THE EFFECTS OF HIV/ART EXPOSURE ON GUT MICROBIOTA AND MITOCHONDRIAL FUNCTION DURING THE POSTPARTUM PERIOD IN BLACK SOUTH AFRICAN WOMEN

Asanda Mtintsilana (PhD)

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Division of **Epidemiology** & Biostatistics
School of Public Health
Faculty of Health Sciences
University of Cape Town

School of Public Health
Departement Openbare Gesondheid
Isikolo Sempilo Yoluntu

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

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BACKGROUND

High burden of HIV and non-communicable diseases (NCDs) in South African (SA) women

- HIV affects 18.3% of adult SA and the prevalence is highest in women (24.5%), especially among pregnant women (28%).

- High prevalence of obesity and type 2 diabetes (T2D)-related mortality among women of reproductive age (15-49 years of age).
  - 35.2% of SA women are obese.
  - T2D is the leading underlying natural cause of death in SA women.

(UNAIDS, 2022; Woldesenbet et al 2021; South African Demographic and Health Survey (SADHS), 2019; Statistics SA Mortality Report, 2020)

BACKGROUND

Emerging evidence suggests an influence of HIV/ART exposure on gut microbiota and mitochondrial function

- Anti-retroviral therapy (ART)-controlled people living with HIV still present with excessive **activation of the immune system and chronic inflammation,** which may lead to impairments in several biological processes including **gut dysbiosis and mitochondrial dysfunction.**
- Gut microbiota is a **diverse community of microorganisms** occupying the digestive tract that controls various functions through the **production of signalling molecules and metabolic substances.**
  - **Primary function-** fermentation of fibre which produces short-chain fatty acids (SCFAs).
- SCFAs are key signalling molecules that regulate adiposity and energy homeostasis and epithelial barrier functions (e.g., gut permeability)

