Epigenetic Modifications Predictive of Cognitive Frailty in Cocaine-Using People Living With HIV

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BACKGROUND

- **People living with HIV (PLWH) are disproportionately burdened by neurocognitive impairment (NCI)** (Wei et al., 2020) **and physical frailty** (Strain et al., 2022). Cognitive frailty, the combination of NCI and physical frailty, results in poorer outcomes than NCI or physical frailty alone (Bu et al., 2021). While epigenetic modifications are linked to NCI (Day et al., 2011) and physical frailty (Li et al., 2022), cognitive frailty remains understudied, and HIV and cocaine use may worsen outcomes.
- **We (1) investigated epigenetic profiles and (2) identified methylation patterns predictive of cognitive frailty in people living with and without HIV and cocaine use.**

METHODS

- We conducted a preliminary epigenome-wide association study (**EWAS**) with a subset of participants from the **Miami Adult Studies on HIV (MASH) cohort.**
- DNA samples from **PBMCs** of a random sample were stratified by HIV serostatus and cocaine use and analyzed using the Illumina MethylationEPIC_v-2-0 beadchip.
- HIV serostatus was confirmed with **medical records** and cocaine use was determined with **urine toxicology** and validated questionnaires to assess **frequency of use**.
- **Cognitive frailty was defined with the IANA/IAGG criteria** (Won et al., 2018), **combining NCI (Mini Mental State Examination) and physical frailty (Fried criteria).**
- Statistical analysis included linear regression models to examine associations between methylation patterns, HIV serostatus, cocaine use, and cognitive frailty, adjusting for confounders.
- Significant CpG sites were identified with F-tests for the overall model (p<5x10-7) and t-tests for cognitive frailty (p<0.050).

ADDITIONAL KEY INFORMATION

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Cocaine use may exacerbate epigenetic effects of HIV, potentially contributing to cognitive frailty.

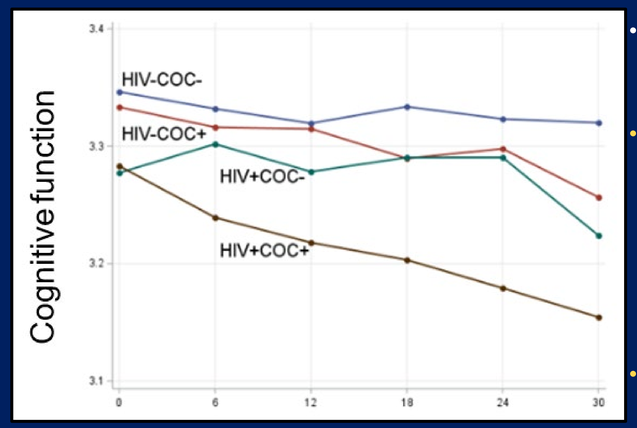
RESULTS

- **Average age of the EWAS sample (n=31) was 63.4 ± 3.2, 54.8% were PLWH, 51.6% used cocaine heavily, 100% were male, 100% identified as non-Hispanic Black, and 61.3% had a high school education or less.**
- **All PLWH were virally suppressed with an average CD4 cell count of 564.4 ± 295.6.**
- **Overall, 26% of the MASH cohort have mild NCI, 52% are pre-frail, associated with triple the odds of progressing to physical frailty** (Fried et al., 2001)**, and 22% have cognitive frailty.**

