Poster # P-Q2

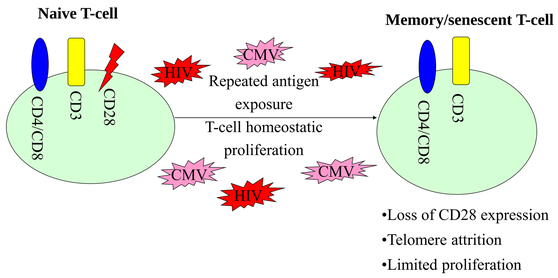
Presence of the Immune Risk Phenotype and Telomere Shortening Among HIV Treated Patients

Patricia Ndumbi*, Julian Falutz, Orin Rosengren, Jason Szabo and Chris Tsoukas

McGill University Health Centre, Montreal (Canada)
patricia.ndumbi@mail.mcgill.ca & chris.tsoukas@muhc.mcgill.ca

Background

Although the hallmark of HIV infection is progressive CD4+ T-cell depletion, other impairments in immune phenotype occur, including a marked reduction of the CD4:CD8 T-cell ratio. In the short term, effective combination antiretroviral therapy (cART) increases CD4+ T-cell counts. However, profound T-cell dysregulation often persists in the long-term. These residual immune changes resemble the Immune Risk Phenotype (IRP) which is associated with all cause mortality in uninfected octagerians. The IRP consists of laboratory markers that include: low CD4:CD8 T-cell ratio (<1), high CD4+CD28- negative T-cell percentages (>10%) and CMV IgG seropositivity. CMV is a ubiquitous virus that has been associated with immune senescence. One of the hallmarks of immune ageing is the attrition of telomeres at the end of chromosomes. In this pilot study we investigated the prevalence of the IRP among a subset of successfully treated HIV patients and assessed how this phenotype relates to markers of immune senescence such as telomere shortening.



Rationale

The IRP is associated with immune senescence and increased risk of morbidity/mortality in uninfected elderly. However its prevalence and its association to other markers of immune senescence, such as telomere length, have never been evaluated among HIV patients.

Objective

•To investigate the prevalence of the IRP among successfully treated HIV patients.
•To assess whether an association exists between the IRP and telomere length.

Methods

IRP Prevalence

IRP prevalence was evaluated in 126 successfully treated adult male HIV patients and in 21 age and sex-matched controls. Patients and controls were assessed for CMV serology, CD4:CD8 T-cell ratio and CD4+CD28- T-cell percentages.

Telomere Length measurement

Telomere length was measured on a random subset (n= 24) of the 126 HIV patients with sustained HIV viral suppression. All patients were male and all but one were caucasian. Patients were categorized into 2 groups based on their IRP status: "HIV-IRP" (n=13) and "HIV-noIRP" (n=11). Telomere length was assessed by Flow-FISH analysis and measured as a relative telomere length (RTL) in comparison to an internal cell line control (1301 cells).

Statistical Analysis

Comparisons between groups were performed using the Mann Whitney test for continuous variables. A P-value <0.05 was considered significant.

Results

•The IRP was detected in 32% (40/126) of the HIV patients

•None of the age-matched controls exhibited an IRP profile

•The median relative telomere length (RTL) was shorter in the HIV-IRP group (median RTL [IQR] = 9.9 [8.7-10.7] and 10.9 [10.3-12], respectively). This difference approached statistical significance (p=0.087).

