Transcriptomic Changes in Adipose Tissue of People with HIV on BIC/FTC/TAF or DTG/3TC Treatment

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BACKGROUND

Optimizing combined antiretroviral therapy (cART) is key to improving the quality of life of people with HIV (PWH). Bictegravir/emtricitabine/tenofovir alafenamide (**BIC/FTC/TAF**) and dolutegravir/lamivudine (**DTG/3TC**) are frequently recommended, but direct comparisons of switching to these regimens, or between them, are scarce. Both are effective but associated with weight gain; however, their specific impact on adipose tissue (AT) biology remains unclear.

Here, we hypothesized whether **cART switching may induce distinct AT transcriptomic signatures related to weight gain.**

METHODS

This is a sub-study of **PASO-DOBLE**, a phase 4 Spanish clinical trial (NCT04884139). Abdominal subcutaneous AT biopsies (5 mm^3) were analyzed in asymptomatic, clinically stable PWH at **baseline** (**BS**, pre-switch), **week 48** (**W48**), and **week 96** (**W96**) after switching to BIC/FTC/TAF or DTG/3TC. One fragment was stained with hematoxylin and eosin; another was used for RNA extraction. After quality control (RIN>6), 24 valid triplets were sequenced (mean age 45 years; BIC/FTC/TAF *n*=10, 90% men; DTG/3TC *n*=14, 57% men). Reads were mapped to the human genome (HISAT2), and expression quantified (counts, FPKM). Differential expression was analyzed with DESeq2 (|log2FC|>1, p_{adj}<0.05), followed by pathway enrichment analysis with clusterProfiler (KEGG database). Biomarker expression in AT was tested with age- and sex-adjusted repeated measures ANCOVA. *p*-values were adjusted using FDR correction.

RESULTS

1 | Although participants **gained weight**, histology revealed **no obvious morphological changes in adipocytes** with any cART.

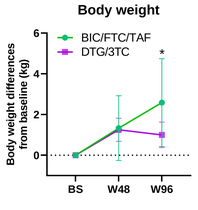

Fig. 1: Body weight differences (ΔBS) of cART-treated PWH at W48 and W96 after switching to BIC/FTC/TAF (*n*=10) and DTG/3TC (*n*=14). *: *p*<0.05 vs BS.

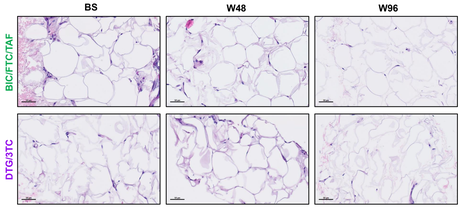

Fig. 2: Representative histological images (hematoxylin/eosin staining) of subcutaneous white adipose tissue from cART-treated PWH at baseline (BS), W48 and W96 after switching to BIC/FTC/TAF or to DTG/3TC. The same individual is show for each treatment. Scale bar = 50 µm.

Switching to BIC/FTC/TAF or DTG/3TC is associated with distinct changes in adipose transcriptomic signatures

RESULTS

2 | Transcriptomics revealed **decreased energy metabolism pathways** from BS to W48 (*p*=0.002), followed by an **increase from W48 to W96**, while **inflammation and tissue remodeling** showed the **opposite trend** (*p*=0.0001, *p*=0.0003)**.**

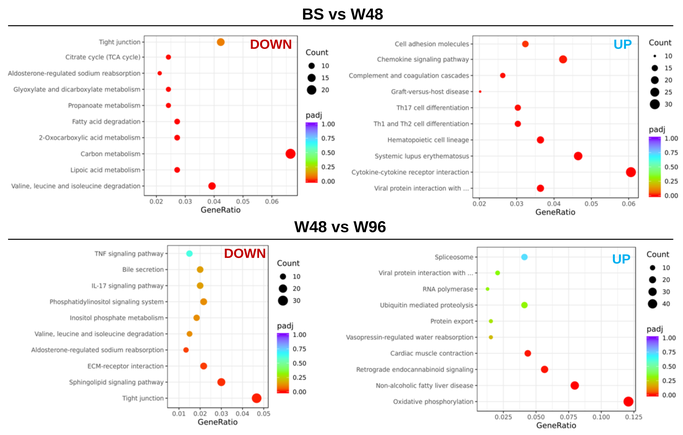

Fig. 3: Pathway enrichment analysis (KEGG database) showing downregulated (left) and upregulated pathways (right) considering all significatively differentially-expressed transcripts from BS to W48 (upper panels) and from W48 to W96 (lower panels) in the whole cohort (*n*=24). "Count" indicates the abundance of differentially-expressed transcripts belonging to that pathway (circle size), and "gene ratio" indicates the Count value corrected by the total amount of transcripts listed on that specific category. p-adjusted values are shown as a color-coded parameter; statistical significance was considered below *p*<0.01.

