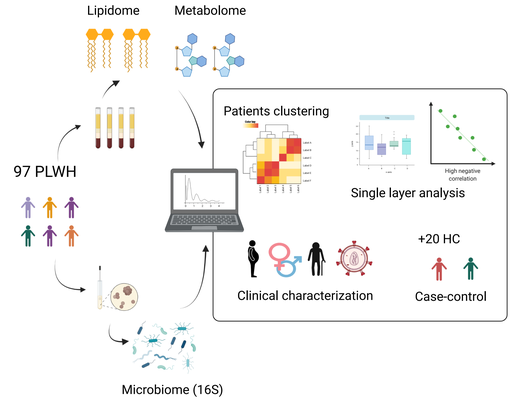
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BACKGROUND

People living with HIV under long-term successful antiretroviral therapy (PLWH) may suffer from cardiometabolic comorbidities, among other aging-related disorders. Though case-control studies comparing PLWH and HIV-negative control (HC) have been done previously, the heterogeneity among PLWH related to the incidence of metabolic diseases has not been investigated. To predict metabolic changes in PLWH, we aim to determine clusters of patients based on three omics layers integration and the underlying mechanisms separating these clusters using advanced bioinformatics analysis.

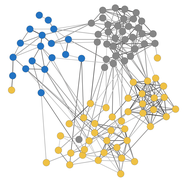
METHODS

Samples from 97 patients from the Copenhagen Comorbidity in HIV-infection (COCOMO) study and 20 age, BMI, and gender-matched HC were used for this study. Untargeted plasma metabolomics and lipidomics were performed using ultra-high-performance liquid chromatography/mass spectrometry (UHPLC/MS/MS) and microbiome profiling by bacterial 16S rRNA analyses. PLWH were clustered using similarity network fusion (SNF) and clusters further characterize at single omics level (LIMMA, DESeq2) I and clinical parameters (X^2 test, Mann Witney U test).



RESULTS

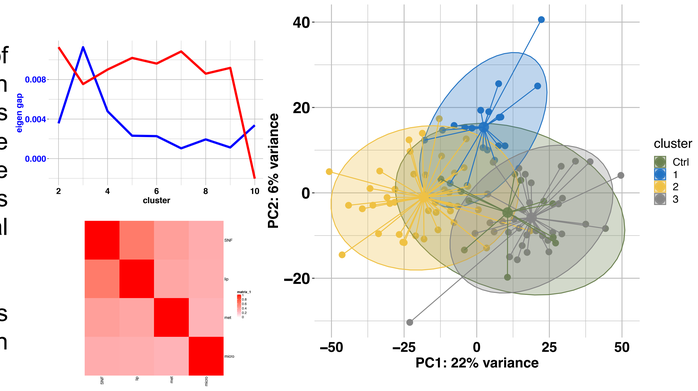
- **Similarity network fusion identify three underlying clusters based on lipidomics, metabolomics and microbiome integration in PLWH**



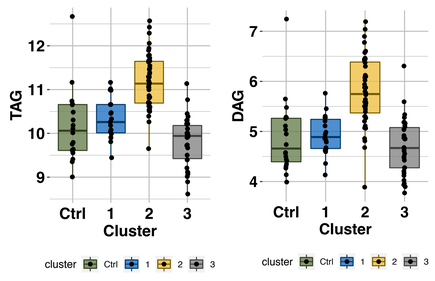
Patient by patient similarity matrices and networks for single omic were first calculated. Then, they are fused together by iteratively updating each of the networks with information from the other networks until convergence to the final network.

Based on the maximisation of eigen gap and the minimisation of rotation cost, 3 optimal clusters were selected. Concordance matrix based on NMI score showed that lipids network has the most influence in the final network.

The segregation of patients based on cluster is observed in PCA plot.

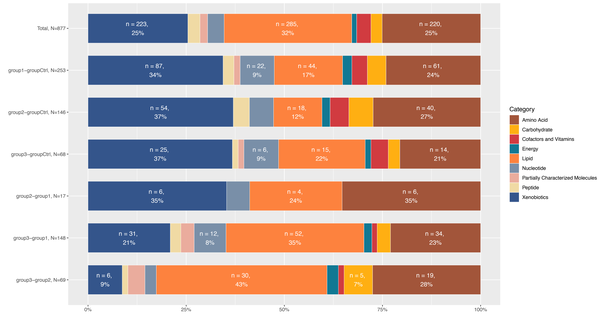


- **Single omics analysis highlights clusters associated profiles matching with clinical parameters**



Lipids were shown to have the most influence in the cluster repartition. C2 showed a drastic increase in triglycerides and diglycerides compared to C1, C3 and HC (FDR<0.1). C2 represented patients with high BMI, metabolic syndrome, high visceral adipose tissue, subcutaneous adipose tissue (SAT) and hypertension (all p<0.05). Cluster 3 has high VAT and hypertension but has the less MetS. Cluster 1 has the lower BMI, SAT and VAT and number of hypertension.

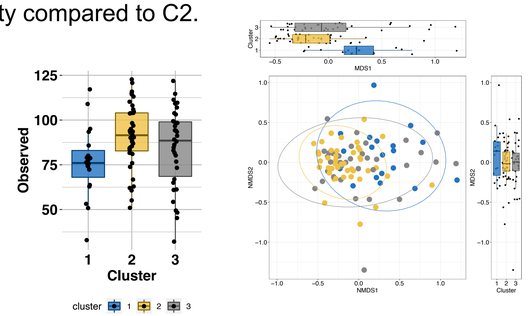
C1 and C2 have similar metabolic profile (3 clusters are different from HC), Amino acids are changin in HIV compared to HC, xenobiotics and lipids are changing among clusters. As in lipids data, C3 is closer to HC.



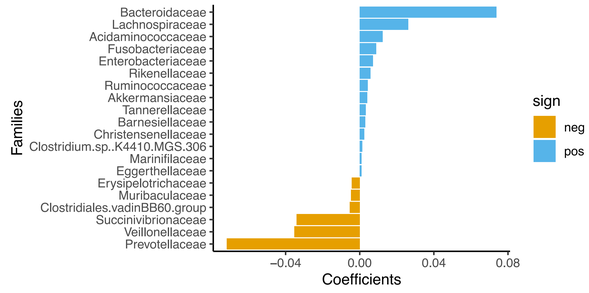
RESULTS

- **Transmission mode is driving clusters differences in microbiome data**

Cluster 2 has more homosexuals/bisexuals compared to the other clusters (all p < 0.05). C1 display lower alpha and beta diversity compared to C2.



C1 is enriched in Bacteriodes and Lachnospira while C2 and C3 are enriched in Prevotella, Veilonellae and Succinvibriona



CONCLUSIONS

In conclusion, we have shown that the molecular heterogeneity among the patients should be considered while defining immunological and virological success to determine the healthy state as PLWH displayed different profiles at -omics and clinical levels. Certain patients have dysregulated metabolic profiles despite having suppressed viral load and high .

AUTHOR INFORMATION

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