Schank et al 2021; Zhang Y et al 2023; Vázquez-Castellanos JF et al 2015

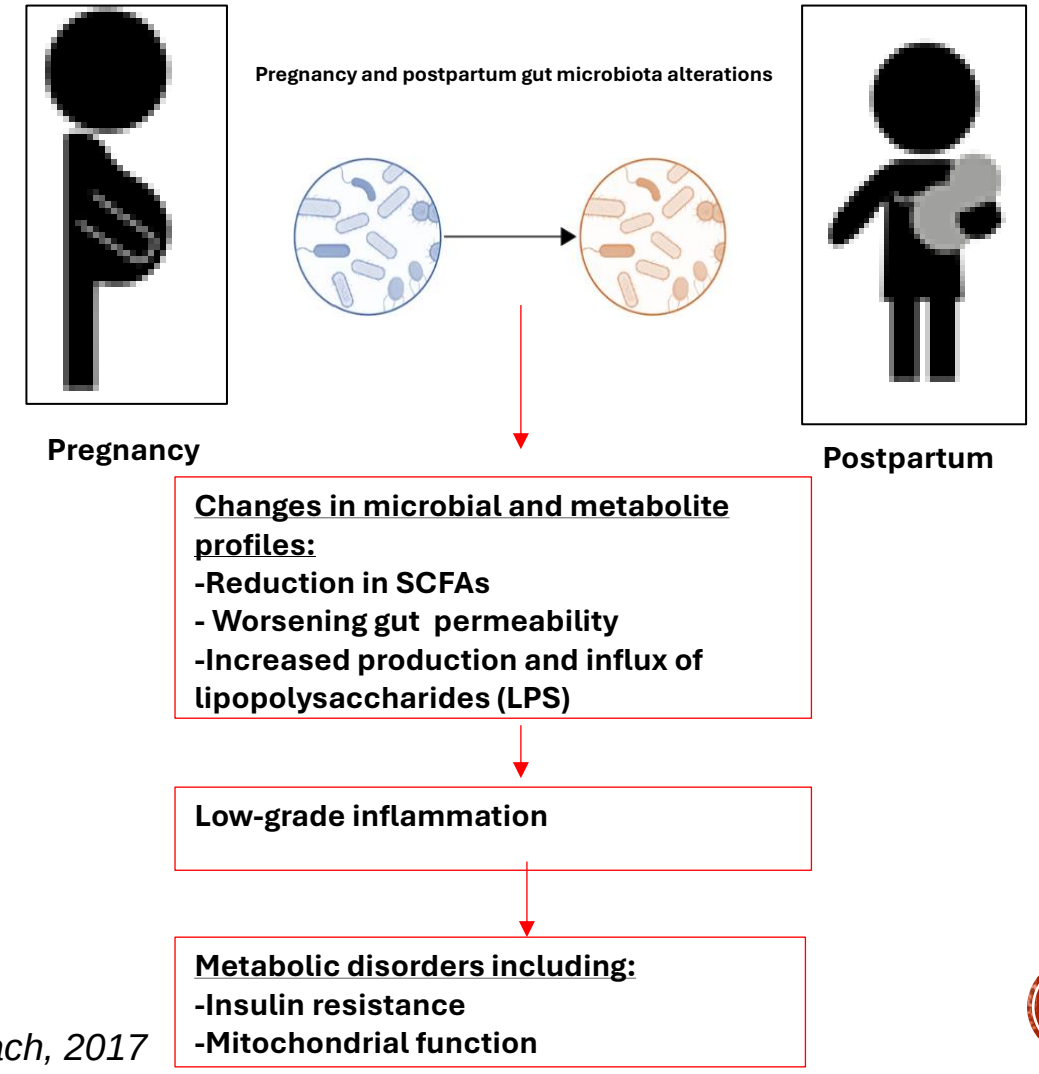
BACKGROUND

Gut microbiota shift during pregnancy and the postpartum period

- During the 3rd trimester, the gut microbiome shifts to support foetal development.
  - **Increased abundance of pro-inflammatory bacteria**
  - **Anti-inflammatory bacteria are significantly reduced.**

- During the postpartum period, the gut microbiota and immune system **start reversing to pre-pregnancy states**, but this transition is dependent on several factors (e.g., HIV).

- Pregnancy and postpartum gut dysbiosis in the presence of HIV/ART exposure might increase or exacerbate **the production of toxic microbial (e.g., LPS) and metabolite substances, leading to low-grade inflammation,** and subsequently causing metabolic disorders.



Huttenhower et al 2012; Koren eta l 2012; Weeerasuriiya et al 2023; Clark and Mach, 2017

RATIONALE AND AIM

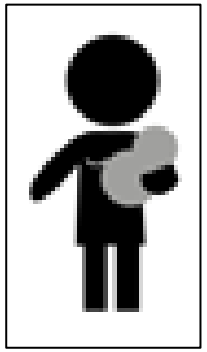
Rationale

- There is a lack of data on the biological mechanisms linking HIV and metabolic disorders in people living with HIV, especially during pregnancy and the postpartum period.

Study Aim

- Therefore, we aimed to explore the effect of HIV exposure on gut microbiota and mitochondrial function during the postpartum period in Black South African women.

METHODS



P-CAMP (6-24 months postpartum)
(n=65, 71% women living with HIV [WLWH])
(30.4 ± 5.6 years of age)

Demographic questionnaires including medical history
- Age
- Education
- Marital status
- HIV status
- ART treatment **(98%)**
  - Dolutegravir (DTG, **53.3%)** and Efavirenz (EFV)-based antiretroviral regimen.

- **Resting metabolic rate(RMR) measured using indirect calorimetry**

- **Body composition**
- Basic anthropometric measures (height, weight)
- DXA-derived body composition (fat mass (kg and %)), muscle mass (fat-free soft tissue mass [muscle mass])

- **Biochemical analysis**
- Fasting insulin and glucose (HOMA-IR)
- OGTT (insulin sensitivity, Matsuda index)

- **Stool collection and analysis**
- Early morning was analysed for gut microbiota composition using 16S rRNA amplicon sequencing

- **Mitochondrial respiration measured using high-resolution respiratory**
- Tissue fat biopsies collection (skeletal muscle, **a**bdominal and **g**luteal **s**ubcutaneous **a**dipose **t**issue [aSAT and gSAT])

- Mitochondrial respiration was measured as oxygen flux at leak, oxidative phosphorylation complex I (COXI) and complex I and II (COXI+II) and electron transport system (ETS) respiratory states, reported relative to tissue mass (pmol/[s*mg]).

