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Family history of dementia and APOE e4 status predict neurocognitive trajectories among persons with HIV

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Family history of dementia and APOE ε4 status predict neurocognitive trajectories among
persons with HIV

A dissertation proposal submitted in partial satisfaction
of the requirements for the degree of Doctor of Philosophy

in

Clinical Psychology

by

Maulika Kohli

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2024

The dissertation of Maulika Kohli is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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<div align="right">Chair</div>

University of California San Diego

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2024

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LIST OF ABBREVIATIONS

AD = Alzheimer's disease
AIDS = acquired immunodeficiency syndrome
aMCI = amnestic mild cognitive impairment
APOE-ε4 = apolipoprotein ε4
ART = antiretroviral therapy
Aβ = amyloid beta
CHARTER = CNS HIV Anti-Retroviral Therapy Effects Research
CNS = central nervous system
FDA = Food and Drug Administration
FHD = family history of dementia
HAND = HIV-associated neurocognitive disorders
HCV = Hepatitis C virus
HIV = human immunodeficiency virus
HNRP = HIV Neurobehavioral Research Program at UC San Diego
MDD = major depressive disorder
PWH = people with HIV
SUD = substance use disorder

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ACKNOWLEDGMENTS

VITA

EDUCATION

2024   **San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology**, San Diego, CA
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AWARDS AND HONORS

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2012 – 2016   Undergraduate Dean's List, University of Minnesota, College of Liberal Arts
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Award
2015   Best poster, International Behavioral Neuroscience Society Annual Meeting

RESEARCH PUBLICATIONS

Peer Reviewed Papers

1. **Kohli, M.,** Verstaen, A., Trittschuh, E.H. (*under review*). Factors associated with life satisfaction among Veterans enrolled in the Healthy Aging Project - Brain (HAP-B) psychoeducational class

2. **Kohli, M.,** Saloner, R., Ham, L., Dung, D., Franklin, D., Iudicello, J., Heaton, R., & Moore, D.J. (2024*).* Latent profile analysis of neurocognitive performance and symptoms of depression among people with HIV. *AIDS Patient Care and STDs, 38*(2), 93-106.

3. **Kohli, M.,** Fisher, A., Sun-Suslow, N., Heaton, A., Dawson, M., Marquie, J., Franklin, D., Marquine, M., Iudicello, J., Heaton, R., & Moore, D.J. (2023). Concurrent validity and reliability of teleneuropsychological evaluations among people with and without HIV. *Journal of the International Neuropsychological Society*. doi: 10.1017/S1355617722000777

4. **Kohli, M.,** Serrano, V., Montoya, J.L., Gouaux, B., Atkinson, J.H., & Moore, D.J. (2022). Daily self-report of substance use via text message corresponds to retrospective assessment in people with HIV who use methamphetamine. *Addiction Research & Theory.* doi: 10.1080/16066359.2022.2101639

5. Ham, L., Tang, B., **Kohli, M.,** Grant, I., Moore, D.J. (2022). Four-year trajectories of internal psychological strengths and socio-emotional support among people with HIV. *AIDS and Behavior*. doi: 10.1007/s10461-022-03798-z

6. Paolillo, E. W., Saloner, R., **Kohli, M**., Watson, C. W-M., Moore, R. C., Heaton, R. K. & Moore, D. J. (2021). Binge drinking relates to worse neurocognitive functioning among adults aging with HIV. *Journal of the International Neuropsychological Society*. doi: 10.1017/S1355617721000783

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8. **Kohli, M.,** Pasipanodya, E.C., Montoya, J., Marquine, M., Hoenigl, M., Serrano, V., Cushman, C., Garcia, R., Kua, J., Gant, V., Rojas, S., & Moore, D.J. (2020) A culturally-adapted text-messaging intervention to promote antiretroviral therapy adherence among African Americans: Protocol for a single-arm trial. *JMIR Research Protocols*. doi: 10.2196/21592

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analysis. *Journal of the Association of Nurses in AIDS Care, 31*(5), 587-597. doi: 10.1097/JNC.0000000000000184

10. **Kohli, M.**, Paolillo, E.W., Saloner, R., Umlauf, A., Ellis, R.J., & Moore, D.J. (2020). The effects of low-risk drinking on neurocognition among older persons living with HIV as compared to those without HIV. *Alcoholism: Clinical and Experimental Research.* doi: 10.1111/acer.14379

