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Agrarian Dietary Matching to Prevotella-Rich Bacteroides-Poor Microbiomes Reduces Immune Activation and Metabolic Outcomes in People Living with HIV

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Background

- People living with HIV (PLWH) suffer from increased incidence of metabolic disease and chronic systemic inflammation, even with effective antiretroviral therapy[1]
- *Prevotella*-rich, *Bacteroides*-poor (PRBP) microbiomes are commonly found in men who have sex with men (MSM), which make up a large portion of PLWH in the US[2,3]

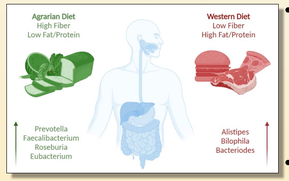


Figure 1: Schematic of Dietary Microbiome Matching Western diets high in fat and agrarian diets high in fiber select for different gut microbes and can result in differential health responses depending on the established gut microbiome

- High-fiber agrarian diet (AD) has been found to be metabolically beneficial in PRBP microbiomes also seen in agrarian populations[4,5]
- AD has been found to be metabolically beneficial in PRBP microbiomes also seen in agrarian populations[6]
- High-fat western diet (WD) can exacerbate disease in HIV animal models[7]
- AD have potential for metabolic benefit in HIV positive MSM (HIV(+)MSM)
- We sought to understand the effects of a 4-week AD intervention in HIV(+)MSM compared to control groups

Methods

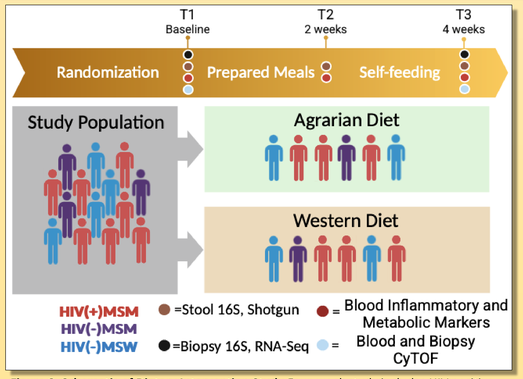


Figure 2: Schematic of Dietary Intervention Study Four-week study includes HIV positive and HIV negative individuals randomized to a high-fiber agrarian diet (AD) or a high fat western diet (WD) with data collected at baseline (T1), 2 weeks (T2), and 4 weeks (T3)

Results

Cohort	HIV(+)MSM	HIV(-)MSM	HIV(-)MSW
Sample Number	36	21	9
Age	46.03 (33.11-54.57)	39.57 (30.24-46.96)	29.38 (24.07-34.57)
BMI	25.90 (23.30-28.40)	25.60 (24.00-27.00)	26.30 (25.60-27.00)
Diet			
Agrarian	18 (50.0%)	13 (61.9%)	4 (44.4%)
Western	18 (50.0%)	8 (38.1%)	5 (55.6%)
Metabolic Markers			
HDL-C (mg/dL)	40.00 (34.50-52.00)	49.00 (39.00-55.00)	42.00 (34.00-48.00)
LDL-C (mg/dL)	102.00 (83.00-117.50)	94.00 (78.00-121.00)	80.00 (72.00-112.00)
Triglycerides (mg/dL)	119.00 (93.00-203.00)	83.00 (63.00-181.00)	99.00 (84.00-130.00)
HOMA-IR	1.44 (0.78-2.32)	0.92 (0.76-2.53)	1.06 (0.64-1.17)
Inflammatory Markers			
LBP (µg/µL)	34.96 (33.03-36.54)	35.6 (33.73-36.64)	35.03 (32.03-35.58)
IL-6 (pg/mL))	3.95 (1.91-5.50)	2.81 (1.73-3.41)	2.75 (2.32-8.02)
CRP (mg/L)	3.21 (2.3-5.22)	2.68 (1.95-4.07)	2.39 (1.22-3.42)

Table 1: Study Population Comparable at Baseline : Baseline data split by HIV and MSM status with data presented as *n*, median (IQE) or n (%), unless otherwise stated. BMI: body mass index; LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, LBP=lipopolysaccharide binding protein, HOMA-IR=Homeostatic Model Assessment for Insulin Resistance, IL-6=Interleukin-6, CRP=C-reactive protein.

