Changes in Cell Free Mitochondrial DNA Fragments in Acute and Chronic HIV Infection

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Introduction

- Circulating cell-free mitochondrial DNA (ccf-mtDNA) fragments are released into the bloodstream following cell death, can activate the innate immune system, and have been associated with aging-related outcomes, including frailty, in the general population.
- While prior studies have reported increased ccf-mtDNA levels with age and conditions such as frailty and cognitive decline, data on ccf-mtDNA dynamics in people with HIV (PWH) remain inconsistent.
- In this study, we hypothesized that HIV infection is associated with higher levels of ccf-mtDNA fragments and this association is attenuated after ART initiation.

Methods

Human Study Population

We included participants from two prospective cohort studies: AIDS Linked to Intravenous Experience (ALIVE) in Baltimore and Multicenter AIDS Cohort Study (MACS, now part of the MACS/WIHS Combined Cohort Study [MWCCS]).

- ALIVE enrolled people with and without HIV who inject drugs, while MACS focused on men who have sex with men.
- The two cohorts represented PWH with different challenges in HIV long-term care.

Measurements

- Ccf-mtDNA levels were quantified in serum samples from the ALIVE and MACS cohorts using ultrasensitive digital PCR systems at the Johns Hopkins Genetic Resources Core Facility.
- Measurements were taken at intervals of 1, 3, or 5 years.

Statistical Analyses

- Baseline characteristics were compared between cohorts and by HIV status.
- We used mixed-effect linear regression models to compare levels of ccf-mtDNA by HIV serostatus and CD4 T-cell counts (<350 vs. ≥350 cells/mm^3), controlled for demographics, BMI, active injection drug use, and alcohol use to compare

Nonhuman Primate Study

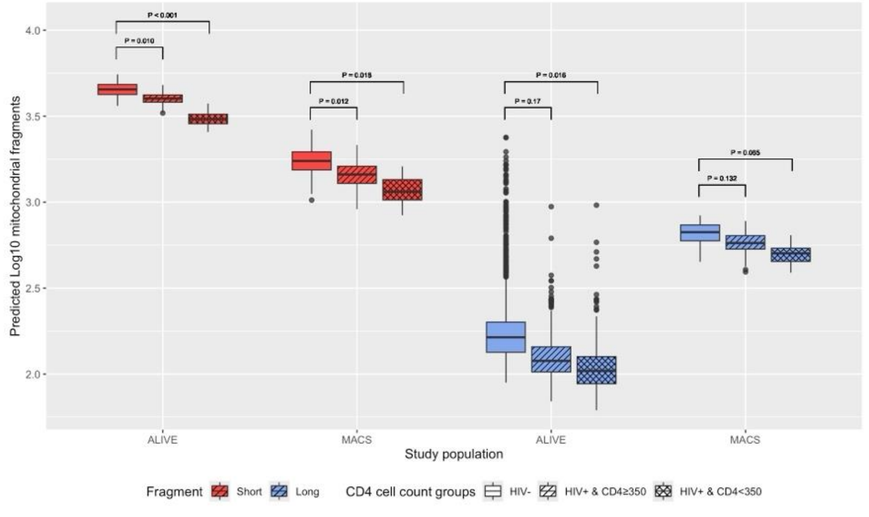
- We measured ccf-mtDNA levels in non-human primates (n=6) before and after SIV infection and following antiretroviral therapy (ART) initiation. Samples were drawn at baseline, peak viremia (2 weeks post-infection), pre-ART (5 weeks post-infection), and 3- and 6-months post-ART initiation.

ART-suppressed HIV-infection is associated with lower circulating cell free mitochondrial DNA short and long fragments, after an initial increased levels after acute infection.

Results

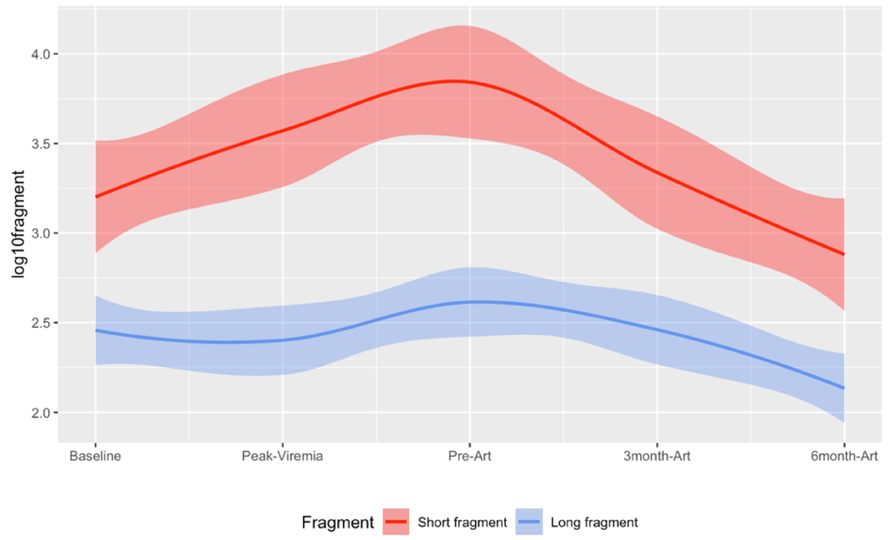
- Total N = 890 with 2150 person-years of follow-up from the ALIVE cohort; N = 427 with 1989 person-years of follow-up from the MACS cohort.
- PWH had lower levels of short and long ccf-mtDNA fragments in both ALIVE and MACS cohorts, with a more pronounced difference in ALIVE (0.119 log scale units lower) than in the MACS cohort (0.094 units lower) (both p<0.05).
- Lower CD4 T-cell counts (<350 cells/mm^3) were linked to lower short and long fragment levels in ALIVE, though only the short fragment was significantly lower in MACS.
- In nonhuman primates, short ccf-mtDNA levels increased shortly after infection, peaking just before ART initiation (p=0.001), and subsequently declined, reaching levels below baseline after 6 months on ART.

Figure 1. Serum level of circulating cell-free mitochondrial fragments in human samples (ALIVE and MACS cohorts).



Results (cont.)

Figure 2. Serum level of circulating cell-free mitochondrial fragments in nonhuman primate.



Conclusions

- ART-suppressed HIV-infection, detectable viral load, and low CD4 T-cell counts are associated with reduced levels of short and long ccf-mtDNA fragments.
- Nonhuman primate data suggest that ccf-mtDNA levels initially rise during acute HIV infection before declining in chronic infection.
- The findings highlight the importance of further investigation into the mechanisms regulating ccf-mtDNA in people with HIV and its role in aging-related diseases.

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