ANALYSIS OF THE *mRNA EXPRESSION* OF *DNA DAMAGE RESPONSE GENES* IN HIV INFECTED PATIENTS.

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Introduction Though combined antiretroviral therapy (cART) in HIV-1 positive patients allows a massive suppression of viral replication, many aspects of persistance and pathogenesis of infection are still unknown.

It has been reported that virus-induced cell killing is triggered by viral integration. Infection by wild-type HIV-1, but not an integrase-deficient mutant, induced the death of activated primary CD4 lymphocytes. Similarly, integrase inhibitors abolished HIV-1-induced cell killing both in cell culture and in $CD4^+$ T cells from acutely infected subjects. The mechanism of killing during viral integration involved the activation of DNA-dependent protein kinase (DNA-PK), a central integrator of the DNA damage response, which caused phosphorylation of p53 and histone H2AX.

Aim The aim of the study was to evaluate if Inhibitor Integrase (INI) containing regimen could affect *mRNA expression* profile of *DNA damage response genes involved,* in HIV infected patients.

Methods Forty PBMC samples from HIV+ patients (18 treatment naïve and 22 treated with ART containing INI) and 10 sample from healthy donors (HD) were collected; mRNA levels of FasR, XRCC1, Lig IIIα, Parp-1, DNA PkI, DNA PkII were evaluate using Syber Green Real time PCR (Agilent Technologies). All HIV treated patients had undetectable viremia. Results *were* normalized using housekeeping genes *beta-actin (ΔCT)*. The *fold-difference* of *expression* levels between three groups were measured comparing *ΔCT* values. *Differences between* the *groups were* analyzed for statistical *significance using T-test*.

Results A significantly higher expression of mRNA levels of XRCC1, DNA PkI and FasR was detected in HIV infected individuals than in HD (XRCC1: *ΔCT* naïve =13,7; *ΔCT INI-cART=15,2 and ΔCT HD=-5,5;* ***p<0,05****. DNA Pk1:* *ΔCT* naïve =9,7; *ΔCT INI-cART=14,3 and ΔCT HD=-2.2;* ***p<0.05****; FasR:* *ΔCT* naïve =14,5; *ΔCT INI-cART=12,3 and ΔCT HD=-0,4 ;* ***p<0,05****)* (Figure 1) .

No significant differences in expression of DNA Pk II, *Lig IIIα* and Parp-1 mRNA levels between treatment naïve patients, ART containing INI treated patients and healthy donors were detected (DNA Pk II: *ΔCT* naïve=6,7; *ΔCT INI-cART=5,3; ΔCT HD =11,14; Lig IIIα*: *ΔCT* naïve=8,1; *ΔCT INI-cART=8,44; ΔCT HD =13,08;* Parp-1: *ΔCT* naïve= 4,6; *ΔCT INI-cART= 5,6; ΔCT HD 8,1; p>0.05)* (Figure 1).

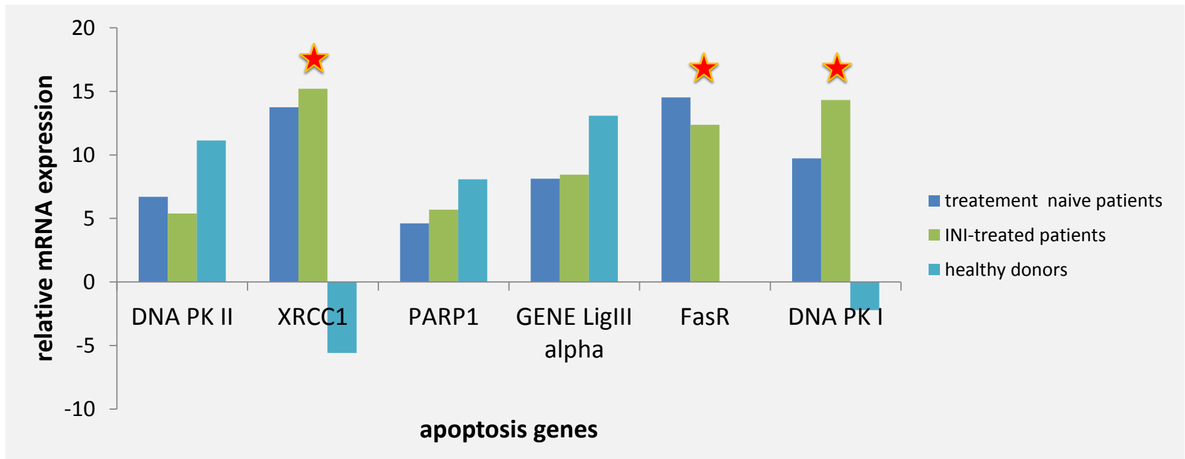

Figure 1

Conclusions The expression levels of some *DNA damage genes* (XRCC1, FasR and DNA PKI) are higher in HIV+ patients than in healthy donors. No difference of DNA PK II, Parp-1 and Lig III alpha mRNA expression levels were observed between HIV+ patients and healthy donors. Interestingly, no significant difference between naïve and INI-cART treated patients was observed. This data suggests that a cellular damage persist despite suppression of viral replication.

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