

Impact of maternal HIV infection on the dynamics of the infant microbiota in the first eighteen months of life

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Abstract

Background: Improved access to anti-retroviral therapy (ART) for HIV-infected mothers during pregnancy has resulted in fewer children acquiring HIV peri- and postnatally, which has in turn led to an increase in the number of children who are exposed to the virus but are not infected (HEU). HEU infants have an increased likelihood of childhood infections and adverse growth outcomes, as well as increased mortality compared to their HIV-unexposed (HUU) peers.

Methods: Three hundred mother-infant-pairs were followed prenatally to 18 months postpartum (seven time points). Demographic, clinical, feeding, anthropometric and microbiome data were collected at each visit. Demographic and clinical characteristics were compared between HEU and HUU children and their mothers using Wilcoxon, Fisher's exact and t tests. Longitudinal comparisons of alpha diversity were performed using univariable and multivariable linear regression. Multivariate association with linear models (MaAsLin2) was used to efficiently determine multivariable association between clinical metadata and microbial meta'omic features. The metabolite levels were compared using two-way repeated measures ANOVA.

Results: We observed differences in the composition of maternal stool, vaginal and breast milk microbiota based on HIV status that were associated with differences in the oral and gut microbiota of HEU vs. HUU infants. Our data also demonstrated that the taxonomic composition of the infant gut microbiota differs between HEU and HUU infants for at least 15 months. Several significant correlations were found between breast milk metabolites from HIV-infected and uninfected mothers and bacterial taxa in the infant gut microbiota. Lamivudine, an ART drug, was present at high concentrations in the breast milk of our HIV-infected mothers, and we observed a significant negative correlation between lamivudine levels and the relative abundance of *Bifidobacterium breve* in HEU infants' gut. The presence of ART drugs in the breast milk of our HIV-infected mothers also correlated with an underweight growth outcome in their infants.

Conclusions: Our data suggest that acquisition of an altered gut microbiota from an HIV-infected mother, further exacerbated by differences in breast milk composition between HIV- infected and uninfected mothers, negatively impacts growth and increases the risk of adverse clinical outcomes among HEU.

