CHANGES IN GUT MICROBIOTA PROFILE IN PWHIV WHO SWITCH FROM EFV/FTC/TDF TO BIC/FTC/TAF

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BACKGROUND

Integrase Strand Transfer Inhibitors (InSTIs) are now the preferred ART regimen for people living with HIV (PWHIV)[1]. InSTIs have superior benefits. One possible drawback is the unintentional weight gain associated with InSTIs, and tenofovir alafenamide (TAF, nRTIs). Factors likely to mediate weight gain include adipocyte dysfunction, host drug metabolism[2], together with traditional risk factors.

IMPORTANCE

Reasons linking InSTIs and TAF to weight gain remain incompletely elucidated; plus long-term health complications; i.e. cardiometabolic complications, remain unclear. Weight management, rather than switching off of InSTIs and TAF is the current recommended strategy for improving cardiometabolic parameters and overall health.

AIM

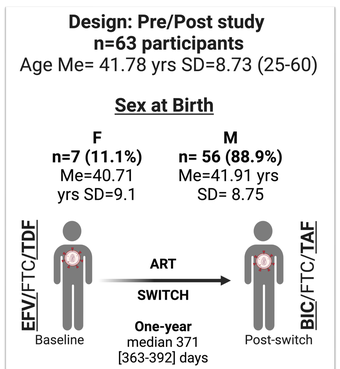
Research is needed to evaluate InSTI- and TAF-related weight gain and the putative role of the gut microbiota as evidence exists on the reciprocal causal relationship between the gut microbiome and host metabolism. This is particularly relevant in the setting of the global obesity epidemic, and in the context of the aging HIV population with increased comorbidities and polypharmacy.

OBJECTIVE

Evaluate changes in gut microbiota in treatment-experienced virologically-suppressed PWHIV, who switch to BIC/FTC/TAF, from EFV/FTC/TDF.

FIGURE 1:

Objective: Host and gut microbiota responses after shifting to BIC/FTC/TAF.



Abbreviations:
ART: Antiretroviral therapy, BIC: Bictegravir, EFV: Efavirenz, F: Female, FTC: Emtricitabine, IQR: interquartile range, TAF: Tenofovir alafenamide, TDF: Tenofovir Disoproxil Fumarate, M: Male, Me: Mean, SD: standard deviation

METHODS

Prospective single-center cohort. Treatment-experienced virologically-suppressed PWHIV (n=63) were invited to participate and signed the informed consent. Stools were collected at baseline (prior to ART shifting) and one-year after shifting to BIC/FTC/TAF and subjected to 16S rRNA sequencing. Analysis were performed in Qiime2, R, GraphPad Prism.

After shifting to BIC/FTC/TAF for a year:

Part I: Host Response

A total of 49 (77.8%) PWHIV (4 F and 45 M) gained weight. The magnitude of absolute weight gain was + 3.85 (2.85-5.70) kgs. A total of 19 and 6 PWHIV gained more than 5% (3 F and 16 M) and 10% (6 M) weight, respectively. A total of 20 PWHIV switched to a higher BMI category (N → OW, n=14, OW → O-1, n=5, and O-1 → O-2, n=1). A total of 14 (22.2%) PWHIV (3 F and 11 M) lost weight. The magnitude of absolute weight loss was -1.25 (-2.638 to -0.712) kgs. One PWHIV (M) lost more than 5% weight. All remained within the same BMI category (6 N, 3 OW, and 4 O).

Plasma levels of sCD14 and I-FABP decreased, while levels of sCD163 increased. The magnitude of change is shown in Figure 2. No differences in plasma markers were observed when stratifying by sex at birth.

Part II: Gut Response (Figure 3)

Compared to baseline (EFV/FTC/TDF), PWHIV exhibit increased alpha diversity.

Beta-diversity analysis showed an overlap between the two groups, and no clear clustering when stratifying by ART (PWHIV, R2= 0.0156, PERMANOVA p= 0.01). Microbial community clustering was mostly influenced by intra- and interpersonal variation (subjects), explaining 67.3% (R2= 0.673, PERMANOVA p<0.0001). Sex at birth also influenced microbial community clustering (see Figure 3 for PERMANOVA p values).

The most abundant phyla were Firmicutes and Bacteroidota; at the genus level, *Bacteroides* and *Prevotella* were abundant in females and males, respectively. A decrease in Proteobacteria, and Fusobacteriota was observed for both sexes. At genus level, *Faecalibacterium* (Firmicutes), an anti-inflammatory commensal bacterium, increased (in both sexes). No differentially abundant taxa were identified when assessing ART shifting, overall (including all PWHIV) or when stratifying by sex at birth.

