CONTRACEPTIVE USE INDUCES DURABLE SHIFTS IN THE FEMALE GENITAL-TRACT MICROBIOTA

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BACKGROUND

Vaginal bacterial microbiota modulate genital immunity and susceptibility to HIV and other sexually transmitted pathogens. However, it is unclear how contraceptive use affects the composition and dynamics of these communities.

METHODS

Within the ECHO trial, designed to compare the relative HIV-1 incidence among women randomized to copper intrauterine device (Cu-IUD), levonorgestrel implant (LNG-implant), or DMPA-IM, this nested sub-study aimed to evaluate the impact of these contraceptives on genital tract microbiota. 218 were randomly selected from among the 430 in the sub-study.

Women co-enrolling in ECHO and ECHO BioMech studies at the Cape Town (Ema), Johannesburg (WITS), and Kisumu (KEMRI) sites

Randomized (1:1:1 ratio)

DMPA-IM (~66 women)	LNG Implant (~66 women)	Cu- IUD (~66 women)

Time points: Enrollment (pre-contraception), month-1, and month-6 (post contraception)

Approach: V3-V4 16S rRNA gene sequenced using 300bp PE chemistry on Illumina MiSeq from lateral vaginal wall swabs

RESULTS

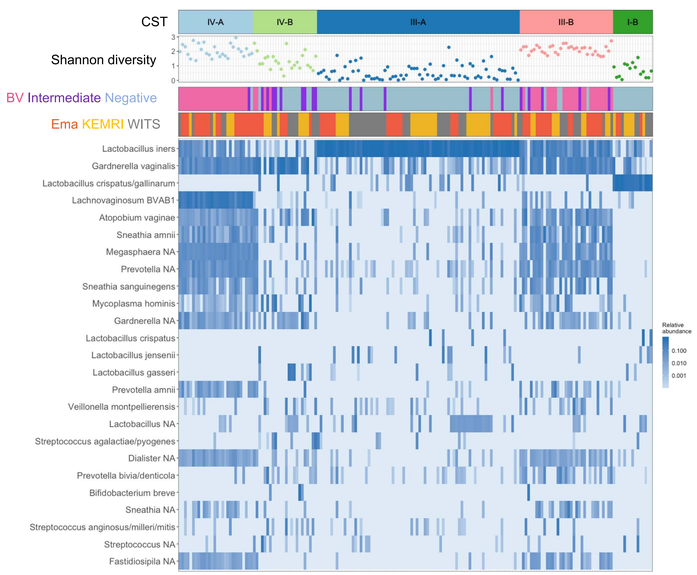

Figure 1. Relative abundance heatmap of the top 25 taxa across all participants (n=218) at baseline. Community state type (CST), Shannon diversity, clinical BV status, and study site are indicated above the heatmap.

Cu-IUD elicits increases in overall bacterial diversity and abundance of dysbiotic taxa relative to DMPA-IM and LNG-Implant, suggesting that non-hormonal IUDs may have consequences on vaginal microbiota. These results are central to informing contraceptive options for sexual and reproductive health.

RESULTS, continued

- Longitudinally, only Cu-IUD caused significant elevations in alpha diversity after one month of use (Chao1: Wilcoxon P = 0.038, Shannon: Wilcoxon P = 0.062; Figure 2A) and after six months of use (Chao1: Wilcoxon P = 0.029, Shannon: Wilcoxon P = 0.017; Figure 2A).
- Cross-sectionally, participants randomized to Cu-IUD displayed significantly elevated bacterial diversity compared to those using DMPA-IM after six months (Chao1: Wilcoxon P = 0.0098, Shannon: Wilcoxon P = 0.0078; Figure 2B).
- Randomization arm had a significant effect on inter-community distance (Bray-Curtis) after one (PERMANOVA P = 0.024, pseudo F = 2.14; PERMDISPERSION P = 0.054, pseudo F = 2.9) and six months of use (PERMANOVA P = 0.006, pseudo F = 2.9; PERMDISPERSION P = 0.759, pseudo F = 0.3; Figure 3).

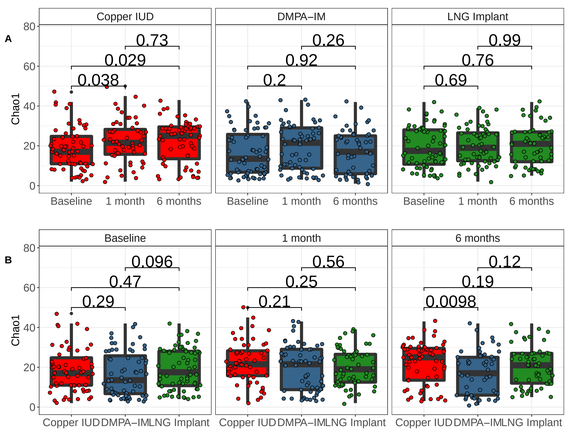

Figure 2. Chao1 diversity boxplots across 218 participants. A. Longitudinal comparisons. B. Cross-sectional comparisons. P values were calculated using a Wilcoxon rank sum test.

