# *Chronic Cannabis Use is Associated with Faster Epigenetic Aging in People with HIV*

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## BACKGROUND

- **Cannabis** consumption is more prevalent in people with HIV (**PWH**) than the general population (Haley *et al.*).
- DNA methylation (**DNAm**) clocks are quantitative, reproducible markers of biological aging (Horvath *et al.*).
- Cannabis is linked to altered DNAm (Nannini *et al.*), but whether these effects are **modified by HIV** is unclear.
- HIV has been linked with accelerated **biological aging** using several DNAm clocks.
  - **GrimAge** predicts mortality risk based on time-to-death curves.
  - **PhenoAge** measures disease-related morbidity and includes smoking pack-years.
  - **DunedinPACE** predict longitudinal rate-of-change based on a cohort study.
  - **Telomere length** can be predicted from DNAm profiling and reflects cellular aging and senescence (Lu *et al.*).
- Relevance of DNAm clocks in **virally suppressed** PWH who use cannabis remains unclear.

## HYPOTHESES

- Epigenetic clocks are **accelerated** in virally suppressed PWH who use cannabis compared to non-users and persons without HIV (PWoH).
- An **interaction** between HIV and chronic cannabis exists such that the combination is more deleterious than either alone or their sum.

## METHODS

- Participants comprised four groups (**Table 1**): cannabis users (**HIV+/CB+** and **HIV-/CB+**); and non-users (**HIV+/CB-** and **HIV-/CB-**).
- DNA was extracted from peripheral blood mononuclear cells (**PBMCs**).
- DNA methylation profiling utilized Illumina MethylationEPIC **microarrays** with preprocessing used the *minfi* R package.
- **Statistics**: multiple linear regression, with age, race, birth sex, white blood cell proportions, and sample plate (to reduce batch effects) as covariates.

Cannabis and HIV independently and interactively affect epigenetic aging, as measured with DNA methylation clocks. PWH who are chronic cannabis users may be at increased mortality risk.

