

# METHAMPHETAMINE USE INDEPENDENTLY PREDICTS PREMATURE AGING IN HIV+ INDIVIDUALS

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## Objective

To determine the effects of methamphetamine (METH) dependence and HIV on physiologic and functional measures of aging.

## Background & Significance

- As HIV+ adults grow older, aging-related comorbidities occur more frequently than in age-matched controls.
- Little is known about the role of substance use, which is common in this population, in this "premature" aging process.

## Methods

- We obtained clinical, demographic and laboratory assessments from 124 participants in four groups
  - HIV-/METH- n=31
  - HIV-/METH+ n=24
  - HIV+/METH- n=35
  - HIV+/METH+ n=34
- We examined the impact of HIV serostatus and METH dependence in relation to epigenetic changes (telomere to single copy gene ratio [T/S], mitochondrial DNA [mtDNA] level, and relative abundance of the mitochondrial "common deletion" [RACD] (a 4.5kb deletion that is an epigenetic marker of aging) within the mtDNA population, as well as to functional status, cardiovascular comorbidity (Framingham risk scores), renal functional changes, and age-related anthropometric (hip/waist ratio) changes.

## Results

Table 2: HIV Infection is Associated with Worsening Measures of Physiologic and Functional Aging

| Outcome                       | Age     |         | HIV Status |         | Interaction |         |
|-------------------------------|---------|---------|------------|---------|-------------|---------|
|                               | $\beta$ | P value | $\beta$    | P value | $\beta$     | P value |
| Karnofsky Rating              | -0.02   | 0.87    | 0.30       | 0.28    | 0.02        | 0.02    |
| Framingham CVD Risk           | 0.53    | <0.01   | -0.31      | 0.16    | 0.05        | 0.05    |
| Framingham Stroke Risk        | 0.34    | <0.01   | -0.45      | 0.07    | 0.02        | 0.02    |
| Hip Circumference             | 0.034   | 0.38    | -0.21      | 0.02    | 0.35        | 0.35    |
| Midwaist Circumference        | 0.29    | <0.01   | -0.12      | 0.19    | 0.85        | 0.85    |
| Hip to Waist Ratio            | 0.48    | <0.01   | 0.16       | 0.05    | 0.84        | 0.84    |
| Creatinine                    | 0.22    | 0.01    | 0.28       | <0.01   | 0.45        | 0.45    |
| T/S Ratio                     | -0.59   | <0.01   | -0.24      | <0.01   | 0.14        | 0.14    |
| mtDNA copy per cell           | -0.21   | 0.05    | 0.002      | 0.99    | 0.36        | 0.36    |
| mtDNA with deletions per cell | -0.05   | 0.64    | 0.05       | 0.65    | 0.91        | 0.91    |

Table 2: Multivariate regression of Age and HIV status as predictors of physiologic and functional aging related outcomes. HIV infection is associated with worsening of many aging related markers independently or as an interaction with chronological age.

Figure 1: Methamphetamine Use and HIV Status are Independently Associated with Shorter T/S Ratio

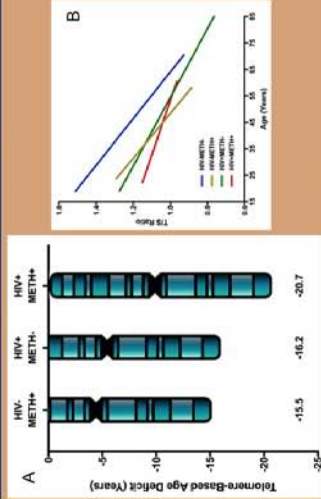


Figure 1: METH and HIV as predictors of T/S ratio. Figure 1A. In this model based on our cohort, the T/S ratio for a HIV+/METH+ individual was equivalent to a HIV-/METH- individual who was 20.7 years older. Similarly the difference was 16.2 years for HIV-/METH+, and 15.5 years for HIV+/METH- individuals respectively. Figure 1B. Multivariate regression of T/S ratio for each study group.