Full Text

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Figures

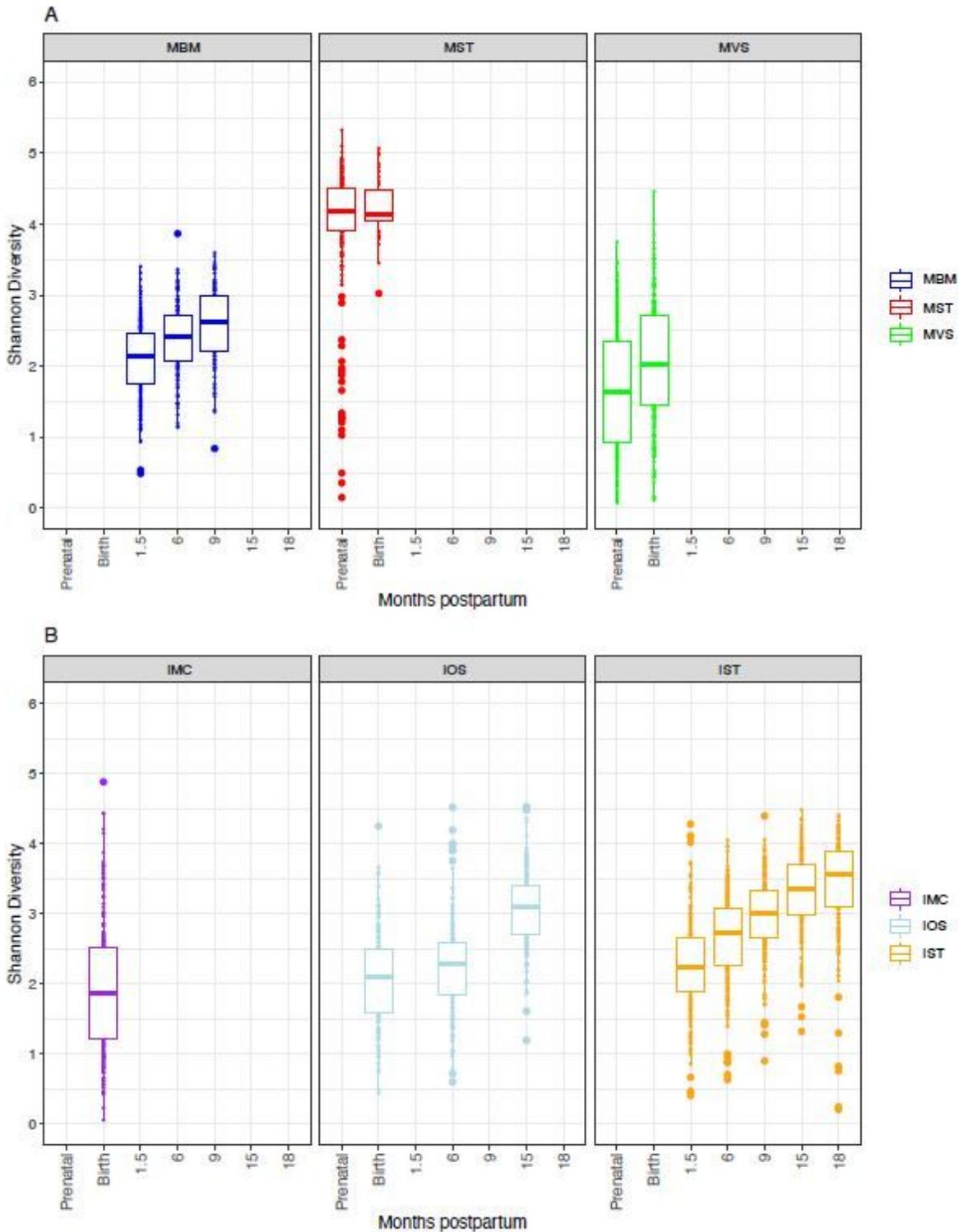


Figure 1

Alpha diversity (Shannon index) for each sample type and timepoint. (A) Maternal breast milk (MBM) samples exhibited a significant increase in microbial diversity from six weeks to 9 months postpartum (Shannon index, $P < 0.001$), maternal stool (MST) microbiome diversity was unchanged (Shannon index, $P = 0.138$) and maternal vaginal (MVS) microbiome diversity significantly increased after birth (Shannon index, $P < 0.001$). (B) Infant meconium (IMC) and infant stool (IST) microbiome diversity, as well as infant

oral (IOS) microbiome diversity displayed significant increases from birth to 15 or 18 months postpartum, respectively (Shannon index, both $P < 0.001$).