11. Campbell, L.M., **Kohli, M.**, Lee, E.E., Delagdillo, J.D., Heaton, A., Higgins, M., Kaufmann, C.N., Heaton, R.K., Moore, D.J., Moore, R.C. (2020). Objective and subjective sleep measures are associated with neurocognition in middle-aged and older adults with and without HIV. *The Clinical Neuropsychologist.* doi: 10.1080/13854046.2020.1824280

12. Pasipanodya, E.C., **Kohli, M.**, Fisher, C., Moore, D.J., & Curtis, B. (2020). Perceived risks and amelioration of harm in research using mobile technology to support antiretroviral therapy adherence in the context of methamphetamine use: A focus group study among minorities living with HIV. *Harm Reduction Journal*. doi: 10.1186/s12954-020-00384-1

13. Saloner, R., Paolillo, E.W., **Kohli, M.,** Murray, S.S., Moore, D.J., Grant, I. & Cherner, M. (2020). Genetic variation in alcohol dehydrogenase is associated with neurocognition in men with HIV and History of Alcohol Use Disorder: Preliminary Findings. *Journal of NeuroVirology.* doi: 10.1007/s13365-019-00825-z

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15. Kennedy, B. C., Tran, P. V., **Kohli, M**., Maertens, J. J., Gewirtz, J. C., & Georgieff, M. K. (2018). Beneficial effects of postnatal choline supplementation on long-Term neurocognitive deficit resulting from fetal-Neonatal iron deficiency. *Behavioural Brain Research.* doi: 10.1016/j.bbr.2017.07.043

16. Kennedy, B. C., **Kohli, M.,** Maertens, J. J., Marell, P. S., & Gewirtz, J. C. (2016). Conditioned object preference: an alternative approach to measuring reward learning in rats. *Learning & Memory.* doi: 10.1101/lm.042598.116

Invited Book Chapters

1. Moore, D.J., **Kohli, M.** & Fazeli, P.L. (2024). Geriatric Psychiatry: Assessment of Functioning, 57.3a. In: Sadock BJ, Sadock VA, Ruiz P, (Eds.) Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 11th Edition. Lippincott Williams & Wilkins.

PEER-REVIEWED ABSTRACTS AND PRESENTATIONS

1. **Kohli, M.,** Saloner, R., Ham, L., Dung, D., Franklin, D., Iudicello, J., Heaton, R., & Moore, D.J. (2024, February). Latent profile analysis of neurocognitive performance and symptoms

of depression among people with HIV. Poster presentation accepted to the *52nd meeting of the International Neuropsychological Society*. New York, NY

2. **Kohli, M.,** Campbell, L.M., Sundermann, E., Bondi, M., Gilbert, P., Franklin, D., Letendre, S., Heaton, R.K., Patel, P., Morgello, S., Gelman, B., Clifford, D., Moore, R.C., Moore, D.J. (2023, February*).* Examining the independent and additive effects of family history of dementia and apolipoprotein ε4 on neurocognitive performance among people with HIV. Poster presented the *51st meeting of the International Neuropsychological Society.* San Diego, CA

3. Campbell, L., **Kohli, M.,** Sundermann, E., Fennema-Notestine, C., Barrett, A., Bondi, M., Clifford, D., Ellis, R., Franklin, D., Gelman, B., Grant, I., Heaton, R.K., Letendre, S., Marra, C., Moore, D.J., Morgello, S., Moore, R.C. (2023, February) Apolipoprotein E4 genotype is associated with worse memory and medial temporal lobe integrity in middle-aged persons with HIV. Paper presented at the *51st meeting of the International Neuropsychological Society.* San Diego, CA

4. Ham, L., **Kohli, M.,** Jeste, D.V., Grant, I., Moore, D.J. (2023, February). Differential benefits of internal strengths and socioemotional support on neurocognition and daily functioning among people with HIV. Poster presented at the *51st meeting of the International Neuropsychological Society.* San Diego, CA

5. **Kohli, M.,** Serrano, V., Montoya, J.L., Gouaux, B., Atkinson, J.H., & Moore, D.J. (2022, April). Daily self-report of substance use via text message corresponds to retrospective assessment in people with HIV who use methamphetamine. Poster presented at the *43rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine*. Baltimore, MD.