3 | mRNA expression of biomarkers of relevant adipose functions was quantified to assess differences between cART**.** Biomarkers of **adipogenesis** (*PPARG*, *CEBPB*) and **lipolysis** (*PNPLA2*, *HSL*) remained largely stable, but **insulin sensitivity** markers (*INSR*, *AKT1*) and **mitochondrial function** transcripts (*SDHA*, *PPARGC1A*) were significantly downregulated in both groups. In BIC/FTC/TAF, dysregulation of **lipid biosynthesis** genes (*FASN*, *SREBF1*) and **adipokines** (*ADIPOQ*, *RETN*) was observed, along with increased **proinflammatory** markers (*TNF*, *IL6*, *CCL2*). In DTG/3TC, **browning** markers (*UCP1*; *p*=0.02; *CIDEA*, *DIO2*) were downregulated.

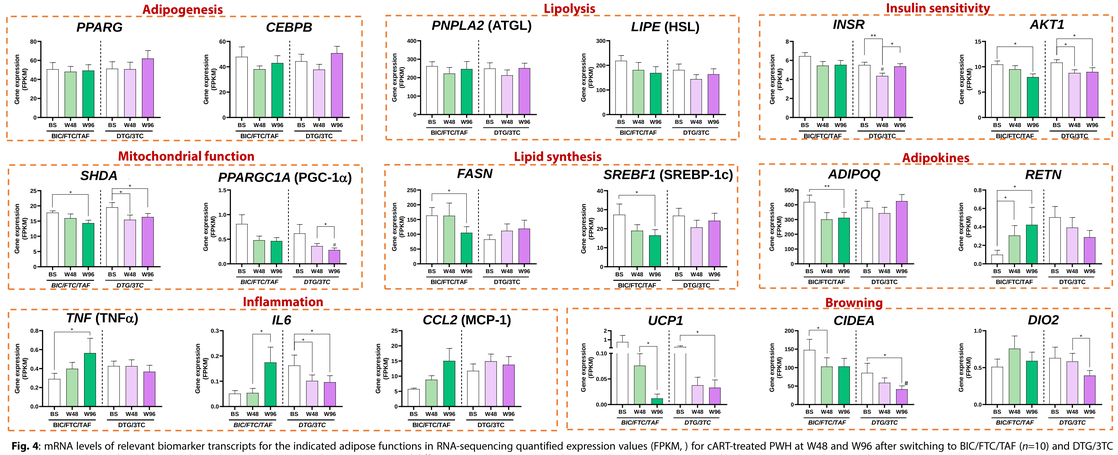

Fig. 4: mRNA levels of relevant biomarker transcripts for the indicated adipose functions in RNA-sequencing quantified expression values (FPKM,) for cART-treated PWH at W48 and W96 after switching to BIC/FTC/TAF (*n*=10) and DTG/3TC (*n*=14). Age- and sex-adjusted repeated measures ANCOVA was used to assess statistical differences. *: *p*<0.05, **: *p*<0.01 between the timepoints connected by lines. #: *p*<0.05 vs the equivalent timepoint in DTG/3TC vs BIC/FTC/TAF.

CONCLUSIONS

- Switching to BIC/FTC/TAF or DTG/3TC was associated with weight gain and also with **distinct adipose tissue transcriptomic signatures**.
- **Differential adipose functional alterations occur post-switch depending on each arm**. While adipose insulin sensitivity marker expression is reduced in both, inflammation was exacerbated only in BIC/FTC/TAF and thermogenesis was more reduced in DTG/3TC.
- This suggests **cART-specific mechanisms may reflect adipose tissue dysfunction potentially relevant to adipometabolic risk.** These findings highlight the need for further mechanistic and clinical research, as they are exploratory and hypothesis-generating and require validation in larger cohorts with functional metabolic endpoints.

CONTACT INFORMATION

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PLAIN LANGUAGE SUMMARY

Changing from previous drugs to treat HIV to two newer ones leads to higher weight. This changes important mechanisms for fat tissue functions, such as sugar uptake and use of fat stores, and some are different depending on the drug combination included in each HIV treatment.

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