Table 1. Participant Characteristics

|                          | All participants (n=124) | HIV+ (n=69)   | HIV- (n=55)   | METH Users (n=58) | METH Non-Users (n=66) | p-value* |
|--------------------------|--------------------------|---------------|---------------|-------------------|-----------------------|----------|
| Sex (M:F)                | 97:27                    | 66:3          | 31:24         | 46                | 51                    | 0.83     |
| Race (no. of European)   | 60                       | 33            | 27            | 22                | 38                    | 0.03     |
| Age (years)              | 45.2 +/- 14.5            | 46.4 +/- 13.5 | 43.6 +/- 15.6 | 40.7 +/- 11.2     | 49.0 +/- 15.9         | 0.01     |
| Education (median years) | 14 (12-16)               | 14 (12-16)    | 14 (12-16)    | 13 (11-15)        | 15 (13.5-16.5)        | <0.01    |
| CD4 count (HIV+ only)    | 700 +/- 308              | 700 +/- 308   | -             | 646 +/- 296       | 756 +/- 315           | 0.14     |
| BMI                      | 27.9 +/- 6.0             | 26.8 +/- 4.9  | 29.3 +/- 7.0  | 28.2 +/- 6.3      | 27.6 +/- 5.7          | 0.59     |
| Impairment by GDS        | 39                       | 24            | 15            | 20                | 19                    | 0.56     |

Table 1: Characteristics of our study participants. Mean values with standard deviations or median values with IQR are shown for the entire cohort and by groups defined by HIV and METH status. \*Represent the p-value of a two-tailed Mann-Whitney or a Fisher test. GDS = Global Deficit Score; METH+ = Methamphetamine; METH- = non-methamphetamine; BMI = body mass index.

Table 3: Methamphetamine Use is Associated with Worsening Measures of Physiologic and Functional Aging

| Outcome                       | Age     |         | METH Status |         | Interaction |         |
|-------------------------------|---------|---------|-------------|---------|-------------|---------|
|                               | $\beta$ | P value | $\beta$     | P value | $\beta$     | P value |
| Karnofsky Rating              | -0.26   | <0.01   | -0.71       | 0.44    | 0.64        | 0.64    |
| Framingham CVD Risk           | 0.68    | <0.01   | 0.035       | 0.62    | 0.06        | 0.06    |
| Framingham Stroke Risk        | 0.50    | <0.01   | -0.1        | 0.22    | 0.25        | 0.25    |
| Hip Circumference             | 0.008   | 0.94    | -0.025      | 0.80    | 0.32        | 0.32    |
| Midwaist Circumference        | 0.29    | <0.01   | 0.034       | 0.71    | 0.60        | 0.60    |
| Hip to Waist Ratio            | 0.53    | <0.01   | 0.14        | 0.10    | 0.44        | 0.44    |
| Creatinine                    | 0.20    | 0.03    | -0.20*      | 0.03    | 0.21        | 0.21    |
| T/S Ratio                     | -0.66   | <0.01   | -0.25       | <0.01   | 0.62        | 0.62    |
| mtDNA copy per cell           | -0.23   | 0.03    | -0.10       | 0.38    | 0.26        | 0.26    |
| mtDNA with deletions per cell | -0.42   | 0.71    | 0.025       | 0.82    | 0.35        | 0.35    |

Table 3: Multivariate regression of Age and METH status as predictors of physiologic and functional aging related outcomes. METH is associated with shorter T/S ratios but lower creatinine.

- In a multivariate regression of creatinine adjusting for age and body mass index, both HIV and METH remained statistically significant, while tenofovir exposure was not a predictor of creatinine level.
- When examining RACD:
  - HIV infection was not associated with RACD
  - METH+ participants had significantly smaller RACD (p=0.03) but only in the HIV seronegative group.
- After adjusting for age:
  - CRP, sCD14, D-Dimer, IL-6, CXCL10, total cholesterol, HDL, LDL were not associated with shorter T/S ratios
  - Current tobacco smoking was associated with shorter T/S ratios (p=0.02), but was not included in the best model possibly as tobacco use is more common in HIV+ and METH+ individuals.

## Conclusions

- HIV and METH contribute to premature biological aging, with HIV having broader physiologic and epigenetic effects than METH.
- Consistent with earlier observations, METH was associated with less mtDNA damage, possibly due to induction of autophagy and cell turnover.
- This may explain the association with improved renal function in METH users, as mitochondrial dysfunction is known to play a significant role in renal disease.

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