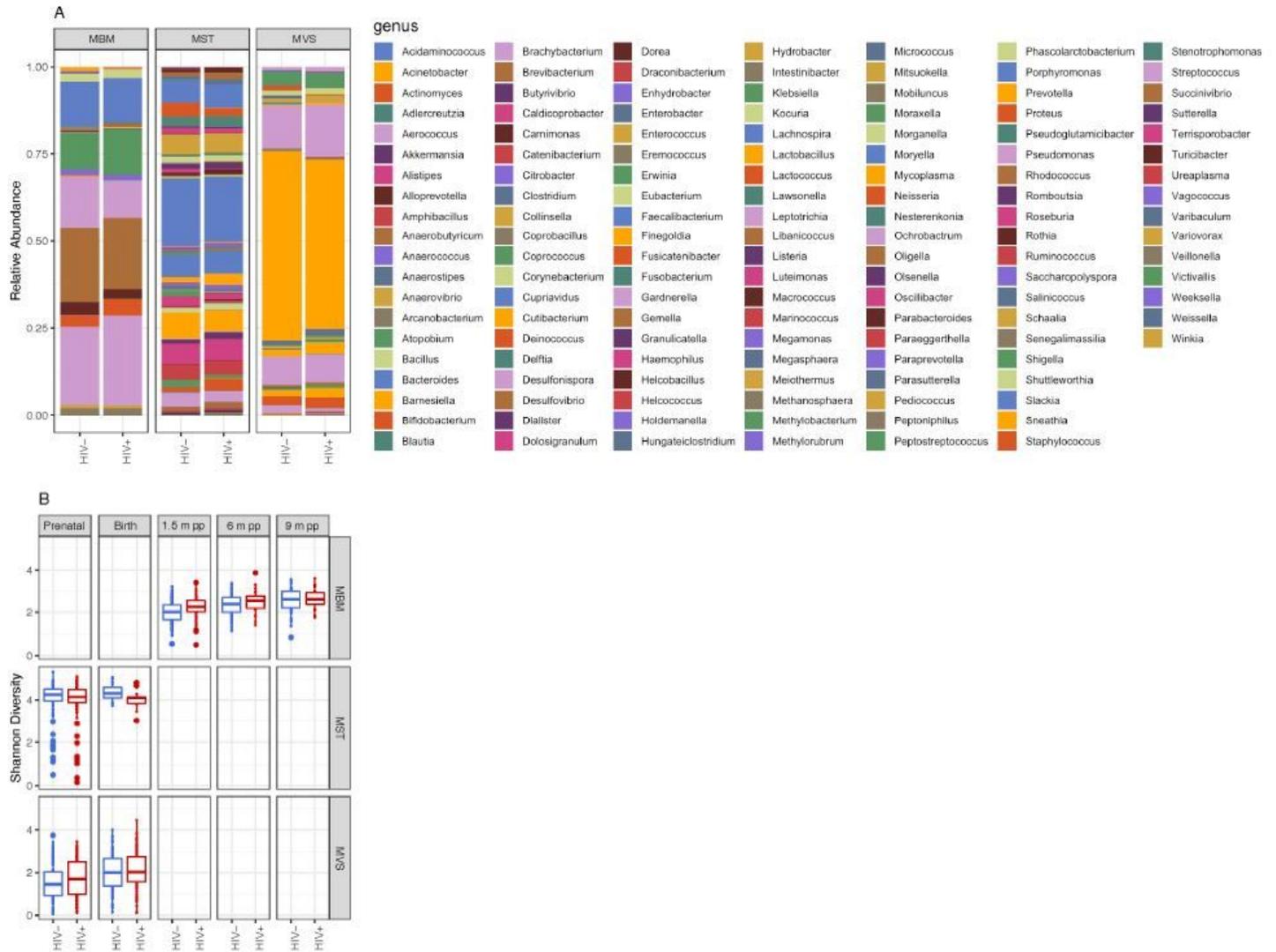


Figure 2

Maternal microbiome composition showed differences based on HIV status. (A) Bacterial compositions across maternal sample types (MBM: maternal breast milk, MST: maternal stool, MVS: maternal vaginal swab) for HIV-infected (HIV+) and HIV-uninfected (HIV-) mothers at the taxonomic level of genus (only genera with >2% relative abundance are shown). (B) Alpha diversity (Shannon index) for each sample type (MBM: maternal breast milk, MST: maternal stool, MVS: maternal vaginal swab) based on the mothers' HIV status (HIV+: HIV- infected, HIV-: HIV-uninfected) at five consecutive timepoints (prenatal, birth, 1.5, 6 and 9 months (m) postpartum (pp)).

