**MICROBIAL TRANSLOCATION, IMMUNE ACTIVATION, AND GUT DYSBIOSIS IN HIV-EXPOSED INFANTS (the MITABs study).**

Charles D. Mitchell1, Sady Dominguez2, Varghese George3, Stefano Rinaldi4, Eddy Peres-Then5, Carlos V. Castillo6, Juan L. Santana-Guerrero7, Jeannette Baez7, Margaret Roach8, David Ludwig9, William Walters9, Qiannot Shj10, Ruth Ley8, Savita Pahwa1

1University of Miami, Miami, FL, USA, 2O&M School of Medicine, Santo Domingo, Dominican Republic, 3Robert Reid Children’s Hospital, Santo Domingo, Dominican Republic, 4Max Planck Institute for Developmental Biology, Tübingen, Germany, 5Cornell University, Ithaca, NY, USA

Abstract:

Introduction: The MITABs study (Microbial Translocation[MT], Immune Activation[IA], and Altered Bowel Flora Study[ABSS]) is the first prospective, longitudinal study assigned to simultaneously assess MT, IA, and alterations in the gut microbiome with clinical events in young (enrolled at <6 months) HIV perinatally infected (HEI), and perinatally exposed, uninfected(HEU) infants in the Dominican Republic (DR) before and after starting antiretroviral therapy(ART).

Methods: Cellular immune markers of IA (HLA-DR+CD38+ coexpression) in CD4 and CD8 T cell compartments were determined by flow cytometry using the method of Hanekom et al., J Immune Meth, 2004. Plasma MT (LPS, sCD14 and sCD163) were measured by standard assays. Metagenomic analysis was performed on both stool and plasma. Simultaneous assessments of MT, IA, ABS, and clinical events occurred at Entry and 6 weeks and 6 months post entry. No HEI was on ART at entry. HIV-exposed infants in the DR are formula fed. Results: Between 6/6/13 and 3/17, 78 infants (31 HEI-47 HEU) were enrolled in the DR. Median age at entry for 78, the HEI were 106, 145, and 89 days respectively. 19/31 HEI started ART. 10/31 developed AIDS (CD4 criteria); whom died. No statistically significant difference of HEU to HEI was noted for the clinical events that occurred at each visit. Data analysis was performed by both visit number and age grouping. No HEI was on ART at entry. HIV-infected infants in the HEI group demonstrated a higher frequency of CD8+ T cells and increased plasma iFABP, 165/300 vs HEU 756 pg/ml. On follow-up 6 months, both CD4+ (94 vs 71, p<0.001) and lower CD4/CD8 ratio (0.33 vs 0.29). HEU also had a high trend for sCD163 (1470 pg/ml, p<0.001), and a trend for higher sCD163 (1212 vs 932 ng/ml, p=0.06) but surprisingly, the 2 groups had similarly elevated markers of MT (LPS, HEI 250 vs HEU 245pg/ml; FABP 265 vs HEU 275 pg/ml). On prospective follow up MT markers (LPS, sCD163) in HEU normalized by 6 months. 10 cell counts were all within the normal range in HEU over time. HEI, although the MT values decreased following ART, they were higher than in HEU. HEI gut microbiome was associated with lower diversity (Richness, LDA). HEU (n=38), and an unknown member of the Megaspheara genus was enriched in HEI on ART compared to HEI on ART. Conclusions: HEU infants like HEI have high gut permeability during early infancy which gradually normalizes over time. Increased biomarkers of MT and IA in HEI are prevalent from early infancy and persist after starting ART. HEI have a less diverse microbiome than HEU, with enrichment of the genus Megaspheara in HEU on ART.

Background:

Chronic inflammation is the primary driver of HIV disease progression. Within the last dozen years, Microbial Translocation [MT] has been recognized as a major contributor to the chronic immune activation. MT occurs in SIV-infected macaques and both HIV-infected adults and children but most of the data collected to date has been retrospective in nature. The MITABs (Microbial Translocation[MT], Immune Activation[IA], and Altered Bowel Flora Study[ABSS]) was designed as a prospective, longitudinal study designed to assess MT, IA, and alterations in the gut microbiome with clinical events among HIV-perinatally exposed Dominican infants and children in Santo Domingo, the Dominican Republic. The Specific Aims were as follows:

1. Specific Aims: Determine whether the persistently increased cell surface markers(CD8+CD38+, CD8+DR+, and CD8+CD38+CD8+T cell subpopulations) of immune activation on CD8 lymphocytes correlate on longitudinal testing with increased plasma levels of biomarkers of microbial translocation (Lipopolysaccharide[LPS], sCD14, sCD163, and IFAP ) among prospectively followed, young, newly diagnosed HIV infected infants when compared with perinatally exposed, uninfected infant controls. Determine whether perinatal HIV infection is associated with a consistent shift in the microbial community diversity and composition of the gut microbiome (enteric flora) in exposed infants infected with a variety of bacterial pathogens in various stages of their HIV disease relative to perinatally exposed but uninfected children.

Conclusions:

1. HEU infants like HEI have high gut permeability during early infancy which gradually normalizes over time.
2. Increased biomarkers of MT and IA in HEI are prevalent from early infancy, which sharply decreases after starting ART.
3. HEI have a less diverse microbiome than HEU, with enrichment of the genus Megaspheara in HEU on ART.

Acknowledgements

NAID ROI Microbial Translocation and Alterations in Gut Microbiomes in HIV Infected Infants (U54 AI109025), PI: Charles D. Mitchell, funded by a grant (5R02AI57391) from the National Institutes of Health (NIH), PI: Savita Pahwa.