Figure 1. IRP Prevalence in HIV patients and age-matched controls

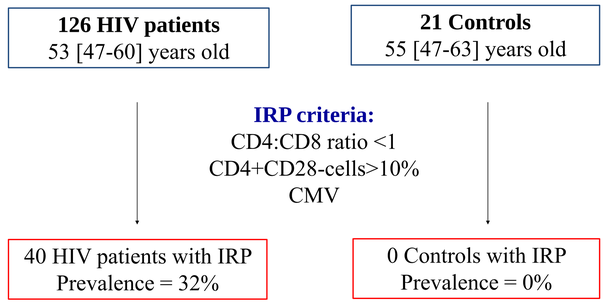
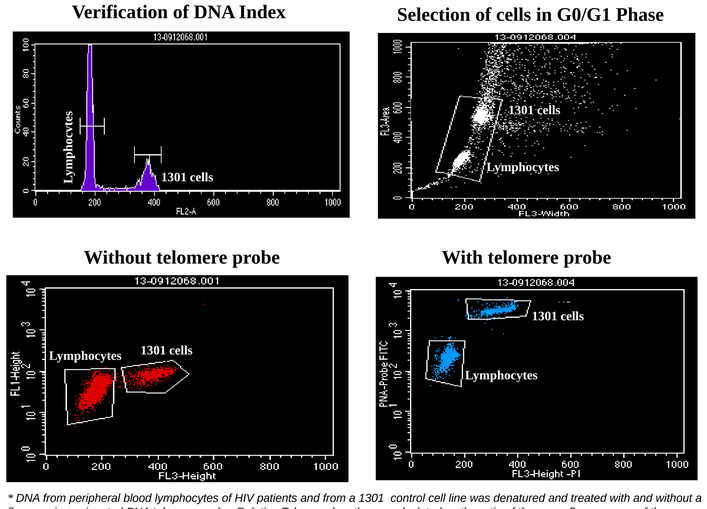


Table 1. Characteristics for 24 HIV patients evaluated for telomere length

Characteristics	All HIV (n=24)	HIV - IRP (n=13)	HIV - noIRP (n=11)	P-Value
Age	57 (48-61)	58 (55-63)	52 (48-60)	0.1
CD4+ T-cell counts (Cells/mm3)	465 (342-663)	392 (351-507)	651 (340-812)	0.20
CD4:CD8 T-cell ratio	0.7 (0.4-0.9)	0.4 (0.4-0.8)	0.7 (0.4-1.1)	0.33
CD4+CD28- T-cell percents (%)	11 (4-22)	18 (13-40)	4 (1-5)	<0.001
CD8+CD28- T-cell percents (%)	51 (30-63)	51 (40-70)	40 (18-59)	0.09

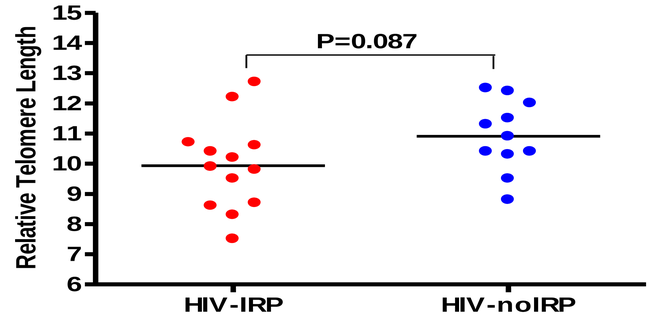
** Values are number and percentage, or median and interquartile range.*

Figure 2. Relative Telomere Measurement by Flow-Fish Analysis



** DNA from peripheral blood lymphocytes of HIV patients and from a 1301 control cell line was denatured and treated with and without a fluorescein-conjugated PNA telomere probe. Relative Telomere length was calculated as the ratio of the mean fluorescence of the lymphocytes and the mean fluorescence of the 1301 control cell line.*

Figure 3. Relative Telomere Length in HIV patients with an IRP and without an IRP



Conclusions

•IRP prevalence was higher in treated HIV patients than in age-matched healthy controls.

•The IRP observed in uninfected octagerians (>80 years old) has been linked with morbidity and mortality outcomes. Our findings reveal that the same immune phenotype occurs at a much younger age in HIV patients (<60 years old), than in uninfected elderly. It is unknown if the IRP in those with treated HIV will also be predictive of negative clinical outcomes or death.

•The IRP profile might be associated with telomere shortening however larger studies are needed to substantiate this finding.

•To our knowledge this is the first study assessing telomere shortening and the IRP in the context of treated HIV infection.

References

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