6. Serrano, V.B., Montoya, J.L., **Kohli, M.,** Pasipanodya, E.C., Marquine, M., Hoenigl, M., Kua, J., Rodriquez, H., Gant, V., Rojas, S., Moore, D.J. (2022, April). The Association Between Self Efficacy for Medication Management and Antiretroviral Adherence among African Americans Living with HIV. Poster presented at the *43rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine*. Baltimore, MD.

7. **Kohli, M.,** Kamalyan, L., Saloner, R., Watson, C.W.M., Lobo, J., Montoya, J.L., Umlauf, A., Ellis, R.J., Grant, I., & Moore, D.J. (2021, June). Effect of lifetime substance use disorders on neuropsychiatric distress among persons with and without HIV. Poster presented virtually at the *44th annual meeting of the Research Society on Alcoholism*. San Antonio, TX.

8. Kamalyan, L., Ham, L., Umlauf, A., **Kohli, M.,** Franklin, D.R., Letendre, S.L., & Grant, I., for the CHARTER Group. (2021, June). Effects of Lifetime Methamphetamine and Alcohol Use Disorder and Socioeconomic Status on HIV-Related Quality of Life. Poster presented virtually at the *44th annual meeting of the Research Society on Alcoholism*. San Antonio, TX.

9. **Kohli, M.,** Fisher, A., Sun-Suslow, N., Heaton, A., Dawson, M., Franklin, D., Iudicello, J., Heaton, R.K., & Moore, D.J. (2021, February). Evidence of the feasibility of video-based neuropsychological evaluations among Persons with and without HIV. Poster presented

virtually at the *49ᵗʰ annual meeting of the International Neuropsychological Society.* San Diego, CA

10. Fisher, A., Campbell, L.M., Sun-Suslow, N., **Kohli, M.,** Tang, B., Lee, E.E., Heaton, A., Moore, R.C. (2021, February) Intra-individual variability in objective sleep quality is associated with worse cognition in middle-aged and older adults with and without HIV. Poster presented virtually at the *49ᵗʰ annual meeting of the International Neuropsychological Society.* San Diego, CA

11. Hussain, M.A., **Kohli, M.,** Karris, M., Iudicello, J.E., Heaton, R.K., Jeste, D.V., Moore, D.J. (2020, September) Loneliness is significantly higher in people with HIV than HIV uninfected individuals and is associated with more psychological resources than social resources. Virtual oral abstract at the *11ᵗʰ International Workshop on HIV & Aging*.

12. **Kohli, M.,** Saloner, R., Paolillo, E.W., Umlauf, A., Ellis, R.J., & Moore, D.J. (2020, May). The effects of recent alcohol consumption and HIV disease on perceived cognition among cognitively healthy adults. Poster virtually presented at the *Judd Research Symposium.* San Diego, CA.

13. **Kohli, M.,** Saloner, R., Paolillo, E.W., Umlauf, A., Ellis, R.J., & Moore, D.J. (2020, June). The effects of recent alcohol consumption and HIV disease on perceived cognition among cognitively healthy adults. Poster virtually presented at the *43ʳᵈ annual meeting of the Research Society on Alcoholism.* New Orleans, LA.

14. **Kohli, M**., Sun-Suslow, N., Paolillo, E.W., Gasemaltayeb, R., Tang, B., Jeste, D.V., Ellis, R., Moore, R.C., & Moore, D.J. (2020, February). Slower Gait Speed is Differentially Associated with Worse Neurocognition among Persons with and without HIV. Poster presented at the *48ᵗʰ annual meeting of the International Neuropsychological Society.* Denver, CO

15. Paolillo, E.W., Saloner, R., **Kohli, M**., Watson, C.W-M., Heaton, R.K., & Moore, D.J. (2019, October). Older Age Exacerbates Negative Effects of HIV and Binge Drinking on Neurocognitive Functioning. Poster presented at the *10ᵗʰ International Workshop on HIV & Aging*. New York, NY.

16. **Kohli, M.,** Kamalyan, L., Pasipanodya, E.C., Moore, R.C., Letendre, S.L., Jeste, D.V., & Moore, D.J. (2019, November). Neurocognitive Correlates of Chronological and Subjective Age Differences in Persons Living with HIV compared to those without HIV. Poster presented at the *39ᵗʰ annual conference of the National Academy of Neuropsychology.* San Diego, CA.