RESULTS

Table 1: Descriptive characteristics of women living with HIV (WLWH) and not living with HIV (WNLWH) (n=65)

Variables	Total	WNLWH (n=19)	WLWH (n=46)	Adjusted p-value
Age (years)	30.4 ± 5.6	30.0 ± 5.6	30.5 ± 5.7	
Body fat and fat distribution				
Fat mass (kg)	32.1 (25.5-44.3)	40.3 (27.1-54.5)	31.8 (25.1-43.2)	0.050[a]
Body fat (%)	45.7 ± 6.6	46.7 ± 8.1	45.2 ± 6.0	0.368
Fat free soft tissue mass (kg)	35.5 ± 14.3	42.7 ± 7.8	39.1 ± 7.0	**0.043**
Resting metabolic rate				
Resting metabolic rate (RMR) (kcal/d)	1482.1 ± 241.6	1645.9 ± 255.6	1412.9 ± 201.0	**0.001**
Mitochondrial respiration characteristics				
Abdominal subcutaneous adipose tissue (aSAT) (pmol/[s*mg])				
COX I+II	0.7 (0.6-0.9)	0.6 (0.5-0.7)	0.8 (0.7-1.3)	**0.018**
Gluteal subcutaneous adipose tissue (gSAT) (pmol/[s*mg])				
ETS	1.9 (1.3-2.3)	1.3 (1.0-1.9)	2.1 (2.0- 2.4)	**0.000**

[a]Model p-value not significant

Data reported as mean ± SD for normally distributed variables and as median (Interquartile Range) for skewed variables. Adjusted for age, fat mass, and fat-free soft tissue mass, as appropriate.

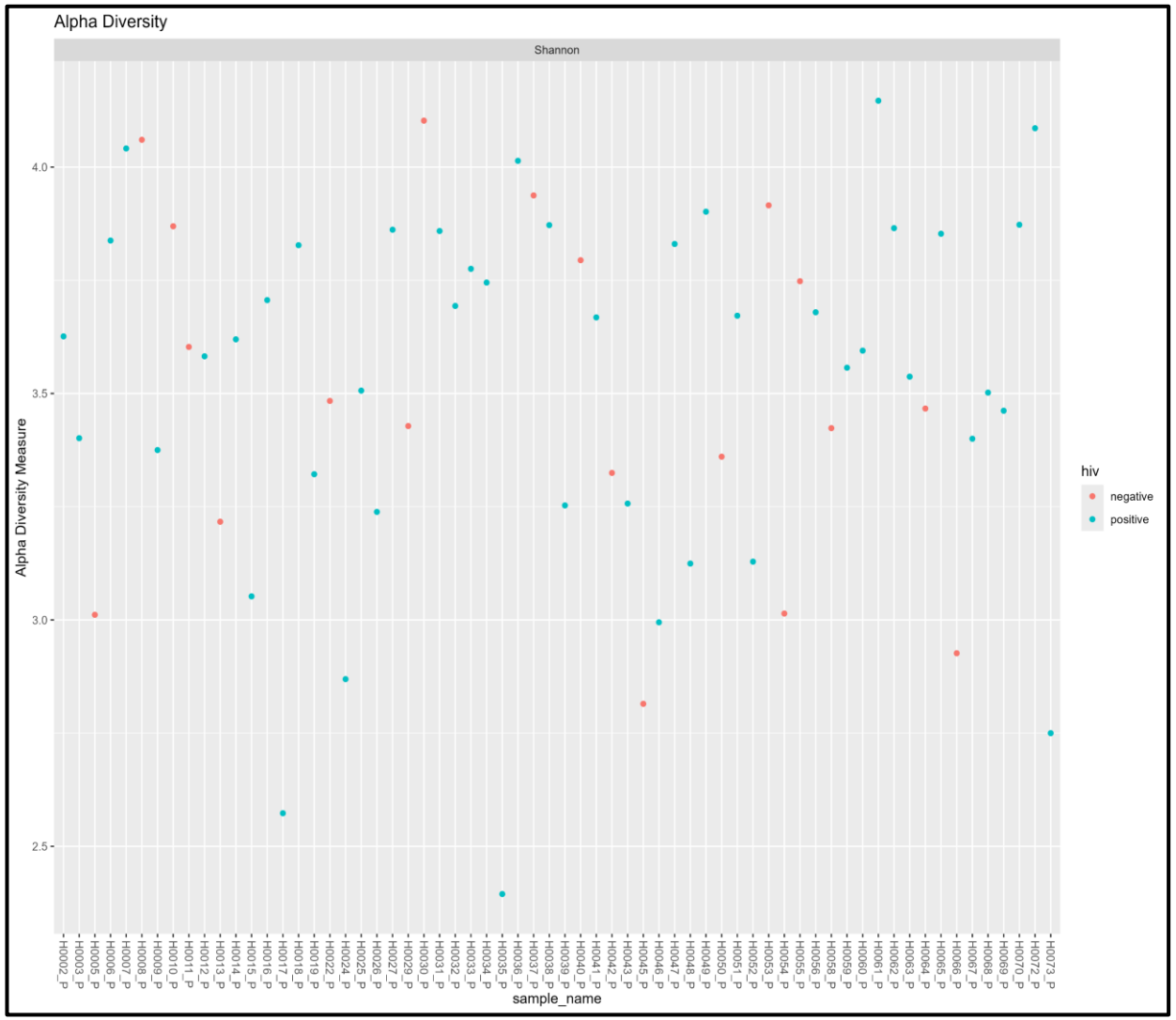
Abbreviations: COXI+II, Complex I+II; ETS, electron transport system respiratory states.

