Abstract

Introduction: The MTABs study (Microbial Translocation[MT], Immune Activation[IA], and Altered Bowel Flora Study[ABS]) is the first prospective, longitudinal study designed to simultaneously assess, in infants, 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 cells were determined by flow cytometry using the method of Hanekom et al, J. Immunol, 2004. Plasma MT, IA, sCD14 and sCD163 were assessed by standard assays. Metagenomic analysis was performed on both stool and plasma. Simultaneous assessments of MT, IA, ABS, and clinical events occurred at each visit. HIV-infected and uninfected HEU infants were recruited in the Dominican Republic (DR) before and after starting antiretroviral therapy (ART). Infants were enrolled by 6 months of age (Baseline/entry visit; postnatal age<145 days) and were followed 6 months post entry. No HEI was on ART at entry. HIV-exposed infants in the DR are formula fed.

Results: Between 66/13 and 3/1/17, 78 infants (31 HEI, 47 HEU) were enrolled in the DR. Median ages at entry for 78, the HEI were 16, 145, and 89 days respectively. 19/31 HEI started ART. 10/31 developed AIDS (CD4 criteria). Aims of the study was to determine whether HEI had higher gut T cell activation (IA, CD8-CD38+) compared to HEU (38), and an unknown of the Megaspheara genus was enriched in HEI on ART compared to HEU. (IA, HEU). HEI had 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. HEU 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 this 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 MTABs (Microbial Translocation[MT], Immune Activation[IA], and Altered Bowel Flora Study[ABS]) study 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 Dominicans infants and children in Santo Domingo, the Dominican Republic. The Specific Aims were as follows: Specific Aim 1. Determine whether the persistent increased cell surface markers (CD8+CD38+, CD8+DR+, and CD8+CD38+DR+ T cell subpopulations) of immune activation on CD8 lymphocytes correlate on longitudinal testing with increased plasma levels of biomarkers of microbial translocation (Lipopolysaccharide[LPS], CD14, sCD163, and IFABP) among peripatently infected, young, newly diagnosed HIV perinatally infected infants when compared with perinatally exposed, uninfected infants. Specific Aim 2. Determine whether perinatal HIV infection is associated with a consistent shift in the microbial community diversity and composition of the gut microbiome (enteric, gut, and enteric) in infected infants, compared to non-infected infants, at various stages of their HIV disease relative to perinatally exposed but uninfected children.

Methods: Prospective Observational Study that simultaneously assessed cellular immune activation, microbial translocation, and alterations in the intestinal microbiome 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). Infants were enrolled by 6 months of age (Baseline/entry visit; postnatal age < 145 days) and were followed 6 months post entry. No HEI was on ART at entry. HIV-exposed infants in the DR are formula fed. Plasma MT, IA, sCD14 and sCD163 were assessed by standard assays. Metagenomic analysis was performed on both stool and plasma. Simultaneous assessments of MT, IA, ABS, and clinical events occurred at each visit. HIV-infected and uninfected HEU infants were recruited in the Dominican Republic (DR) before and after starting antiretroviral therapy (ART). Infants were enrolled by 6 months of age (Baseline/entry visit; postnatal age < 145 days) and were followed 6 months post entry. No HEI was on ART at entry. HIV-exposed infants in the DR are formula fed.

Results: Between 66/13 and 3/1/17, 78 infants HIV-perinatally exposed infants were enrolled in the DR; 30 were perinatally infected (HEI); while 48 were perinatally exposed and infected (HEU). The mean and median age at entry for 30 HEI were 181±103 and 145 days while the mean and median age for 48 HEU were 109±32 and 89 days respectively. There was no difference in gender between the Cases and the Controls (HEI: 56.7% female; HEU: 58.3% female). Eighty-eight-five % of the Cases (and Controls were WH [Dominican] while the rest were Black (Hispanic).

Conclusion: IA showed a strong perturbation of the T cells markers with low frequency of CD8+T cells and high frequency of CD8+ of which a higher proportion is immune activated (HLA-DR+CD38+) after ART.

Beta Diversity Analyses of HEI and HEU subjects

Microbiome Volatility Analyses

We observed a higher volatility (beta-diversity distances between time points) in HEI vs HEU, but no significant differences which can be an indicator for microbial dysbiosis, however this was not significant.

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