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Sommario	ROLE OF CART ON GUT MICROBIAL DYSBIOSIS, STUDYING THE GUT/BLOOD MICROBIOTA DURING THE FIRST TWO YEARS OF SUPPRESSIVE CART BACKGROUND Microbial dysbiosis features HIV+ individuals, both naïve and cART-treated, and is linked to anatomical/structural changes in the gastrointestinal (GI) tract, leading to microbial translocation (MT) and immune activation. Given that data on microbiota modifications during long-term therapy are lacking, we investigated gut/blood microbiota during the first 2 years of suppressive cART. METHODS We enrolled 138 HIV+ subjects. Plasma was collected at baseline (T0) and following 12 (T12) and 24 months (T24) of cART. CD8+ T-cell activation (CD38+; CD38+CD45R0+), MT (sCD14 and EndocAb) and GI damage (IFAB-P) were studied. In a sub-group of 41 patients (pts) we also evaluated GI permeability (urinary LAC/MAN test), inflammation (faecal calprotectin), 16SDNA (MT marker) and gut persistence score, metagenomic function analysis (Picrust) as well as peripheral and faecal microbiota (DNA extraction and 16S Metagenomic Sequencing; MiSeq Illumina®). For the microbiota analyses we enrolled 15 HIV- subjects as controls. All groups were analysed by Wilcoxon test, Kruskal-Wallis test and Permanova analysis. RESULTS

88% were male, 65% MSM, 6% HCV+; median age, CD4+ count, HIV RNA and duration of infection were respectively 38 years, 312/mmc, 5.03 log10cp/mL and 11.5 months. Following cART we registered a reduction of activated and activated/memory CD+8 T-cells (both with p<0.0001), an increase of EndoCab levels (p<0.0001) yet no significant changes in plasma sCD14. In contrast, an increase of I-FABP (p<0.0001) vis- à -vis a reduction of LAC/MAN test (p=0.03) and faecal calprotectin (p=0.01) were found. In faeces, cART resulted in a limited modification of the relative abundance of the microbiota, however differences between pts and controls were detected in the Firmicutes, Bacteroidetes and Actynobacteria phyla. Alpha-diversity showed higher richness in HIV+ vs controls (observed: p=0.006; Chao1: p=0.002) and these differences were maintained at T12 and T24. PCoA plot analyses showed a trend to the separation of pts and controls at all time-points yet the latter overlapped regardless of treatment status and length of cART. Lefse analyses (LDS >2.0) in HIV+ showed a significant increase of Veillonellaceae at T12 (p=0. 007) and T24 (p=0.001) Desulfovibrionaceae at T24 (p=0.022) and Prevotellaceae at T24 (p=0.018). Further, many differences between pts and controls was detected in HIV+ . This persistent dysbiosis was associated with the continuous mucosal damage, despite cART introduction: I-FABP were positively correlated with Veillonellaceae both at T12 (r2=0.197; p=0.030;) and T24 (r2=0.156; p=0.017). Interestingly, when we stratified patients according to cART regimens, we found that only NNRTI-based therapy significantly reduced richness (observed: p=0.038; Chao1: p=0.006), but not evenness indexes over time. Furthermore, the relative abundance analyses showed a different profile at both family and genus levels, with NNRTI-based regimens significantly reducing the families of Coriobacteriaceae, Peptococcaceae and increasing the Veillonellaceae family. On the opposite, INSTI-based regimens resulted in decreased Peptococcaceae and increased Veillonellaceae families, as well as in higher Allisonella genus. No major effects following PI-based regimens were detected; no modifications about gut persistence score analysis as well as predicted functional metagenomic pathway analysis were found. Plasma microbiota analyses revealed no major changes of relative abundance parameters during cART and in comparison with uninfected controls. Decreased alpha-diversity was nonetheless found in HIV+ compared to controls (Shannon: p=0.02, Simpson: p=0.009) and persisted both at T12 and T24. CONCLUSIONS HIV-related modifications of the microbiota occur within the GI tract and not in the blood and are minimally affected by long-term effective cART, despite evidence of the containment of gut inflammation. These data suggest the ability of the virus to irreversibly impact the microbiological core of chronically-infected individuals.

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