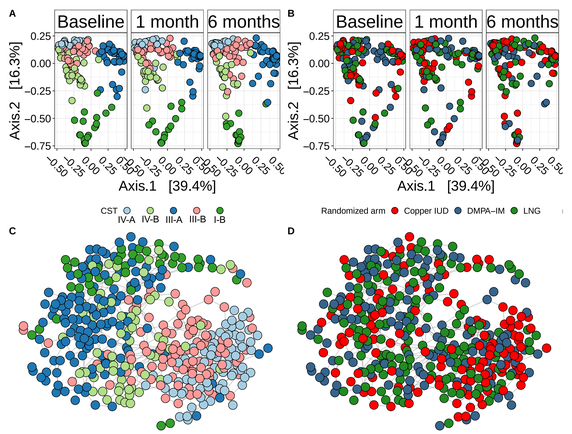

Figure 3. Inter community distance is shaped by contraceptive use. A. PCoA ordination of relative abundance transformed taxonomic abundance using Bray-Curtis distance colored by CST. B. Ordination from subfigure A colored by randomization arm. C. Network analysis of samples visualized using a Bayesian directed acyclic graph (DAG) colored by CST. D. DAG colored by randomization arm. DAGs were generated using Euclidean distance on centered log ratio transformed taxonomic abundance.

RESULTS, continued again

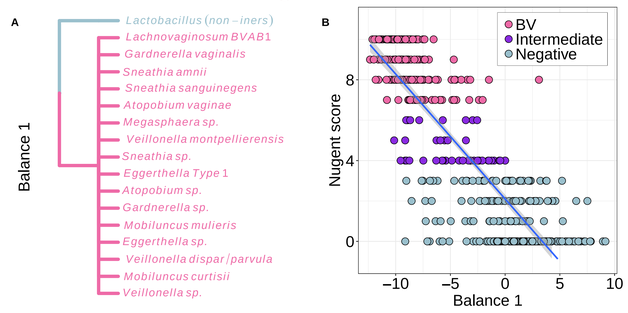

Figure 4. Balance 1 correlates strongly with clinical BV status. A. The taxonomic composition of bacteria included in the numerator (blue) and denominator (pink) of Balance 1 (an isometric log ratio). Positive values indicates a greater ratio of taxa in the numerator as compared to the denominator. B. Balance 1 strongly correlates with clinical BV diagnosis (Nugent).

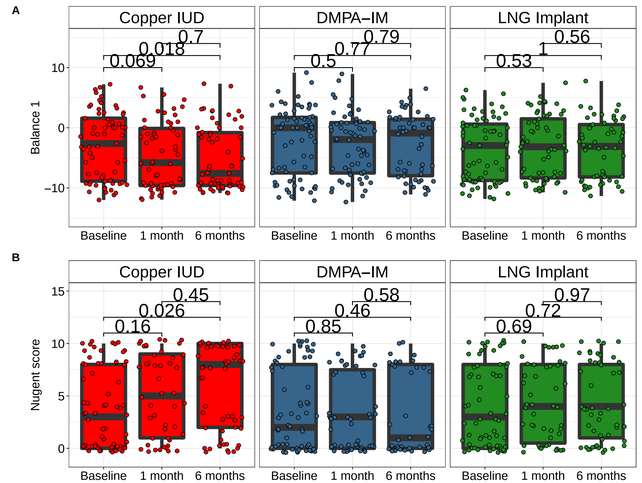

Figure 5. Copper IUD significantly reduces a participant's Balance 1 value and increases Nugent score. A. Longitudinal comparisons of Balance 1 values by randomization arm. B. Longitudinal comparisons of clinical Nugent scores by randomization arm. P values were calculated using a Wilcoxon rank sum test.

CONCLUSIONS

These are the first data comparing vaginal bacteria among women randomized to effective contraceptives. That Cu-IUD elicits increases in overall bacterial diversity and abundance of dysbiotic taxa relative to DMPA-IM and LNG-Implant suggests that non-hormonal IUDs may have consequences on vaginal microbiota. These results are central to informing contraceptive options for sexual and reproductive health.

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