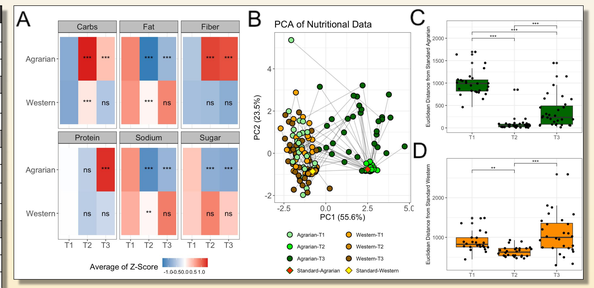


Figure 3: Dietary Intake Changes Greater on AD (A) Heatmap of dietary components at T1,T2, and T3 for individuals split by diet and colored using the average log-midpoint transformed values for macronutrients normalized to 1000 kcals. Significance determined by Friedman test from tT with a Bonferroni correction for multiple comparisons (B) Principal Component Analysis (PCA) plot of Euclidean distances between macronutrient totals colored by diet intervention arm, and timepoint. The target macronutrient compositions (averages of T2) are also plotted as "Standard-Agrarian" and "Standard-Western"; Distances from the standard target diet for those on (C) AD and (D) WD with brackets indicating statistics determined by Wilcoxon-signed rank test *-p< 0.05, **-p< 0.01), ***-p< 0.001.

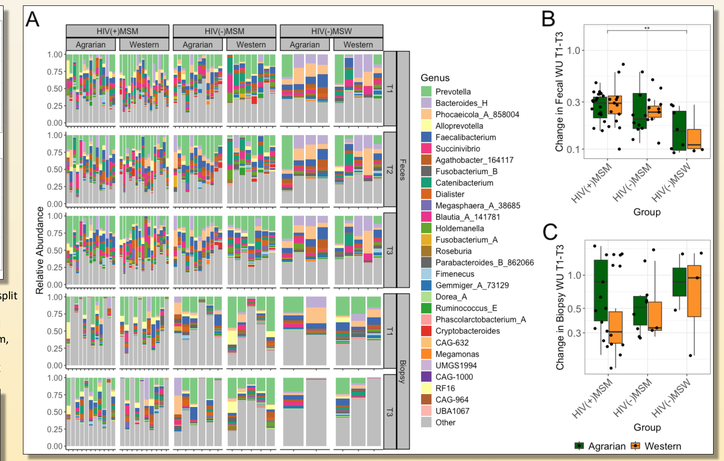


Figure 4: No Changes in Fecal or Biopsy Genera Observed (A) Stacked barplots of 28 most abundant genera identified by 16S rRNA sequencing in fecal and biopsy samples stratified by cohort and diet (columns) as well as sample type and timepoint (rows)l (B and C) Box plots of changes in Weighted UniFrac distances from T1 to T3 separated by cohort and colored by diet in (B) fecal samples and (C) biopsy samples with brackets indicating significance as determined by Kruskal Wallace with Dunn's post hoc test and Bonferroni correction ; *-p≤0.05, **-p≤0.01

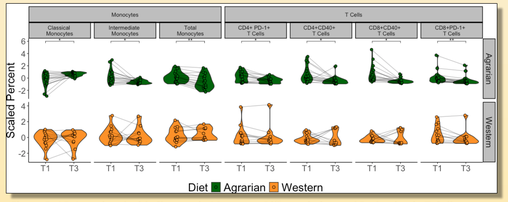


Figure 5: AD Associated with Changes in Monocyte Differentiation and Reduction in T-Cell Exhaustion Violin plots overlaid with spaghetti plots of immune cell populations that changed on the AD colored by diet and separated by cohort with brackets indicating significance as determined by Friedman tests with Bonferroni multiple comparisons correction; *-p≤0.05, **-p≤0.01

