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Autore	M. Basilissi
Titolo	T-CELL HOMEOSTASIS, MODIFICATIONS OF MUCOSAL IMMUNITY POPULATIONS AND ASSOCIATION WITH HIV-MEDIATE MICROBIAL TRANSLOCATION AND DYSBYOSIS: EXTENSIVE IMMUNE PHENOTYPING DURING 1 YEAR OF SUCCESSFUL COMBINATION ANTIRETROVIRAL THERAPY (CART) [Tesi di dottorato]
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Sommario	In the era of combination antiretroviral therapy (cART), a reduction of HIV and AIDS-comorbidities and death has been described. Nonetheless, immune defects persist during treatment and may be linked to increased morbidity and mortality of HIV-infected subjects compared to the general population. Microbial translocation and dysbiosis as well as impaired mucosal immunity likely represent underlying pathogenic mechanisms of the peripheral immune flaws observed during therapy. However, a systematic investigation of these parameters in a longitudinal cohort of HIV-infected individuals starting cART is currently lacking. In this context, the overall objective of our research is to understand the extent by which enduring gut abnormalities represent a cause of impaired T-cell homeostasis during cART. In particular, we aim to study the modifications of T-cell homeostasis, microbial translocation, gastrointestinal function and faecal microbiota composition in a cohort of HIV-infected, antiretroviral-naïve subjects prior to and following 12 months of cART (aim 1). A further goal is to investigate the contribution of Th17/Th22, “gut-homing” and Tscm cells in

sustaining peripheral immune defects in HIV-infected, antiretroviral-naïve subjects prior to and following 12 months of cART (aim 2, immunological substudy). In Aim 1 we consecutively enrolled 160 HIV-infected, antiretroviral-naïve subjects introducing cART (T0), and presenting virological suppression (<40 cp/mL) and active follow-up after 12 months of treatment (T12). We performed: i) flow cytometry surface staining (naïve, memory, activated CD4/CD8 T-cells); ii) microbial translocation parameters analysis (LPS, sCD14, EndocAb); iii) gastrointestinal functional marker assessment (LAC/MAN fractional ration, I-FABP); iv) faecal calprotectin quantification and microbial population analysis. In Aim 2 we selected a subgroup of 28 HIV-infected, antiretroviral-naïve subjects introducing cART (T0) with available cryopreserved biological samples from the cohort of patients enrolled in Aim 1. 18 HIV-uninfected age- and sex-matched individuals were selected as controls. After lymphocyte separation, we performed flow Cytometry surface staining to assess CD4+ and CD8+ activation (HLA-DR+CD38+), maturation (naïve: CCR7+CD45RA+; central memory: CCR7+CD45RA-; effector memory: CCR7-CD45RA-; terminally differentiated: CCR7-CD45RA+) exhaustion (PD-1+), the frequency of stem cell-like memory T cells (Tscm; CCR7+CD45RA+CD27+CD95+) and that of CD4+ T-cells with a “gut homing” (CCR9+?4?7+) and a “Th17/Th22” phenotype (CCR6+CD161+). Our Aim 1 results showed a significant increase in central memory (p<0.0001;) and naïve CD4+ T-cells (p<0.0001) which paralleled the reduction of activated (p=<0.0001) and memory activated T-cells (p<0.0001). No differences were observed in terms of naive and central memory CD8+ T-cells. No changes were observed in microbial translocation parameters and intestinal permeability at T12, while we registered an increase in I-FABP (p=0. 0002) and a decay in faecal calprotectin levels (p=0.0099) after introducing cART. Qualitative analysis of the faecal microbiome revealed an outgrowth of Lactobacillus (p<0.0001) and Bacteroides spp. (p=0.0006) as well as Proteobacteria (p=0.027) following cART. Regarding Aim 2, we registered a significant reduction of activated CD4+ (p=0.02) and CD8+ lymphocytes (p=0.0003) following cART introduction, reaching levels comparable to those observed in uninfected controls. Analysis of T-cell maturation showed a significant reduction in CD4+ effector memory subsets in the course of cART (p=0.01), leading to persistent impairment of this subset compared to controls. Measure of PD-1 displayed a hierarchy in PD-1 expression, with the highest levels in cART-naïve subjects, followed by those measured in treated individuals and uninfected controls. Study of Tscm revealed significant reduction of the CD4+ Tscm subset in HIV-infected subjects during the first 12 months of cART (p=0.002) and no variations of the CD8+ Tscm pool. Overall, HIV infection accounted for lower CD4+ and CD8+ Tscm frequencies compared to uninfected controls. Interestingly, Tscm correlated negatively with naïve cells (CD4+: r=-0.7; p=0.004; CD8+: r=-0.7; p=0.006) and positively with effector memory cells in healthy controls. (CD4+: r=0.6; p=0.01; CD8+; r=0.6; p=0.01). In HIV disease, these correlations were lost in the course untreated infection and only the relationship between CD4+ naïve and Tscm cells was restored in the course of cART. Analysis of Th17/Th22 frequency showed enrichment in the course of cART (p=0.03;), but significantly lower frequencies compared to HIV-uninfected controls (p=0.04). Interestingly, this subset correlated positively with CD4+ Tscm prior to cART (r=0.6; p=0.002). Finally, a progressive contraction of CD4+ T-cells with a “gut-homing phenotype was

	reported (p=0.02), which maintained significantly lower frequencies compared to HIV-uninfected controls (p=0.04). A positive correlation was found between T cells with a “gut-homing” phenotype and plasma HIV RNA prior to cART introduction (r=0.5; p=0.003). In line with this finding, this phenotype also correlated with activated CD4+ T-cells (r=0.5, p=0.003) at the same time-point; this association was nonetheless lost in the course suppressive treatment. In conclusion our study demonstrated that 1 year of virally-successful cART results in an amelioration of peripheral T-cell homeostasis with reduction of T-cell activation and exhaustion parameters despite persistent microbial translocation and intestinal damage/permeability, possibly linked to the impairment of Th17/Th22 and cells with a “gut-homing” immunephenotype. Further research is necessary to investigate the effects of longer cART on circulating T-cell subpopulations and markers of gut homeostasis and function.
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