17. Campbell, L.M., **Kohli, M.**, Heaton, A., Higgins, M., Lee, E.E., Kaufmann, C.N., Heaton, R.K., Moore, D.J., & Moore, R.C. (2019, November). Objective and Subjective Sleep Measures are Associated with Neurocognition in Middle-Aged and Older Adults with and without HIV. Poster to be presented at the *39ᵗʰ annual conference of the National Academy of Neuropsychology.* San Diego, CA.

18. **Kohli, M.**, Paolillo, E.W., Saloner, R., Umlauf, A., Ellis, R.J., & Moore, D.J. (2019, June). The Effects of Light-Moderate Drinking on Cognition Among Persons Living with HIV as Compared to those without HIV. Poster presented at the *42ⁿᵈ annual meeting of the Research Society on Alcoholism*. Minneapolis, MN.

19. Paolillo, E.W., Saloner, R., **Kohli, M.**, Watson, C.W-M., Heaton, R.K., & Moore, D.J. (2019, June). Recent Binge Drinking Relates to Neurocognitive Functioning in Adults Living with and without HIV. Poster presented at the *42ⁿᵈ annual meeting of the Research Society on Alcoholism*. Minneapolis, MN.

20. Saloner, R., Paolillo, E.W., **Kohli, M.**, Moore, D.J., Grant, I., & Cherner, M. (2019, June). Alcohol Dehydrogenase 4 Genetic Polymorphism (rs1126671) is Associated with Executive Function and Working Memory in Men with HIV and History of Alcohol Use Disorder. Poster presented at the *42ⁿᵈ annual meeting of the Research Society on Alcoholism*. Minneapolis, MN.

21. Pasipanodya, E.C., **Kohli, M.**, Fisher, C., Moore, D.J., & Curtis, B. (2019, June). Barriers and Facilitators for Participation in Research Using Mobile Technology to Support Antiretroviral Therapy Adherence among Minorities Living with HIV in the Context of Methamphetamine Use. Poster presented at the *14th International Conference on HIV Treatment and Prevention Adherence*. Miami, FL.

22. Richie, M.M., Au, R., Alosco, M.L., Mez, J., **Kohli, M.**, Lin, H., Pfeifer, N., & Comeau, D. (2018, November). Brain Health Monitoring Platform: The Clinical Applications of Digital Technology in Neurological Disorders. Lecture presented at the *Annual Meeting of the Gerontological Society of America.* Boston, MA

23. Au, R., Lin, H., **Kohli, M.**, Zhang, Y., Wong, A., Yang, J., An, A., & Mok, V. (2018, February). E-Cog and e-Home Technologies: Wearable Activity Monitoring and Assessment Technology. Lecture presented at the *46ᵗʰ annual meeting of the International Neuropsychological Society*. Washington DC.

24. Kennedy, B.C., **Kohli, M.**, Maertens, J., Pisansky, M.T., Tran, P.V., Gewirtz, J.C., & Georgieff, M.K. (2015, October). Postnatal Choline Supplementation Ameliorates Long-Term Disruptions in Behavior and Hippocampal Gene Expression Resulting from Fetal Iron Deficiency. Poster presented at the *Society for Neuroscience,* Chicago, IL.

25. Kennedy, B.C., **Kohli, M.**, Maertens, J., Marell, P., & Gewirtz, J.C. (2015, September).

26. Conditioned Object Preference: A Novel Measure of Drug- seeking Behavior in Rodents. Poster presented at the *Pavlovian Society Annual Meeting*, 2015. Portland, OR.

27. Kennedy, B.C., **Kohli, M.**, Maertens, J., Marell, P., & Gewirtz, J.C. (2015, June). Conditioned Object Preference: A Novel Measure of Drug- seeking Behavior in Rodents. Poster presented at the *International Behavioral Neuroscience Society Annual Meeting*, Victoria, BC, Canada.

LOCAL ORAL PRESENTATIONS

1. **Kohli, M.**, Trittschuh, E.H. (2023, September). *Geriatrics for Allied Health Professionals.* Oral presentation at the monthly GRECC Interprofessional Seminar Series, Seattle, WA.