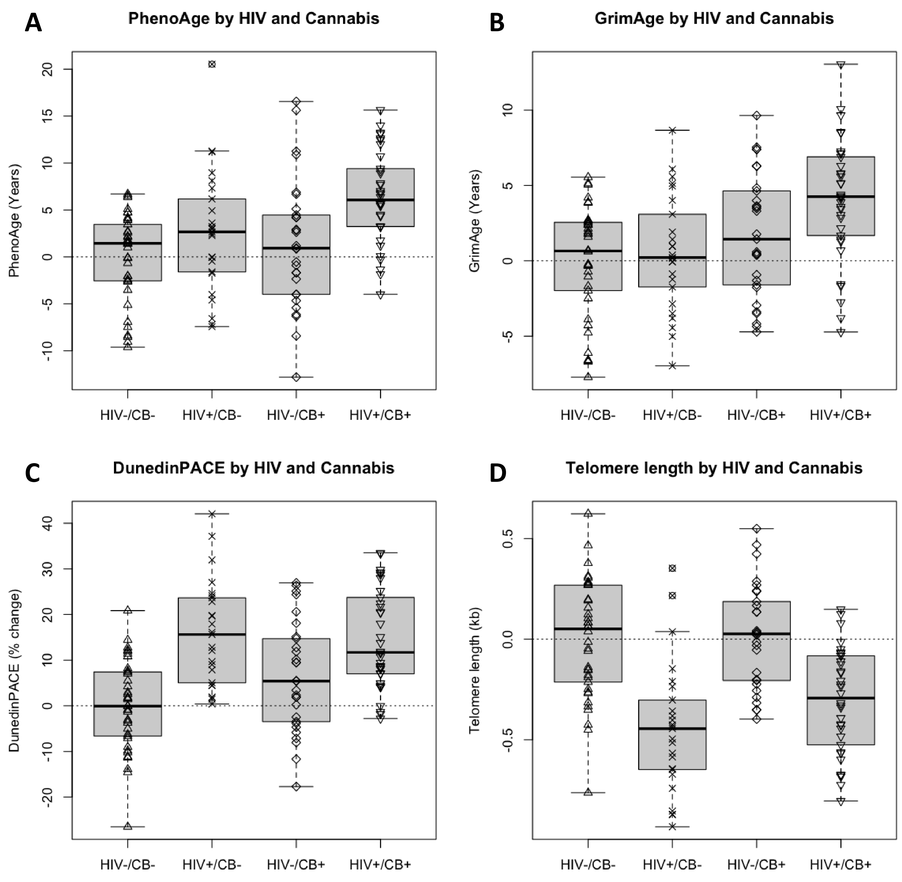



**Fig. 1: Unadjusted epigenetic age residuals.** *(A) PhenoAge was more elevated among PWH cannabis users than any other group. (B) GrimAge was similarly increased in PWH using cannabis. (C) Both groups of PWH showed increased DunedinPACE vs. PWoH, with an intermediate effect for cannabis use among PWoH. (D) DNAm-based telomere length estimation was reduced in PWH regardless of cannabis use, but unaffected in user PWoH.*

## ACKNOWLEDGMENTS

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| *Table 1: Demographics* | HIV-/CB- | HIV-/CB+ | HIV+/CB- | HIV+/CB+ |
|---|---|---|---|---|
| Number | 38 | 29 | 25 | 34 |
| Sex (M/F) | 17 / 21 | 13 / 16 | 19 / 6 | 26 / 8 |
| Age (mean ± SD) | 39.7 ± 14.4 | 40.2 ± 13.7 | 52.6 ± 12.6 | 42.6 ± 12.5 |
| Race (W / AA / Other) | 22 / 9 / 7 | 17 / 10 / 2 | 10 / 14 / 1 | 4 / 26 / 4 |

## RESULTS

- PhenoAge showed a significant effect of HIV (approx. +4 years) but not of cannabis, for which only a trend-level effect was observed (**Fig. 1A, Table 2**).
- GrimAge was sensitive to both HIV and cannabis with effect sizes of approximately +1-2 years (**Fig. 1B**).
- DunedinPACE was increased in PWH vs. PWoH, but this effect was slightly mitigated by cannabis (**Fig. 1C**).
- Predicted telomere length was shorter in PWH regardless of cannabis use (**Fig 1D**).

| *Table 2: Results* | HIV-/CB- | HIV-/CB+ | HIV+/CB- | HIV+/CB+ | Interaction |
|---|---|---|---|---|---|
| PhenoAge | *ref* | +1.8 yr. *p=0.06* | +4.6 yr. *p<0.001*** | +3.6 yr. *p=0.001*** | -2.8 yr. *p=0.05* |
| GrimAge | *ref* | +1.5 yr. *p=0.009*** | +2.1 yr. *p=0.002*** | +2.5 yr. *p<0.001**** | -1.1 yr. *p=0.19* |
| DunedinPACE | *ref* | +5.5% *p=0.019** | +10.2% *p<0.001**** | +8.2% *p=0.002*** | -7.6% *p=0.03** |
| Telomere length | *ref* | -0.05 kb *p=0.17* | -0.18 kb *p<0.001**** | -0.13 kb *p=0.002*** | -0.10 kb *p=0.08* |

## CONCLUSIONS

- GrimAge and PhenoAge were sensitive to both HIV and chronic cannabis use, indicating increased morbidity and mortality risk.
- DunedinPACE and predicted telomere length were primarily sensitive to HIV serostatus, though cannabis use showed a slight protective effect against accelerated DunedinPACE aging rate.

## CITATIONS

- Haley D, *et al., "Cannabis Use Disorder Among People With and Without HIV." J Addiction Medicine* (2021).
- Horvath S. "DNA methylation age of human tissues and cell types." *Genome Biology* 14 (2013).
- Nannini D, *et al.* "Genome-wide DNA methylation association study of recent and cumulative marijuana use in middle aged adults." *Molecular Psychiatry* (2023).
- Lu A, *et al.* "DNA methylation-based estimator of telomere length." *Aging* (2019).