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MULTIOMICS PLASMA PROFILE OF SWITCHING FROM 3DR TO DOLUTEGRAVIR PLUS LAMIVUDINE

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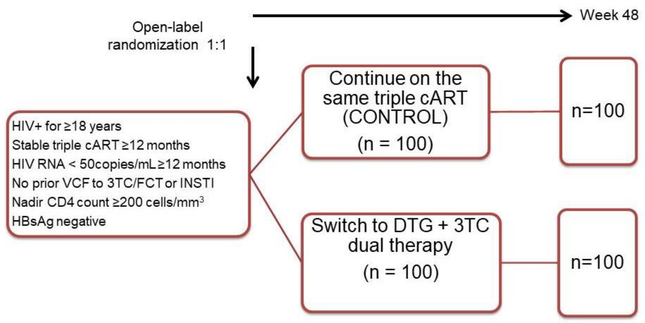
BACKGROUND

The DOLAM trial revealed that switching from triple ART (3DR) to dolutegravir plus lamivudine was virologically non-inferior and as safe as continuing triple ART (Lancet HIV2021; 8:e463-73). And although at 48 weeks, people living with HIV (PLWH) switching from 3DR to dolutegravir plus lamivudine had a higher weight gain compared to those continuing 3DR (1.5Kg [0.5-2.5], p=0.05), no significant changes in fasting glucose and lipids were detected.

- Multiomics plasma profile was performed to gain insight on whether some pathways might be affected by this therapy switch.

METHODS

- DOLAM (EudraCT 201500027435) is a phase 4, randomized, open-label, non-inferiority trial, done at six HIV clinics in Catalonia, Spain.
- PLWH receiving a 3DR regimen were assigned (1:1) to switch to oral dolutegravir 50 mg and lamivudine 300 mg once daily or to continue 3DR for 48 weeks.



- Untargeted proteomics, metabolomics and lipidomics analyses were performed at baseline and 48 weeks. For each patient, the ratio between relative concentrations at 48 weeks and baseline was calculated for proteins, metabolites and lipids identified. All data were log-transformed (log2) before statistical analyses.

Switching from 3DR to dolutegravir+lamivudine 2DR may confer anti-inflammatory properties

RESULTS

- Untargeted proteomic, metabolomic and lipidomic analyses identified 136 proteins, 97 metabolites and 117 lipid species.
- Among the disturbed molecules, metabolomics/Lipidomics analyses revealed that PLWH who switched to the study regimen showed higher plasma relative concentration of ornithine (p=0.033) whereas proteomics analysis showed that patients who switched to dolutegravir+lamivudine had higher plasma hemoglobin subunit alpha (HBA) (p=0.044), insulin-like growth factor-binding protein 3 (IGFBP3) (p=0.026) and lipopolysaccharide-binding protein (LBP) (p=0.03) concentrations.
- The differentially expressed proteins were selected as input in the STRING database to predict protein-protein interactions and to establish which biological processes could be affected. Of interest, HBA, IGFBP3 and LBP revealed a network of predicted functional associations related to the regulation of cell death (RCD, false discovery rate = 0.03, Figure 1).

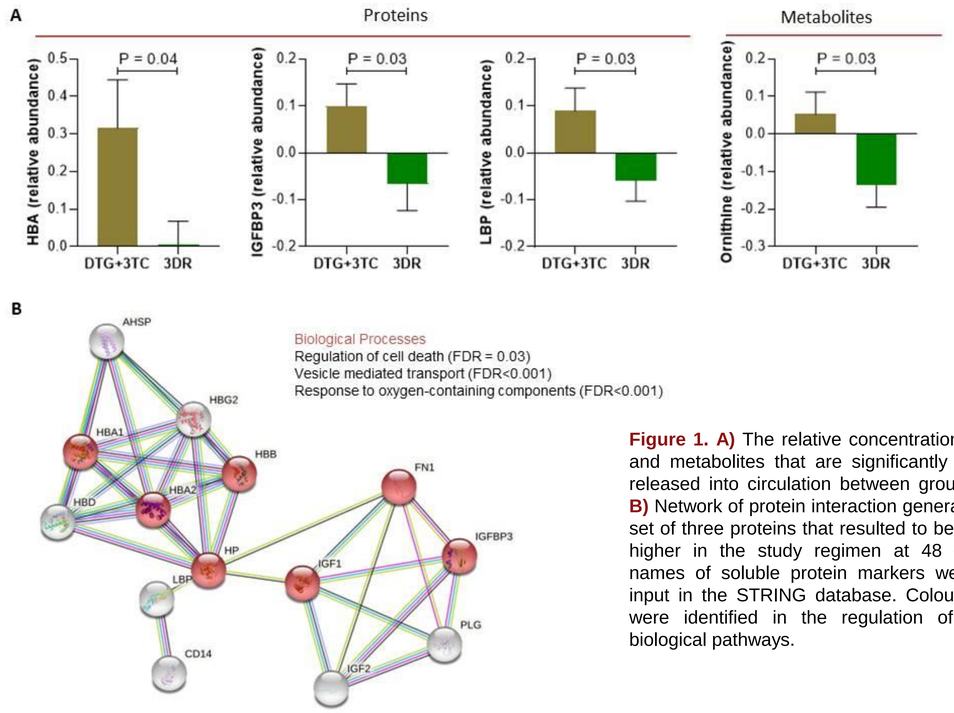


Figure 1. A) The relative concentration of proteins and metabolites that are significantly differentially released into circulation between groups of study. **B)** Network of protein interaction generated with the set of three proteins that resulted to be significantly higher in the study regimen at 48 weeks. The names of soluble protein markers were used as input in the STRING database. Coloured proteins were identified in the regulation of cell death biological pathways.

CONCLUSIONS

Switching from 3DR to dolutegravir+lamivudine dual-therapy was related to a few metabolomic perturbations. Multiomic approach identified some soluble compounds involved on metabolic pathways in PLWH switching from 3DR to dolutegravir plus lamivudine.

- Signaling cascades and molecular effectors for the preservation of a biological equilibrium (RCD) may play an essential role for tissue homeostasis when switching from 3DR to dolutegravir plus lamivudine.
- Preliminary data suggests that switching may activate metabolomics pathways of energy consumption giving an antifatigue effect (Ornithine).
- Previously, plasma ornithine was found markedly lower in T2DM and inversely associated with inflammation markers. Thus, it can be inferred that higher levels of ornithine might confer anti-inflammatory properties.

ADDITIONAL KEY INFORMATION

Keyword

Antiretrovial Therapy, Dolutegravir, Dual therapy, Multiomic, Tritherapy

Limitations

Given a large number of proteins, metabolites and lipid species identified there is a significant risk of multiple testing yielding some false-positive test results. Not taking into account other clinical characteristics that, in turn, could have a direct effect on the metabolomics and lipidomics readouts could yield a cause and effect bias. However, of note, this is a preliminary study and further investigations are being considered to drawn robust conclusions.

Additional Resources

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