Table 1. Overall MASH cohort characteristics

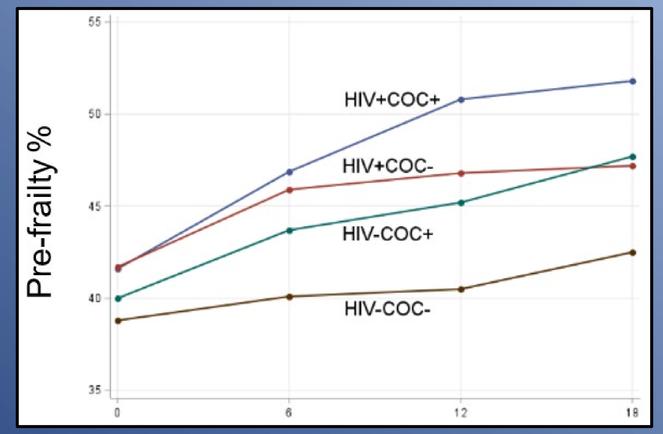
	Total n=1,439	HIV+/COC+ n=231	HIV+/COC- n=445	HIV-/COC+ n=324	HIV-/COC- n=439
Age	61 [57-66]	59 [56-64]	61 [56-66]	62 [57-66]	63 [58-67]
Cis-women	610 (42.4)	92 (39.8)	189 (42.5)	139 (42.9)	190 (43.3)
Race/Ethnicity					
Black	884 (61.4)	171 (74.2)	254 (57.1)	252 (77.8)	205 (46.8)
Hispanic	419 (29.1)	48 (20.9)	146 (32.7)	52 (16.1)	173 (39.4)
White	137 (9.5)	11 (4.9)	45 (10.2)	20 (6.1)	61 (13.8)
≤HS education	876 (60.9)	158 (68.5)	268 (60.3)	208 (64.1)	243 (55.3)
Disabled	767 (53.3)	147 (63.6)	293 (65.9)	140 (43.3)	187 (42.5)
HIV RNA ≤50	631 (93.3)	206 (89.3)	425 (95.5)		

Fig. 1. Decline in cognitive function over 30 months in MASH



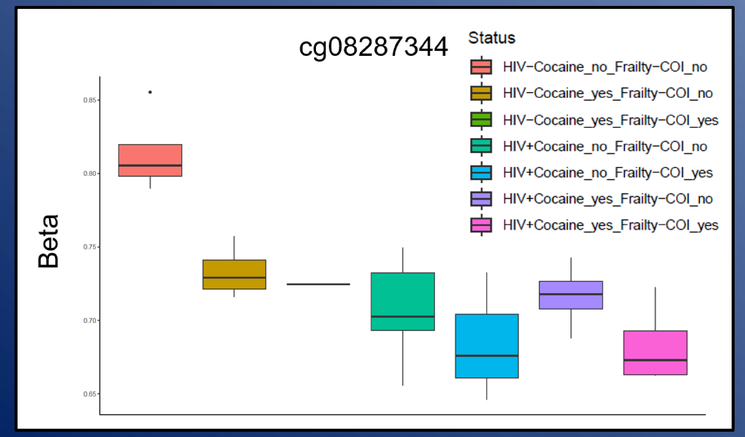
- **Cognitive function declined over time in MASH, with the steepest decline in PLWH who use cocaine (Fig. 1).**

Fig. 2. Increase in pre-frailty prevalence over 18 months in MASH



- **Pre-frailty increased over time in MASH, with the steepest increase in PLWH who use cocaine (Fig. 2).**
- **One CpG site had significant differential methylation patterns among the HIV/COC groups associated with cognitive frailty (p=2.64x10-7 of F-test; p=0.050 for cognitive frailty, p=3.52x10-7 for HIV/COC) (Fig. 3).**
- **DNA methylation levels were lower in PLWH with cocaine use and cognitive frailty compared to participants without HIV, cocaine use, nor cognitive frailty (Fig. 3).**

Fig. 3. CpG site with differential methylation in PBMCs



CONCLUSIONS

- Lower DNA methylation levels indicate changes in gene expression related to inflammation, neurocognitive decline, or drug-related stress.
- PLWH with cocaine use and cognitive frailty show greater epigenetic dysregulation compared to peers without HIV, cocaine use, nor cognitive frailty.
- This suggests cocaine use may exacerbate epigenetic effects of HIV, potentially contributing to poorer cognitive and physical health outcomes. Further research is needed to explore these mechanisms.