Women living with HIV (WLWH) had lower muscle mass and higher complex I+II (COX1+II) and electron transport system (ETS) mitochondrial respiratory states in abdominal and gluteal subcutaneous adipose tissues (aSAT and gSAT).

RESULTS

Table 2. Alpha diversity

HIV status	Measure	N	Mean	SD	SE
WNLWH	Shannon	19	3.500069	0.391051	0.089713
WLWH	Shannon	45	3.531738	0.397407	0.059242



No significant differences in alpha and beta diversity in bacterial families (data not shown) by HIV status.

Figure 1. Alpha diversity by HIV status. Abbreviation: WLWH, women living with HIV (WLWH) and without HIV (WNLWH).

RESULTS

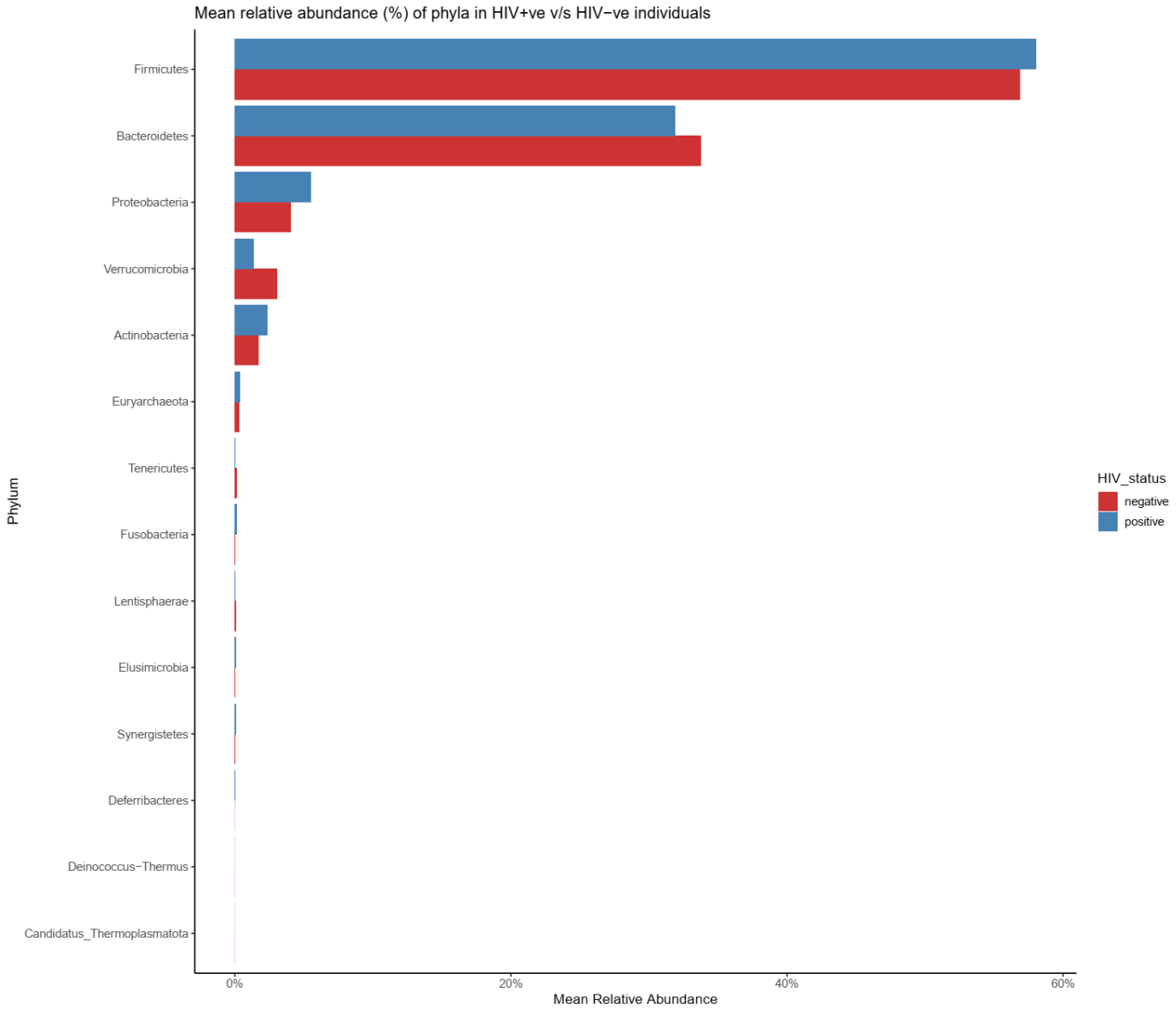
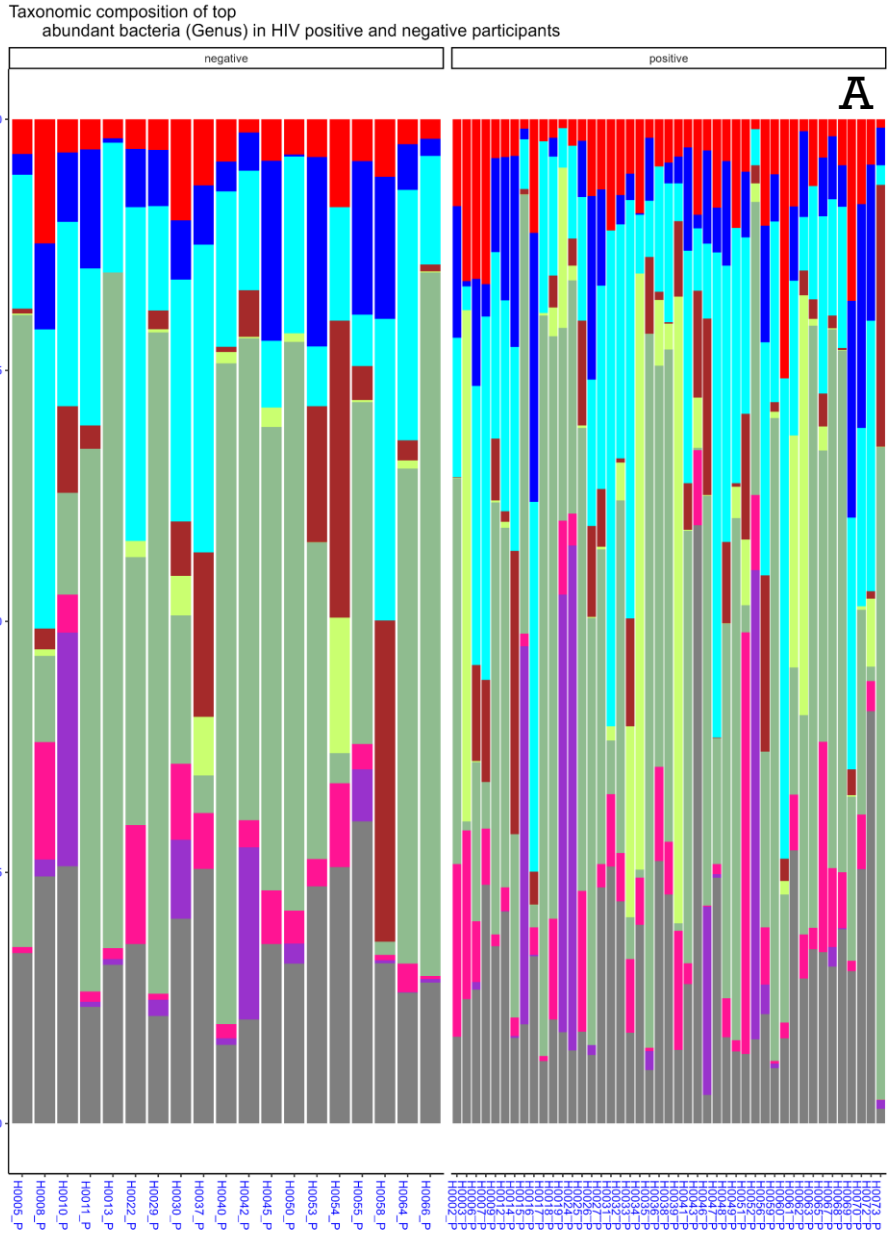
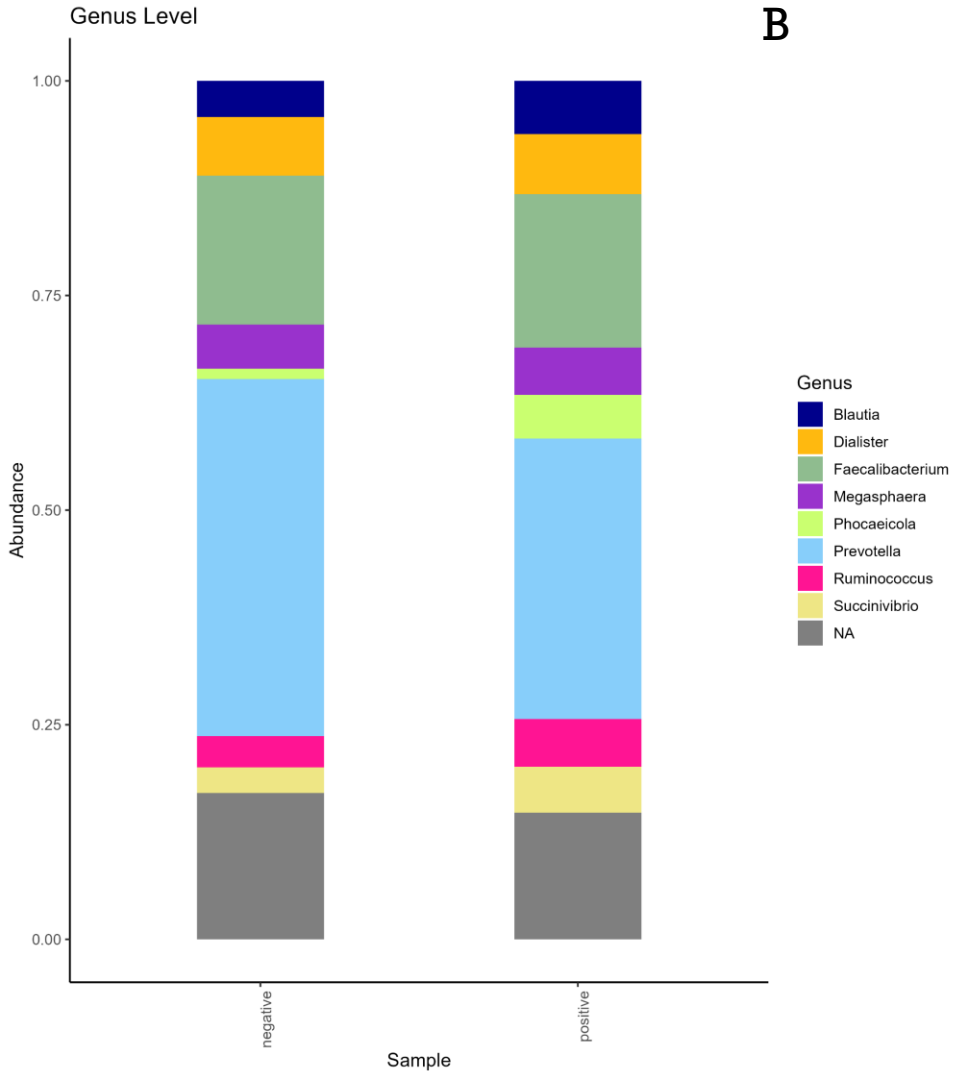


