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Titolo	PATHOGENESIS OF POOR IMMUNE RECOVERY ON COMBINATION ANTIRETROVIRAL THERAPY (CART): THE ROLE OF THE GASTROINTESTINAL TRACT AND MICROBIAL TRANSLOCATION [Tesi di dottorato]
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Sommario	In the era of combination antiretroviral therapy (cART), a remarkable reduction in AIDS-related morbidity and mortality rates has been described. However, 15%–30% of treated individuals display a discordant response to cART, which consists of inefficient CD4+ T-cell recovery despite effective virological control. These subjects are referred to as “Immunological Non Responders” (INRs) and remain at a considerable higher risk of HIV progression and mortality from both AIDS and non-AIDS events and poorly responsive to experimental treatments. It is thus critical to investigate the underlying mechanisms of poor immune recovery on effective cART and elaborate targeted interventional strategies for this population in a timely manner. T-cell activation has been described an independent factor of poor CD4+ T-cell recovery on cART and INR have been shown to present significant higher levels of peripheral immune activation compared to Full Responders (FR). Building on prior evidence of the translocation of microbial bioproducts through the gastrointestinal (GI) tract as a cause of immune activation in HIV disease, studies addressing the pathogenesis of inefficient CD4+ T-cell recovery in INR have shown increased levels of circulating

lipopolysaccharide (LPS) in this setting. Despite evidence of an association between microbial translocation parameters and expression of activation markers in INR, whether stimulation with microbial components per se results in the induction of T-cell activation markers in this population is unknown. Further, a biological model explaining the precise mechanisms by which exposure to microbial components causes T-cell activation in HIV disease is currently lacking. Finally, literature has so far not disentangled the possible links between GI barrier damage and poor immune reconstitution in the course of effective cART in INR. The overall objective of the present study was to understand whether damage of the GI tract and microbial-induced T-cell activation feature HIV-infected individuals with poor immune recovery on cART. Specific Aim 1: Comparative study of gut junctional complexes in HIV-infected individuals with different CD4+ T-cell recovery on cART. We aimed to analyze the structure and function of gut JC in Immunological Non Responder (INR) and Full Responder (FR) and to assess whether the fecal microbiome and/or HIV reservoirs may represent underlying causes of gut epithelial barrier dysfunction in course of treated HIV disease. Specific Aim 2: Expression of activation markers on immune cells following stimulation with microbial components in HIV-infected individuals with different CD4+ T-cell recovery on cART. We aimed to study the expression of activation markers on immune cells following stimulation with microbial components in HIV-infected individuals with different CD4+ T-cell recovery on cART. We analyzed the effect of LPS in vitro stimulation on T-cell activation markers (CD38 and HLA-DR) in HIV-infected patients with different CD4+ recovery on cART and then set up an in vitro model to assess the TLR-mediated signalling pathways in monocyte-derived macrophages (MDM) and PBMCs in a similar study population. Our experiments revealed: i) Immunohistochemical and statistical evidence of INR presenting the lowest expression of junctional complex (JC) proteins at mucosal (ileum and colon) sites, with electron microscopy proof of dilated intercellular spaces; ii) A negative correlation of CD4+ T-cell counts with intestinal JC protein expression as well as HIV reservoirs in the gut and peripheral blood; iii) A higher proportion of HLA-DR-expressing CD4+ and CD8+ T-cells in INR following lipopolysaccharide (LPS) in vitro stimulation, yet the CD38+CD8+ pool only is significantly expanded according to the degree of immunological impairment; iv) Up-regulation of T-cell activation markers following broad microbial challenge in INR, as well as heightened expression of effector and pathogen specific response genes prior to stimulation and selective upregulation of type I interferons following ssRNA stimulation; v) Preserved response of monocyte-derived macrophages (MDM) from INR following broad microbial challenge. Our findings show that incomplete immunological response in the course of effective cART associates with severe damage of the GI epithelial barrier and increased size of the HIV reservoir both at mucosal sites and in circulating T-cells, thus suggesting to target the GI tract in the elaboration of interventional strategies for INR. We also demonstrate the uniqueness of the CD8+CD38+ T-cells subset in depicting T-cell activation following LPS stimulation in individuals with poor CD4+ T-cell recovery, strengthening its possible exploitation in the clinic to monitor the immune response to cART. Consistently with these findings, we show the up-regulation of activation markers on T-cells from INR following ssRNA which appears to be involved in TLR-mediated signaling of

	non-CD14-dependent pathways, highlighting the importance of low-level viremia/HIV reservoirs as sources of persistent antigenic stimulation in this setting.
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