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Suppressive ART is Key to Reduce Neurocognitive Impairment in Aging HIV+ Individuals.

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Background

- Aging and HIV infection share common immunologic and inflammatory characteristics[1], potentially leading to synergistic effects that contribute to the pathogenesis of HIV-associated co-morbidities.
- HIV-associated neurocognitive disorder (HAND) is a co-morbidity that has been independently associated with age and duration of HIV infection[2].
- HAND persists even in the era of suppressive antiretroviral therapy (ART), with reported prevalence ranging from 30 to 50%[3].
- Given the debilitating nature of this disease, it is becoming increasingly important to delineate its host and virologic correlates in the context of suppressive ART.

Objectives

To determine which virologic parameters are associated with aging and neurocognitive impairment in HIV infection.

Methods

Study Participants

Participants (n=36) were chosen from the CHARTER cohort based on the inclusion criteria: (i) ≥45 years of age, (ii) treated in the chronic phase of infection, (iii) self-reported continual ART use for ≥6 months. Participants were subdivided based on level of viral suppression over 4 years: fully suppressed participants had plasma viral load <50 copies/ml with ≤1 blip of ≤200 copies/ml (n=15), partially suppressed participants had plasma viral load <50 copies/ml for >50% measurements with ≤2 consecutive blips (n=12) and non-suppressed participants had plasma viral load >50 copies/ml for >75% measurements (n=9). A subset of participants (n=28) were followed longitudinally for ≥4 years; data from this subset is reported in 'Longitudinal Effects'.

Neurocognitive Assessment

Global deficit score was calculated based on standardized neuropsychological testing[2] and used to diagnose neurocognitive impairment (NCI) in accordance with Frascati criteria[4].

HIV DNA Quantification

DNA was extracted from whole blood using a PAXgene Blood DNA Kit (Qiagen). Droplet digital PCR (ddPCR) was performed with the following primer/probe combinations (900nM primers, 250nM probes): pol HEX-Zen and 2LTR-FAM Zen for HIV DNA, RPP30 HEX-Zen for host genomic DNA (for normalization).

Sequencing

Deep sequencing of envelope C2-V3 (*env), gag* p24 (*gag)* and *pol* reverse transcriptase (*RT*) regions was performed using a 454 FLX Titanium instrument (Roche).

Genetic Analysis

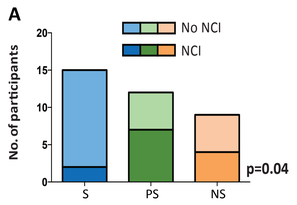
An in-house 454 UDS bioinformatics pipeline was used to generate multiple sequence alignments and calculate intrahost diversity [average pairwise distance (APD), TN93 substitution model], molecular evolution and selective pressures [ratio of non-synonymous to synonymous substitution rates (dN/dS), MG94xREV substitution model]. Viral co-receptor tropism and drug resistance-associated mutations (DRAMs) in *RT* were identified using software package IDEPI.

Results

Table 1: Baseline characteristics of study participants were comparable

	Suppressed (S, n=15)	Partially Suppressed (PS, n=12)	Non-Suppressed (NS, n=9)	S vs PS p-value	S vs NS p-value	PS vs NS p-value
Age, years, median [IQR]	51 [49-57]	49 [46-51.5]	46 [45-56]	0.33	0.29	0.59
Males, n (%)	12 (80)	12 (100)	7 (77.8)	0.23	1.00	0.17
Race, n (%)						
African-American	9 (60)	4 (33.3)	8 (88.9)	0.25	0.19	**0.02**
White	5 (33.3)	5 (41.7)	1 (11.1)	0.71	0.35	0.18
Latino	1 (6.7)	3 (25.0)	0 (0)	0.29	1.00	0.23
Estimated duration of HIV-1 infection, years, median [IQR]	13.2 [7.7-16.6]	11.1 [4.7-17.1]	9.9 [7.0-16.0]	0.39	0.66	0.79
Time on ART, years, median [IQR]	8.6 [2.9-13.6]	9.9 [4.5-15.9]	5.7 [4.2-11.4]	0.39	0.71	0.90
ART, n (%)						
NNRTI-based regimen	6 (40)	8 (66.7)	4 (44.4)	0.25	1.00	0.40
PI-based regimen	9 (60)	4 (33.3)	5 (55.6)	0.25	1.00	0.40
Length of formal education, years, median [IQR]	14 [12-14]	13.5 [12.8-14.5]	12 [11-14]	0.76	0.56	0.33
Nadir CD4 T-cell count, cells/µl, median [IQR]	101 [7-237]	82 [24-140]	255 [97-306]	0.84	0.15	0.08
Absolute CD4 T-cell count, cells/µl, median [IQR]	464 [331-730]	430 [196-519]	655 [521-880]	0.26	0.41	0.06
Plasma viral load, log_{10} copies/ml, median [IQR]	1.7 [1.7-1.7]	1.7 [1.7-2.6]	3.8 [2.7-4.0]	0.09	**0.0001**	**0.02**

Viral suppression and DRAMs are associated with less NCI



- NCI was not associated with age, HIV DNA reservoir size or diversity, co-receptor tropism or viral evolution.