ABSTRACT OF THE DISSERTATION

Family history of dementia and APOE-ε4 status predict neurocognitive trajectories among persons with HIV

by

Maulika Kohli

Doctoral Program in Clinical Psychology

University of California San Diego, 2024
San Diego State University, 2024

Professor David J. Moore, Chair

Rationale: HIV and aging are associated with an increased risk for HIV-associated neurocognitive disorders (HAND) and Alzheimer's disease (AD). Cross-sectional research among people with HIV (PWH) has shown that the apolipoprotein ε4 (APOE-ε4) allele and family history of dementia (FHD+) are independently associated with worse neurocognition. However, these cross-sectional data do not address the potential additive effect of FHD and APOE-ε4 on rates of global and domain-specific neurocognitive decline among older PWH.

Design: This study utilized longitudinal data from the CNS HIV Antiretroviral Therapy Effects Research programs (N=283 PWH; ages 45-69). Aim 1 used a 2x2 factorial analysis of covariance to model independent and interactive effects of FHD and APOE-ε4 status. Aim 2 used linear mixed-effects modeling to examine global- and domain-specific neurocognitive trajectories (average follow-up = 7.0 visits over 5.4 years) in the four FHD/APOE-ε4 groups linearly and non-linearly. The exploratory aim examined if demographic, neuropsychiatric, substance use, daily functioning factors, comorbidities, and HIV disease characteristics impact neurocognitive trajectories by FHD and APOE-ε4 status, using linear mixed-effects modeling.

Results: Cross-sectional analyses revealed lower executive functioning ($p = .03$) and motor skills ($p = .04$) T-scores among FHD+. Global T-scores trended towards significance ($p = .07$), with lower scores among FHD+. Mean differences in motor skills trended towards significance by APOE-ε4 status ($p = .08$), with worse scores among APOE-ε4 carriers. Longitudinal analyses revealed significant and trend-level differences in curvilinear trajectories between the FHD-/APOE-ε4- and FHD+/APOE-ε4+ groups in global performance ($p = .01$), executive functioning ($p = .08$), learning ($p = .02$), delayed recall ($p = .07$), and motor skills ($p = .004$). Lastly, demographics, depression, substance use history, cardiovascular conditions, and HIV-disease characteristics significantly predicted poorer neurocognitive outcomes, with worse global- and domain-specific trajectories in the FHD+/APOE-ε4+ compared to the FHD-/APOE-ε4- group.

Conclusions: FHD+ and APOE-ε4 jointly heighten risk of cognitive decline among middle-to-older age PWH with compounding medical and psychiatric burdens. Additional research is needed to clarify whether domain-specific differences in curvilinear cognitive trajectories between FHD+/APOE-ε4+ and FHD-/APOE-ε4- reflect HAND or early-stages of

AD, considering there were limited sample sizes in follow-up visits and the possibility that

cohorts may have been too young to detect expected neurocognitive decline.

1. INTRODUCTION

Following the introduction of antiretroviral therapy (ART), HIV is now considered a chronic medical condition when treated with ART rather than a rapidly debilitating terminal illness (Antiretroviral Therapy Cohort, 2008). Currently, over 600,000 PWH in the United States are over the age of 45 (Centers for Disease Control and Prevention, 2018). With aging trends projected to continue, the healthcare system is poorly equipped to handle the complex medical needs of the growing number of older PWH experiencing significant comorbidities and conditions of aging (Chu & Selwyn, 2011). Among these challenges is that older PWH are likely at a higher risk for neurocognitive decline associated with both HIV-infection (HIV-associated neurocognitive disorders; HAND) and with age-related neurodegenerative diseases such as Alzheimer's disease (Cohen et al., 2015; D. P. Sheppard et al., 2017). Approximately 40% of PWH have HAND, with the prevalence and severity of impairment increasing in older age (Saylor et al., 2016). Furthermore, both HAND and AD are associated with high health care costs, reduced quality of life, and poor physical health outcomes (e.g., cardiovascular disease) (Association, 2017). As such, there is an urgent public health need to understand pre-determined risk factors that may identify older PWH on the AD trajectory in an effort to promote positive health behaviors that may protect against rapid neurocognitive decline.

The introduction of ART resulted in a significant decrease in the rates of the most severe form of HAND, HIV-associated dementia; however, milder forms of HAND remain prevalent in the ART era, with 30-50% of PWH having neurocognitive impairments associated with HIV (Saylor et al., 2016). HAND is suggested to reflect the neurotoxic impact of HIV infection on the brain, although the exact pathogenesis of HAND remains unclear given the potential impact of other factors that may affect neurocognition (e.g., aging, chronic inflammation) (Mackiewicz et

al., 2019). The most common neurocognitive domain deficits observed in HAND include executive function, learning, and memory (Saylor et al., 2016). Although the specific impact of ART on HAND remains unclear, longitudinal studies have shown that neurocognitive deficits among patients on ART remain fairly stable over time and do not resolve completely. Therefore, HAND is typically non-progressive (Heaton et al., 2023; Heaton et al., 2011; Heaton et al., 2015).

