HIV-RELATED MICROBIOME, PREVIOUS IMMUNODEFICIENCY, AND EXCESS METABOLIC RISK

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BACKGROUND

Aims:

- To identify an HIV-related microbiota profile, independent of sexual behavior and demographic confounders.
- To investigate possible associations between the HIV-related microbiota profile and metabolic comorbidities in a large population from the Copenhagen Comorbidity in HIV infection (COCOMO) study.

METHODS

Bacterial 16S ribosomal RNA analyses (V3V4) were performed on stool samples from 405 people living with HIV (PLWH) and 111 uninfected participants of the Copenhagen Comorbidity in HIV infection (COCOMO) study (Table 1). Individuals were stratified according to sexual behavior (men who have sex with men, MSM and non-MSM). Hypotheses were tested using regression models adjusting for known confounders.

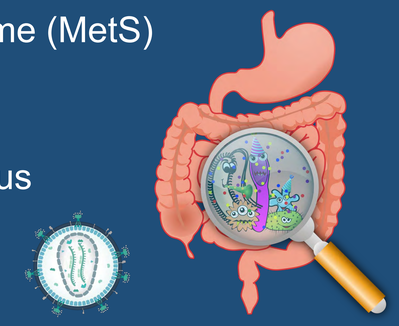
	PLWH MSM n = 281	PLWH non-MSM n = 124	General population n = 68	Uninfected MSM n = 43	*p*
Age, years, mean (SD)	53.2 (11.3)	53.4 (10.4)	60.8 (9.1)	40.1 (9.6)	*< 0.001*
Sex, male n (%)	281 (100)	60 (48.4)	43 (66.2)	43 (100)	*< 0.001*
Smoking status, n (%)					-
Current smoker	78 (27.6)	24 (18.8)	-	-	
Ex-smoker	114 (40.3)	46 (35.9)	-	-	
Never smoker	88 (31.1)	49 (38.3)	-	-	
Origin, n (%)					-
Other	22 (7.9)	34 (27.6)	-	-	
Other EU	37 (13.5)	12 (9.8)	-	-	
Scandinavian	216 (78.5)	77 (62.6)	-	-	
Metabolic syndrome, yes, n (%)	98 (38.9)	33 (32.7)	–	–	-
Lipid lowering therapy, yes, n (%)	46 (17.0)	15 (13.3)	-	-	-
Antidiabetic therapy, yes, n (%)	12 (4.5)	6 (5.4)	–	–	-
Abdominal obesity, yes, n (%)	176 (63.1)	84 (68.9)			-
Physical activity, n (%)					-
Very inactive	13 (4.8)	10 (9.0)	–	–	
Moderately inactive	106 (39.0)	32 (28.8)	–	–	
Moderately active	127 (46.7)	58 (52.3)	–	–	
Very active	26 (9.6)	11 (9.9)	–	–	
Current CD4, mean (SD)	719.9 (281.5)	711.0 (273.8)	-	-	-
Current CD4 < 500, yes, n (%)	57 (20.3)	32 (26.0)	–	–	-
AIDS defining event, yes, n (%)	47 (16.7)	28 (22.6)	-	-	-
cART duration, years, mean (SD)	15.7 (9.3)	15.9 (9.0)	–	–	-
Prior TA and/or ddI, yes, n (%)	163 (58.0)	76 (61.3)	-	-	-
CD4 nadir < 200 cells, yes, n (%)	109 (39.8)	53 (43.4)	–	–	-
Viral load < 50 copies, yes, n (%)	270 (96.1)	116 (94.3)	-	-	-
Receiving cART, yes, n (%)	275 (98.2)	122 (99.2)	–	–	-
Antibiotic use*, yes, n (%)	64 (22.8)	18 (14.5)	5 (7.4)	16 (38.1)	*< 0.001*
PrEP, yes, n (%)	–	–	–	18 (41.9)	-

Table 1. Demographic characteristics of participants. Abbreviations: cART, combination antiretroviral therapy; TA, thymidine analogues; ddI, didanosine; p, p-value; PrEP, pre-exposure prophylaxis *Antibiotic use in the three months prior to stool samples collection.

HIV-related microbiota alterations were associated with:

- Increased risk of metabolic syndrome (MetS)
- Visceral fat accumulation

Particularly in individuals with previous severe immunodeficiency.