Fig. 1: Virologic correlates of neurocognitive impairment
Prevalence of neurocognitive impairment in suppressed (S), partially suppressed (PS) and non-suppressed (NS) groups **(1A)**, and presence of DRAMs in participants with and without NCI (**1B**); p-values calculated by Fisher's exact test.

Aging is associated with decreasing HIV DNA levels and diversity (Cohort effects)

Table 2: Virologic correlates of host age

Correlation of age with HIV DNA, *env*, *gag* and *RT* diversity (APD), drug resistance-associated mutations (DRAMs) in suppressed participants (n=15). Significance (p<0.05, in **bold**) after adjusting for duration of HIV infection.

	Spearman Coefficient	p-value
HIV DNA	**-0.64**	**0.005**
env APD	**-0.51**	**0.04**
gag APD	-0.31	0.32
RT APD	**-0.65**	**0.03**
DRAMs	N/A	**0.04**

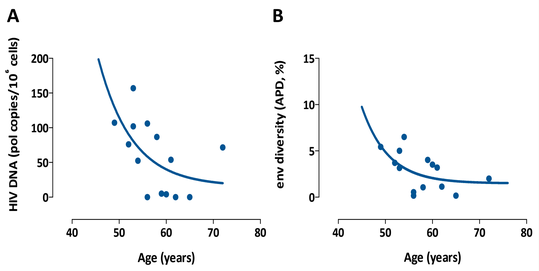
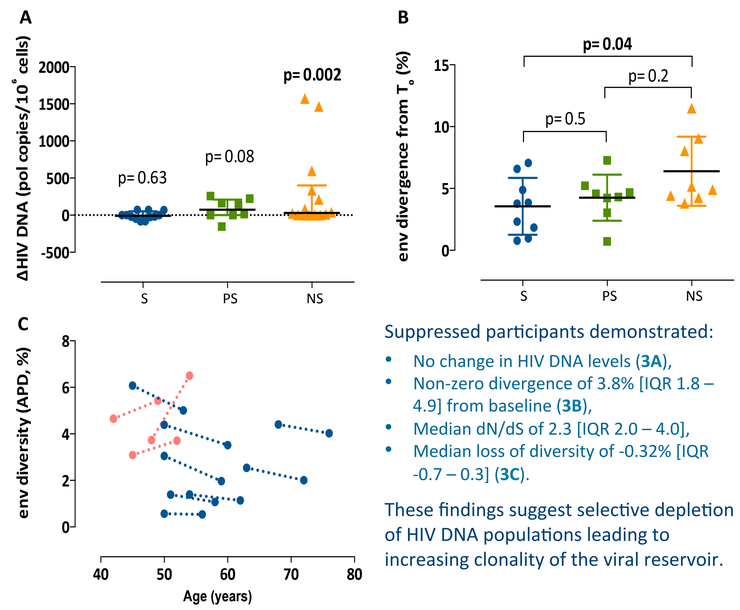


Fig. 2: Effects of age on HIV DNA reservoir size and diversity
HIV DNA (**2A**) and *env* diversity (**2B**) against age of suppressed participants (n=15, cross-sectional data). Fitted curves indicate single-phase decay kinetics.

Results

Selective depletion of HIV DNA in aging suppressed participants (Longitudinal effects)



Suppressed participants demonstrated:

- No change in HIV DNA levels (**3A**),
- Non-zero divergence of 3.8% [IQR 1.8 – 4.9] from baseline (**3B**),
- Median dN/dS of 2.3 [IQR 2.0 – 4.0],
- Median loss of diversity of -0.32% [IQR -0.7 – 0.3] (**3C**).

These findings suggest selective depletion of HIV DNA populations leading to increasing clonality of the viral reservoir.

Fig. 3: Longitudinal effects of age on HIV DNA reservoir size, diversity and evolution
Change in HIV DNA (**3A**) among suppressed (S, n=11), partially suppressed (PS, n=9) and non-suppressed (NS, n=9) groups; p-value of comparison to null hypothesis (i.e. no change), Wilcoxon test. *env* divergence from baseline (T_0) among groups (**3B**); p-value of Mann-Whitney test. Error bars indicate medians and interquartile ranges. *env* diversity at longitudinal timepoints in suppressed participants (**3C**); pink and blue symbols represent participants with increased and decreased diversity, respectively.

Conclusions

- Complete viral suppression leads to less neurocognitive impairment (Fig. **1A**) in aging HIV-infected individuals.
- Drug resistance-associated mutations are associated with better neurocognitive performance (Fig. **1B**), possibly due to reduced neurovirulence of these variants.
- Evidence of selective pressures and decreasing sequence diversity (Fig. **2B** and **3**) suggests selective depletion of HIV DNA populations during host aging in the context of suppressive ART.

[1] Deeks SG, *et al*. Immunity 2013;39(4):633-45. [2] Heaton RK, *et al.* J Neurovirol 2011;17(1):3-16.
[3] Heaton RK, *et al.* Neurology 2010;75(23):2087-96. [4] Antinori A, *et al.* Neurology 2007;69(18):1788-99.

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