PWH have higher rates of comorbid medical conditions (e.g., cardiovascular conditions, chronic inflammation) that put them at a higher risk for neurodegenerative diseases like Alzheimer's disease (AD) (Cohen et al., 2015; Milanini & Valcour, 2017; Rubin, Sundermann, et al., 2019). The hallmark features of AD include progressive cognitive and functional impairment (Jack Jr et al., 2011) as well as a build-up of diffuse amyloid plaques ($A\beta_{42}$), tau tangles, and neuritic plaques (Strittmatter & Roses, 1996; Vidal et al., 2000; Weigand et al., 2020; Wisniewski & Drummond, 2020). The progression of AD can be generally broken down into three stages: preclinical, mild cognitive impairment, and dementia; although the progression of the disease may differ for each individual (Reisberg et al., 1982). Neurodegeneration in AD is typically initially observed in the medial temporal lobe (MTL) resulting in early atrophy of the hippocampus followed by more widespread atrophy in the temporo-parietal cortex, cingulum, and frontal cortex (Association, 2017; Jack Jr et al., 2011).

In persons without HIV, AD affects approximately 11% of adults over the age of 65, with rising prevalence rates as aging progresses (i.e., 35% among persons age 85 and older) (Association, 2017). Among virally suppressed aging PWH, the neuropathogenesis of HIV is commonly characterized by chronic neuroinflammation, which has been associated with a higher risk of AD (Mackiewicz et al., 2019; Rubin, Sundermann, et al., 2019). Studies have additionally

shown that HIV is associated with an increased prevalence of other AD risk factors including cardiovascular conditions and type 2 diabetes mellitus (Heaton et al., 2011; Milanini & Valcour, 2017). While the potential interaction between HIV-disease and AD pathology remains unclear on neurocognitive impairment, neuropathologic markers (e.g., Aβ, extracellular plaques) are more prevalent among older persons with HIV (Green et al., 2005; Mackiewicz et al., 2019; Soontornniyomkij et al., 2012). Furthermore, HIV-infection has detrimental neurotoxic effects on the brain that can cause neuronal loss, astrocytosis, microgliosis, and synapto-dendritic damage (Everall et al., 1999; Garden et al., 2002; Masliah et al., 1997; Nath, 2002). Therefore, an argument can be made that PWH are at an increased risk of AD due to the compounding effects of both HIV and aging on the brain (Cherner et al., 2004; Kuhn et al., 2018; V. Valcour et al., 2004; Wing, 2016).

1.1 Overlap in presentation of HAND and AD in PWH

There are significant overlaps in the presentation of neurocognitive deficits in HAND and AD; therefore, disentangling HAND from AD remains challenging (Rubin, Sundermann, et al., 2019). HAND is a non-progressive condition characterized by neurocognitive deficits in at least two domains. On neuropsychological testing, HAND may present with psychomotor slowing, attention and concentration deficits, executive dysfunction, and poor learning with memory retrieval. This pattern of impairment is typically associated with fronto-striatal (i.e., basal ganglia and prefrontal structures) dysfunction and consistent with a more "subcortical" cognitive presentation (Becker et al., 1995; Heaton et al., 2015; Peavy et al., 1994; Scott et al., 2011; White et al., 1997). Performance on memory tests in PWH with HAND show relatively normal memory storage and retention, but impaired retrieval and recall of information. On recognition

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testing, PWH with HAND tend to be intact (i.e., can recognize previously learned information) (Becker et al., 1995; Peavy et al., 1994; White et al., 1997).

Conversely, AD is a progressive condition associated with accelerated memory decline, rapid forgetting, and confrontational naming impairment, along with decline in other higher level cognitive functions that may have deleterious effects in a real-world setting (Jack Jr et al., 2011; Smith & Bondi, 2013). The pattern of impairment on neuropsychological testing is typically described as "amnestic," with encoding, storage, and retrieval deficits observed as prominent learning, recall, and recognition memory deficits (Smith & Bondi, 2013). This pattern is consistent with early atrophy in the medial temporal lobe. As AD progresses, cortical atrophy advances to the remainder of the cortex along a temporal-parietal-frontal trajectory, with motor areas generally spared until the late disease stages. As such, language (i.e., category fluency), executive function, and visuo-spatial deficits follow after episodic memory impairment, consistent with "cortical" dementia presentations (Pini et al., 2016).