	Baseline (EFT/FTC/TDF)	Post-Switch (BIC/FTC/TAF)	P value
Body			
Weight (kg)	73.10 (63.45-82.70)	76.40 (66.45-83.50)	<0.0001
BMI (kg/m^2)	25.50 (23.90-28.30)	26.50 (25-30.20)	<0.0001
BMI cat.			0.0326
N	29 (46.03)	15 (23.81)	
OW	22 (34.92)	31 (49.21)	
O	12 (19.05)	17 (26.98)	
Latest HIV			
CD4	492 (359-601)	480 (393-656)	ns
CD4%	28 (23-34)	29 (25-35)	0.0006
CD4/CD8	0.89 (0.59-1.13)	0.88 (0.63-1.21)	ns
Markers			
sCD163	541.4 (411.2-726.9)	660.8 (437.2-820.1)	0.0029
sCD14	1476 (1308-1662)	1208 (1134-1367)	<0.0001
I-FABP	1270 (838.1-1787)	785.4 (496.6-1164)	<0.0001

Data is shown as median and interquartile range. Paired data were compared using the Wilcoxon matched-pairs signed rank test. %: percentage, BMI: body mass index, cat: category, CD: cluster of differentiation, I-FABP: intestinal fatty acid binding protein, kg: kilograms, N: normal (18.5-<25), ns: not significant, OW: overweight (25 to <30), O: obese (>30), s: soluble.

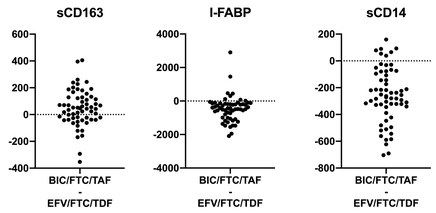


Figure 2: Difference plots showing the magnitude of change in plasma markers of innate immune activation (sCD163, sCD14) and enterocyte integrity (I-FABP) between baseline and after shifting to BIC/FTC/TAF.

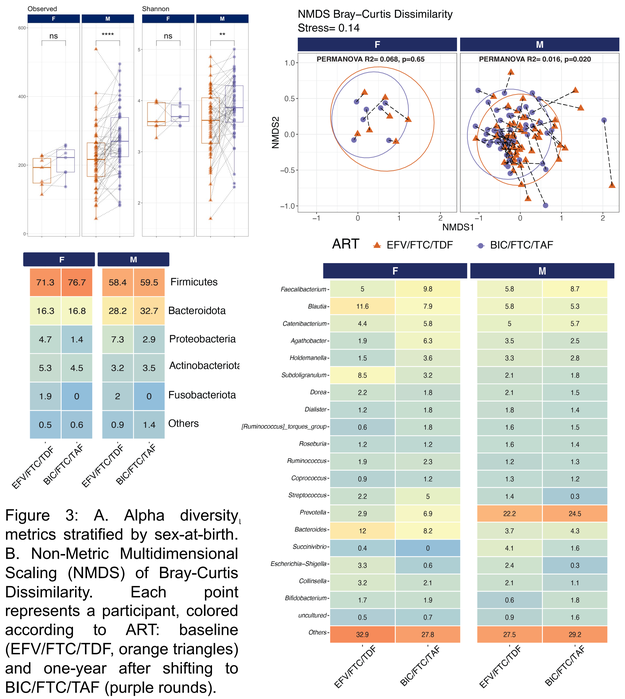


Figure 3: A. Alpha diversity metrics stratified by sex-at-birth. B. Non-Metric Multidimensional Scaling (NMDS) of Bray-Curtis Dissimilarity. Each point represents a participant, colored according to ART: baseline (EFV/FTC/TDF, orange triangles) and one-year after shifting to BIC/FTC/TAF (purple rounds). The trajectory of each participant is shown in dotted lines. Ellipses are centered based on the median for each group. PERMANOVA: permutational multivariate analysis of variance (adonis, permutations =10000). Heatmap showing the top 5 phyla and the top 20 genera stratified by sex at birth.

DISCUSSION

After a one-year follow-up period, most PWHIV shifting to BIC/FTC/TAF, from EFV/FTC/TDF, gained absolute weight. Markers of microbial translocation and enterocyte damage improved, while sCD163, a marker of innate immune activation, linked to cardiometabolic disorders, increased. Alpha diversity increased suggesting that InSTIs might be less deleterious for the gut microbiota as shown in previous studies[3,4]. This might be due to the differential antibacterial effects of antiretrovirals. Proteobacteria and Fusobacteriota, known pathobionts decreased, while *Faecalibacterium* increased. Shifting to BIC/FTC/TAF explained 1.56% of gut microbiota variation (PERMANOVA p<0.05), indicating that most of the variation in bacterial community structure was influenced by other factors (intra- and interpersonal variation). Sex stratification suggests differential gut responses to BIC/FTC/TAF, however because of the small number of females (n=7), and participants overall, there was insufficient statistical power to detect differences in subgroup analyses.

LIMITATIONS

This study was limited by a small size, and the lack of a control group (PHWIV who continued on EFV/FTC/TDF). We also did not assess the effect of co-medication, an important confounder in gut microbiota studies. Also, findings need to be confirmed in larger independent cohorts.

CONCLUSIONS

Assessment of complex biological pathways involved in weight gain, obesity, host metabolism and the gut microbiota in the context of treated HIV infection may lead to the identification of novel therapeutic targets (biomarkers).

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