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Analysis of peripheral HIV reservoir, tropism and soluble immune activation markers during long cART in naïve patients

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Background and aim: Despite viral suppression and immune restoration induced by cART, signs of immune activation and of inflammation may persist, leading to comorbidities. In addition, during effective cART, while it has been reported that HIV cellular reservoir tends to decrease, rare events of tropism switch may occur in proviral DNA harbored by peripheral lymphomonocytes. In this study the changes of soluble markers of inflammation and immune activation (sCD14, sTNFRII and IL6), HIV proviral DNA and tropism quasispecies were analyzed in a group of naïve patients who started their first cART and remained under therapy for ≥5 years. Methods: Samples from 40 patients enrolled in the Italian Cohort of Naïve Antiretroviral (ICONA) Foundation were retrospectively selected, in order to fulfill the following conditions: having been on cART for ≥5 years, showing suppressed HIV-1 viremia (HIV-RNA <50 copies/ml) after this time interval. Two time points were analyzed, the first one prior to initiation of cART (T0), the second one in a time window between 60 and 113 months after cART initiation (T1). The following parameters were evaluated at T0 and at T1: HIV RNA, HIV DNA, sCD14, sTNFRII and IL6. At the same time points viral tropism was assessed by V3 ultra-deep pyrosequencing (UDPS), using geno2pheno. Statistical analysis was based on paired Student's t test (T0 vs T1); correlations were assessed by Spearman's rank correlation test, considering delta T0-T1 values. Results: Plasma viremia (HIV-1 RNA) and PBMC-associated proviral DNA at T0 were positively correlated (rho=0.49, p=0.002); nadir CD4 was inversely correlated with T0 proviral load (rho=-0.34, p=0.041) and with %X4 in T0 DNA (rho=-0.36, p=0.038). Pairwise comparison was possible for 37 patients for HIV DNA, 26 for immune activation markers and 26 for tropism evaluation (FPR of the V3 quasispecies in proviral DNA). Results indicate a significant decrease of HIV DNA 4.126 ±0.084 T0 vs 3.318 ± 0.103 T1 (mean Log copies/million PBMC ± SE, p<0.0001), sTNFRII 5.808 ± 0.506 T0 vs 3.944 ±0.329 T1 (mean ng/ml ± SE, p=0.0027) and FPR of the quasispecies 39.410 ± 4.435 T0 vs 28.180 ± 4.292 T1 (mean ± SE, p=0.0010); 86% , 81% and 80% of patients showed a decrease in HIV
DNA, sTNFRII and FPR, respectively. A modest, close to statistical significance, positive correlation between the reduction of HIV DNA and sTNFRII was observed (rho=0.38, p=0.0689).Conclusions: This study confirms the effectiveness of cART in reducing peripheral blood cells harbouring HIV proviral genomes, and highlights that this reduction may be associated with significant reduction of one of the most important soluble immune activation marker (sTNFRII). At the same time, but without apparent correlation with the previous two phenomena, tropism evolution may occur, as supported by the reduction of the FPR of proviral HIV DNA quasispecies.