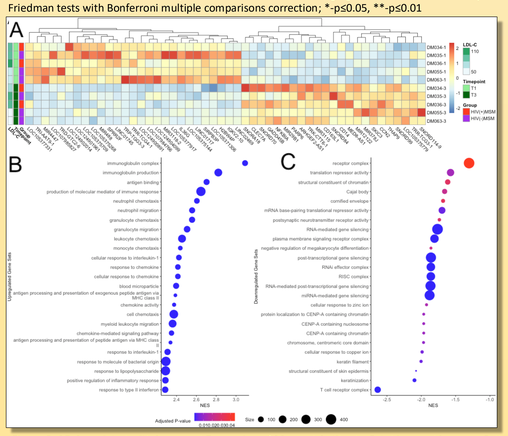


Figure 6: AD Associated with Increased Expression of Mucosal Antibody, Cytokine, and Immune Cell Trafficking Genes (A) Heatmap of most differentially expressed genes from RNA sequencing of colonic biopsies from HIV(+) and HIV(-)MSM on AD, (B and C) Gene set enrichment results of most (A) upregulated gene sets and (B) downregulated gene sets in RNA Sequencing of Colonic Biopsies

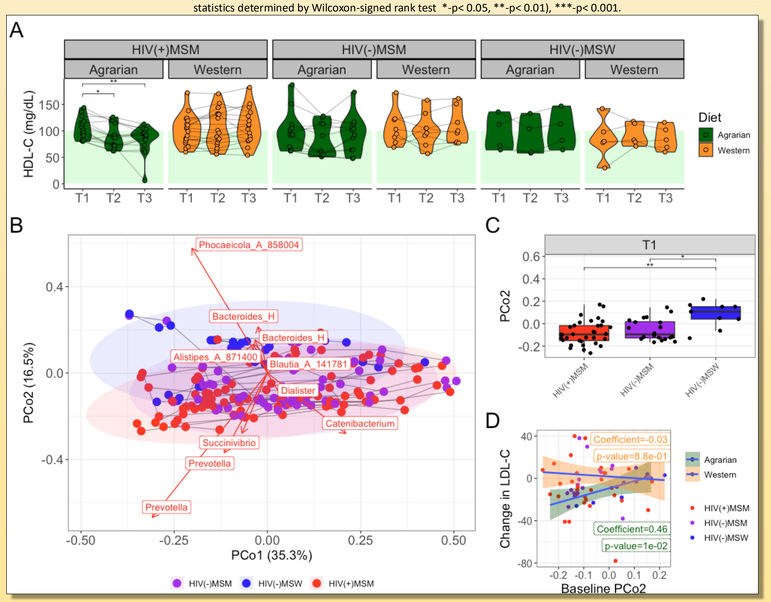


Figure 7: AD-associated HDL-C Reduction in HIV(+)MSM is associated with Baseline PRBP Microbiomes (A) Violin plots overlaid with spaghetti plots of low density lipoprotein cholesterol (HDL-C) colored by diet and separated by cohort with brackets indicating significance as determined by Friedman tests with Bonferroni multiple comparisons correction (B) Weighted UniFrac biplot of fecal 16S data with 10 taxa contributing most to the variation displayed and points and 95% confidence ellipses colored by cohort and segments connecting samples from the same subject (C) Boxplot of baseline principal with brackets across cohorts with brackets indicating significance as determined by Kruskal Wallace with Dunn's post hoc tets and Bonferroni correction ; *-p≤0.05, **-p≤0.01, (D) Scatter plot of change in LDL-C versus Baseline Principal Coordinate Axis 2, with points colored by cohort and linear regressions colored by diet and text indicate Spearman correlations and p-values

Conclusions

- Despite dramatic dietary changes from baseline, an AD did not significantly alter gut microbiome structure in this 4-week intervention
- While AD altered monocyte differentiation and reduced CD40+ and PD-1+ T cells across all groups, LDL-C reduction was specific to HIV(+)MSM
- AD-associated LDL-C reduction appeared to be correlated with *Prevotella* richness and depletion of *Bacteroides*
- Our findings suggest that matching PRBP microbiomes to an AD has the power to reduce dyslipidemia in PLWH, providing clinical utility in HIV-associated metabolic disease

References:

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