Figure 2. Dominant phyla in HIV-affected and non-affected individuals.

The relative abundance of Firmicutes and Proteobacteria was higher, while Bacteroidetes was lower in the HIV-affected group vs. the HIV-unaffected group.

RESULTS





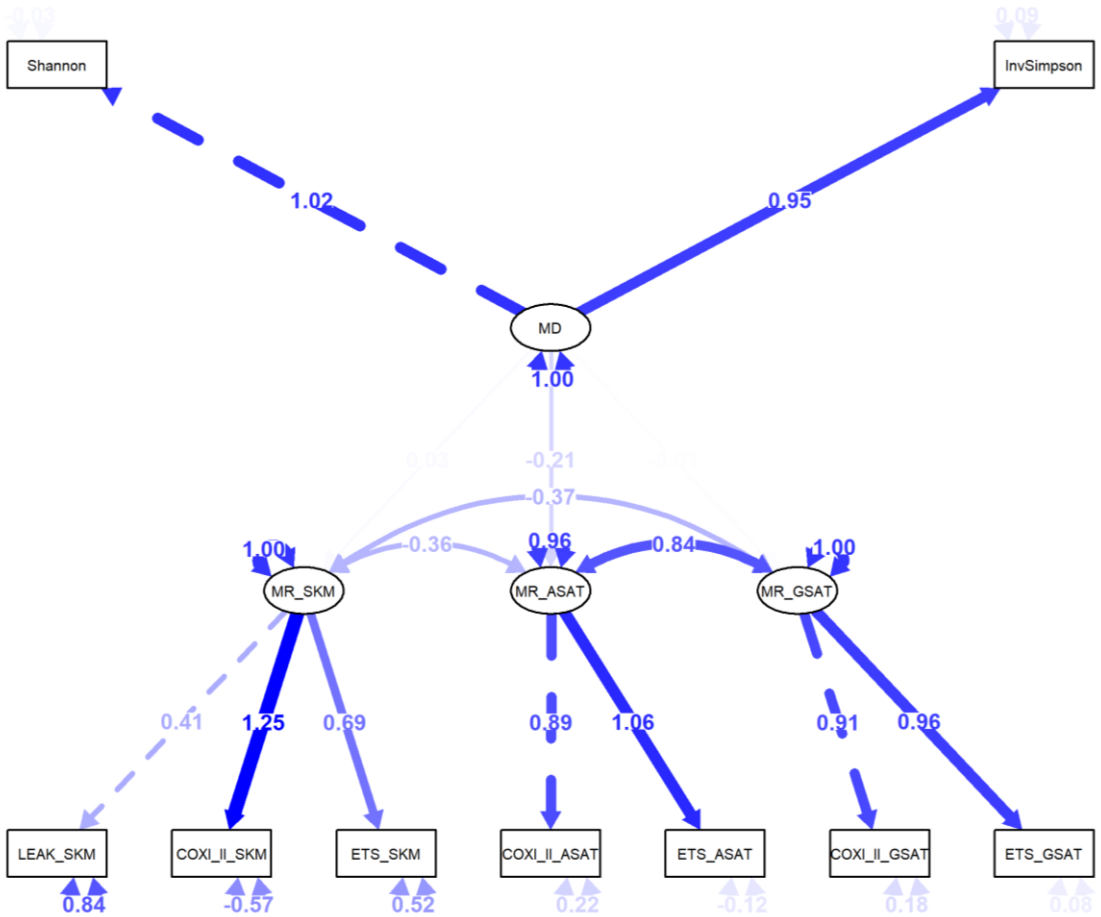
At the genus level, gut microbiota composition differs by HIV status.

E.g., Lower relative abundance of Prevotella and higher abundance of Phocaeicola and Ruminococcus in the HIV-affected group vs. HIV-unaffected group

Figure 3A and B. Taxonomic composition of bacterial genera presented for each participant (A) and by HIV group (B).

