

Peer Review

Review of: "Thrombospondin Regulation Differentiates HIV Patients with Natural and Therapy-Mediated Control of Plasma Viremia: A Genome-Wide Transcriptomic Analysis"

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This study compares PBMC transcriptomes from nine therapy-naïve long-term non-progressors (LTNPs) versus 15 newly diagnosed HIV+ individuals sampled before therapy (TP1) and after >1 year of HAART-mediated viral suppression (TP2), aiming to distinguish natural versus therapy-mediated viral control. The authors report that immune, cytoskeletal remodeling, apoptosis, and T-cell signaling pathways differ between groups and propose THBS1 (thrombospondin-1) as a biomarker associated with viremia and able to discriminate viremic patients from LTNPs (including reported correlations and p-values).

Issues to address:

1. Small cohorts and limited power for biomarker claims: please add confidence intervals, sensitivity analyses, and an independent validation cohort or cross-validation with held-out samples for THBS1 classification metrics (ROC/AUC).
2. Statistical methods description is inconsistent and includes confusing thresholds: There are internal inconsistencies between the abstract and methods regarding FDR thresholds, and the fold-change criteria as written are confusing (including sign conventions and cutoffs). For example, the methods describe SAM/FDR procedures and thresholds (e.g., $FDR < 0.05$, $p < 0.01$) and unusual fold-change bounds. Please clarify: 1) one consistent DE pipeline (normalization, filtering, model, multiple testing correction); 2) clear definition of fold change ($\log_2FC$ vs linear FC, sign convention); 3) explicit reporting of the number of DE genes per contrast and effect sizes.

3. The manuscript says microarray data “will be deposited” to GEO, but no accession is provided.
Please add GEO accession, processed expression matrix, sample metadata, and a minimal analysis workflow (even if just parameter files).

Declarations

Potential competing interests: No potential competing interests to declare.