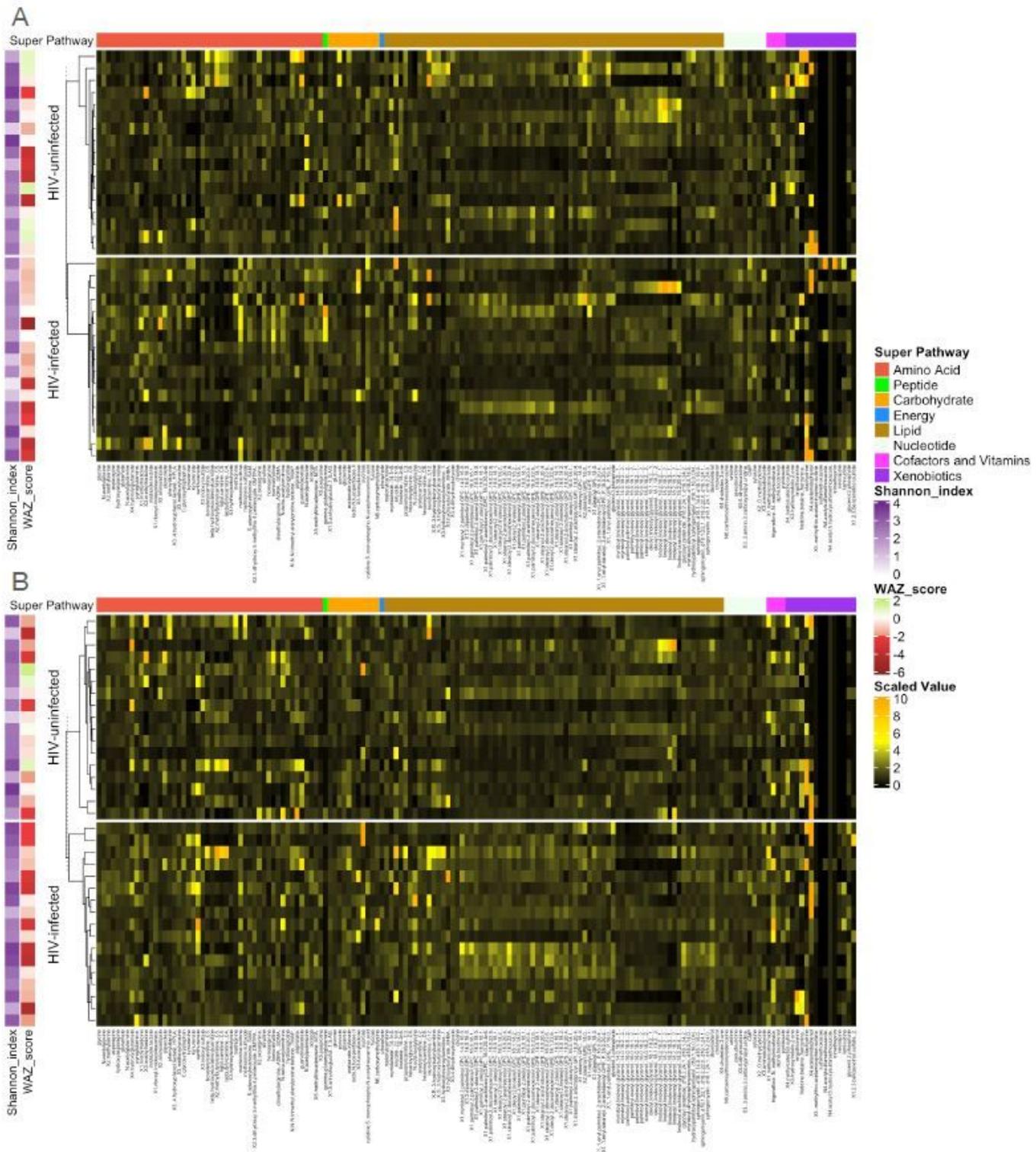


Figure 4

Breast milk composition of HIV-infected mothers is different from HIV-uninfected mothers. 161 breast milk metabolites exhibited a trend/significance towards either a higher or lower expression in mothers with or without HIV infection at six weeks (A) and/or six months (B) postpartum. Stool alpha diversity (Shannon index) and weight-for-age z-score for the mothers' infants are shown to the left of the heatmaps for the respective timepoints.

Supplementary Files

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- [MARGINSupplementaryMaterials03.15.21.pdf](#)