RESULTS

HIV-unaffected group negative [CFI = 0.93]



HIV-affected group [CFI = 0.77]

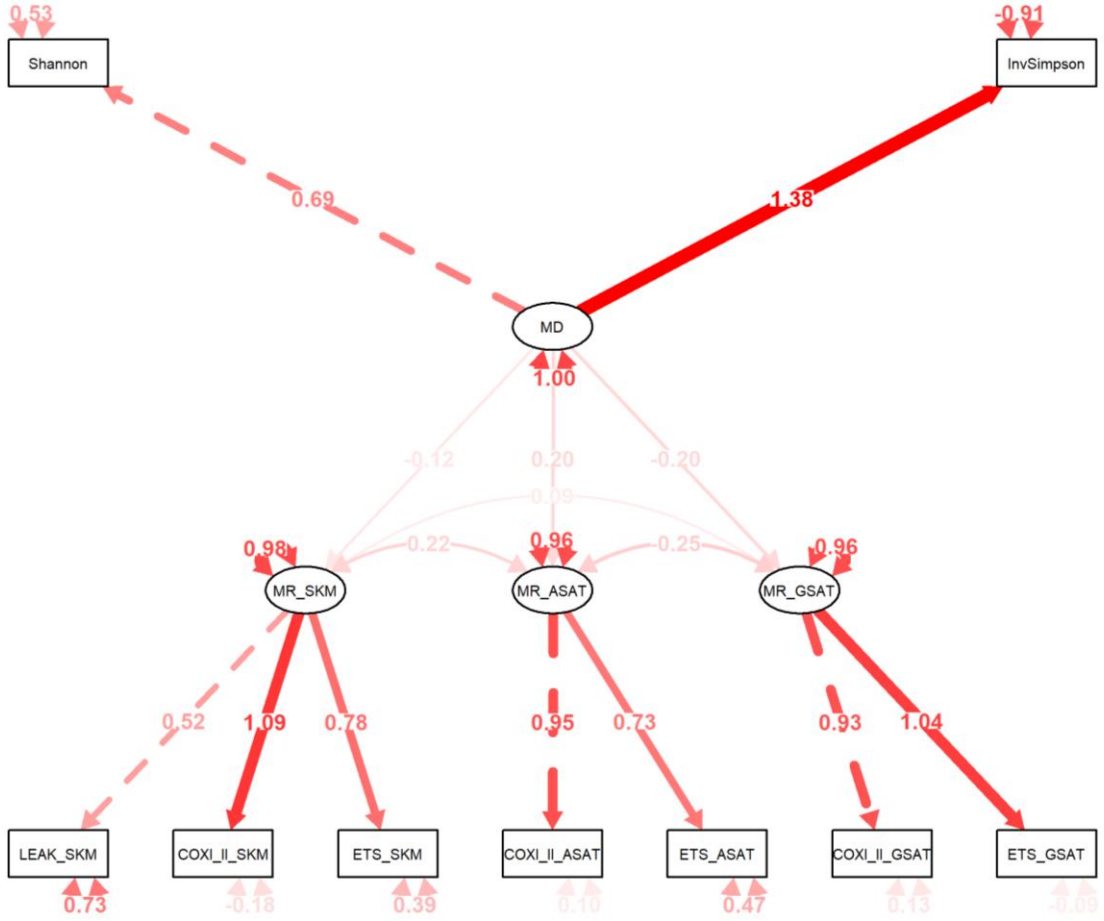


Figure 4. Structural equation models examining the relationship between microbial diversity and mitochondrial respiration in skeletal muscle, aSAT and gSAT, by HIV status. Abbreviations: MD, Microbial diversity; MR_ASAT, Mitochondrial respiration measured in the abdominal subcutaneous adipose tissue; MR_GSAT, Mitochondrial respiration measured in the gluteal subcutaneous adipose tissue; MR_SKM, Mitochondrial respiration measured in the skeletal muscle tissue.

<u>Depending on the HIV status</u>, gut microbiota may negatively or positively influence mitochondrial respiration in the skeletal muscle (SKM), abdominal and gluteal subcutaneous adipose tissues (aSAT and gSAT).

CONCLUSION

- WLWH presented with lower muscle mass and RMR, and a higher aSAT and gSAT mitochondrial respiration states.
- Gut microbiota composition differs within WLWH and WNLWH including bacterial species involved in SCFA production and immune regulation.
- The impact of gut microbiota on mitochondrial function in skeletal muscle, abdominal and gluteal subcutaneous adipose tissues also differs by HIV status.
- Identification of gut microbiota may aid in the management of HIV and the introduction of complementary treatment options (e.g., probiotics) to improve metabolic health in WLWH, especially during the postpartum period.

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