Main HIV-related microbiota alterations were:
↑Desulfovibrionaceae, ↓Clostridia

SUMMARY

- HIV infection and MSM status had opposing effects on gut microbiota diversity (Figure 1).
- We identified an HIV-related microbiota index defined by increased relative abundance of Gammaproteobacteria and Desulfovibrionaceae and decrease in several Clostridia (Figure 2).
- One-unit increase in Shannon diversity index was associated with 28 % reduced risk of MetS (aOR 0.72 [0.51; 1.00]).
- The HIV-related microbiota index was associated with a 2-fold increased excess risk of MetS. The association was further accentuated (5-fold excess risk) in individuals with a history of severe immunodeficiency (Figure 3).
- Excess metabolic risk was driven by increased Desulfovibrionaceae, H2S-producing bacteria with toxic effects on the gut epithelium, and lower abundance of potentially butyrate-producing Clostridia.
- In individuals with previous immunodeficiency, HIV-related microbiota index was associated with 30 cm^2 larger visceral adipose tissue (VAT) area [3.1;58.5].

RESULTS

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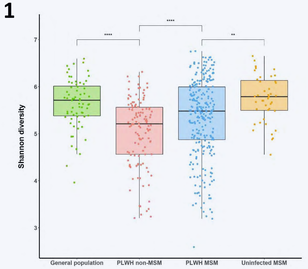
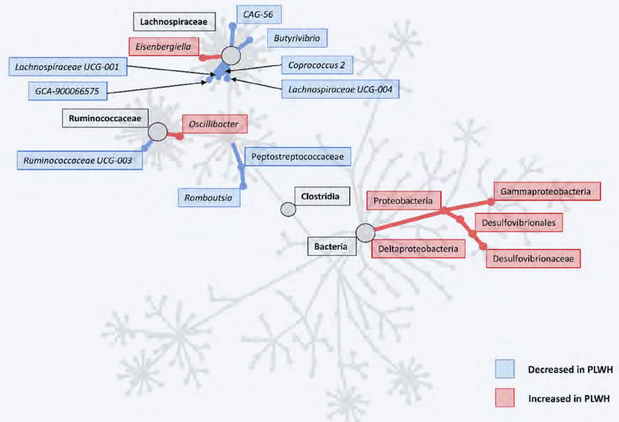


Figure 1. Differences in Shannon diversity index between the four study groups. Shannon diversity index was lower in PLWH MSM than in uninfected MSM, and PLWH non-MSM had lower index than uninfected controls from the general population. The findings were further supported by regression analyses adjusted for relevant confounders (data not shown).

2A



2B

$$\text{Log}_e \frac{\text{Desulfovibrionaceae} + \text{Gammaproteobacteria} + \textit{Eisenbergiella} + \textit{Oscillibacter}}{\textit{CAG-56} + \textit{Butyrivibrio} + \textit{Coprococcus 2} + \textit{Lachnospiraceae UCG-001} + \textit{Lachnospiraceae UCG-004} + \textit{GCA-900066575} + \textit{Ruminococcaceae UCG-003} + \textit{Romboutsia}}$$

Figure 2. Identification of HIV-related microbiota alterations. A) Relative abundance differences of alterations were compared between PLWH MSM and uninfected MSM, and similarly between PLWH non-MSM and uninfected controls from the general population. Differences reproduced in both comparisons were identified as «HIV-related». B) Formula used for defining the HIV-related microbiota index. Calculations were adjusted for MSM behavior, age, sex and antibiotics use in the three months prior to stool sample collection.

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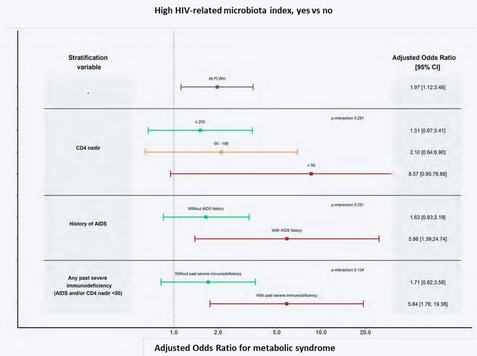


Figure 3. Association of high HIV-related microbiota index (highest quartile) with metabolic syndrome (MetS) before and after stratification according to CD4 nadir, history of AIDS and any past severe immunodeficiency (AIDS and/or CD4 nadir < 50 cells/mL). Confounders included in the base model were age, sex, BMI, smoking, origin, MSM behavior and physical activity. Further adjustment for dietary habits, prior exposure to thymidine analogues (TA) and/or didanosine (ddI) and duration of cART did not affect the association (data not shown).

CONCLUSIONS

- **Our findings suggest a potential interplay between HIV-related dysbiosis, previous immunodeficiency and future risk of metabolic comorbidities.**
- **Interventions targeting the gut microbiome may be warranted to reduce future metabolic risk, particularly in individuals with previous immunodeficiency.**

ADDITIONAL KEY INFORMATION

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