P0032
Paper Poster Session
HIV biomarkers, resistance and diagnostics

Inosine triphosphate pyrophosphohydrolase (ITPase) expression is decreased in leucocytes of HIV-seropositive patients using combination antiretroviral therapy

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Background: The human immunodeficiency virus (HIV) is a retrovirus which uses human nucleotides to copy its single-stranded RNA into double-stranded DNA to incorporate it into the host DNA. This makes nucleotide metabolism both a target and vehicle for anti-viral therapy, which is reflected in the many anti-retroviral nucleoside analogues that have been created. Purine nucleotide homeostasis may be compromised as, the enzyme Inosine triphosphate pyrophosphohydrolase (ITPase), was found to be decreased in erythrocytes of HIV-infected patients. Since antiviral purine analogues are pivotal in the treatment of HIV-infection, a better understanding of ITPase expression in CD4+ lymphocytes may lead to a better understanding of nucleotide metabolism and the (adverse) effects of HIV treatment.

Methods: HIV-seropositive patients, visiting the outpatient clinic of a Dutch University Hospital, aged 18 years and older were included. The control population consisted of anonymous samples from general hospital patients. All DNA samples were genotyped for the two functional *ITPA* SNPs; c.94C>A (rs1127354) and g.IVS+21A>C (rs7270101). ITPase expression was determined by flow cytometry in all leukocyte subsets. The expression of ITPase was determined by measurement of the Median fluorescent intensity (MFI). Independent samples two-tailed T-test was used to determine significant differences.

Results: A total of 59 HIV-infected patients and 50 controls were included. The leucocyte subtype distribution showed no difference in monocytes and granulocytes between HIV-infected and control patients, but lymphocytes were higher in HIV-infected patients ($P<0.001$). However, in HIV-infected patients, the percentage of ITPase positive cells was less in all leukocyte subsets compared to control patients ($p<0.01$). In HIV-infected patients 97.4% of CD4+ lymphocytes were ITPase positive versus 99.9% in controls ($p=0.002$) and 85.9% versus 99.6% of CD8+ lymphocytes ($p<0.0001$), respectively. ITPase expression was highest in activated monocytes and lowest in lymphocytes, in both HIV-

infected and control patients. In all lymphocyte subsets, ITPase expression was significantly lower in HIV-infected patients ($P < 0.0001$). Stratification according to genotype revealed no significant differences in ITPase expression in white blood cells in both HIV-infected and control patients.

Conclusion: HIV-infection seems to be interfering with the purine metabolism in leukocytes by decreasing ITPase expression and activity, independently of *ITPA* genotype. Given that active metabolites of purine-analogue reverse transcriptase inhibitors are potential substrates for ITPase, these results warrant further research towards effectiveness and adverse events of purine analogues and ITPase activity.