Possible distinguishing characteristics in neuropsychological profiles between HAND and AD include rapid forgetting and poor recognition on free recall memory tasks as well as impaired confrontational naming, both of which are hallmarks of typical AD and less common of HAND (see Table 1). Deficits in other domains may not be as helpful in differentiating between these two diagnoses as deficits in other domains are prevalent in both conditions. For instance, executive dysfunction is common in HAND. While deficits in executive function may have a later onset in AD than memory impairment, these deficits are also quite common. Therefore, the presence of executive functioning deficits could point towards HAND, AD, or a mixed HAND and AD profile. Understanding the neurocognitive trajectories of these diseases and whether

certain risk factors (i.e., APOE-ε4, family history of dementia) are associated with varying

trajectories may aid in differential diagnosis.

Table 1. Summary of the key features differentiating HAND from AD in PWH

	HAND	**AD**
Neurocognitive dysfunction	Focal cognitive impairment	Global cognitive impairment
Memory	Poor learning Impaired recall Intact recognition	Impaired learning Impaired recall Impaired recognition
Activities of Daily Living	Typically intact	Impaired
Disease Progression	Fluctuating course	Progressive decline
Aβ$_{42}$	Inconsistently increased	Very increased
p-tau	Inconsistently increased	Increased

1.2 Importance of Distinguishing between HAND and AD

Given these similarities in cognitive presentation, older PWH with cognitive impairments

are at a risk of being misclassified as HAND, due to HIV diagnosis, when they may be on an AD

trajectory (Sperling et al., 2011). AD is associated with progressive atrophy that results in

cognitive and functional decline; whereas HAND is more stable (see Figure 1) (Rubin,

Sundermann, et al., 2019). Therefore, it is important to correctly identify the etiology of

neurocognitive impairments among PWH to allow for early intervention (e.g., immunotherapy,

lifestyle modifications to reduce risk factors) when interventions may be most effective and

beneficial, considering the progressive nature of AD. A misdiagnosis of HAND when an older

PWH is on the AD trajectory limits the opportunity to slow or prevent the development of future

disease (Sperling et al., 2011). Furthermore, accurate diagnosis of HAND may relieve concerns in PWH without indication of AD trajectory.
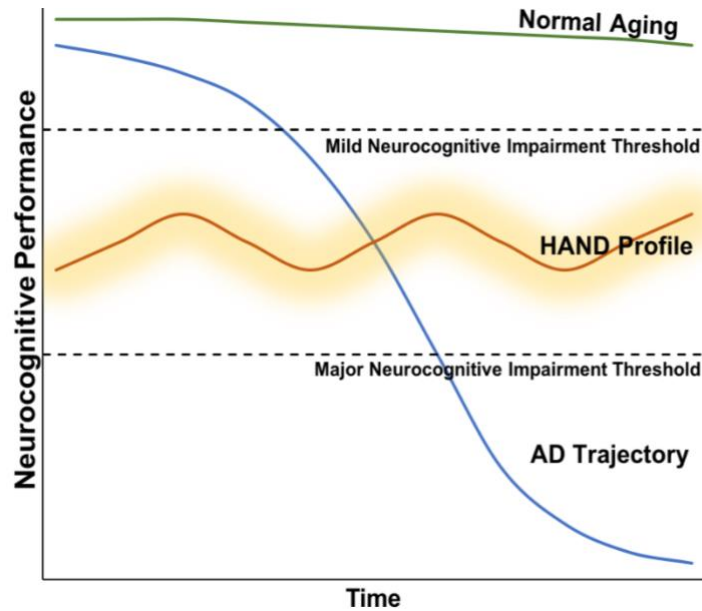
Figure 1. HAND vs. AD Trajectories
The green line shows the hypothesized normal aging trajectory, in which there may be some decline, but impairment does not reach the threshold to meet criteria for mild neurocognitive disorder. The red line depicts the HAND trajectory, where there may be some fluctuation, but it does not progress to major neurocognitive impairment. The blue line depicts the AD trajectory, in which there would be a significant decline over time to major neurocognitive impairment (i.e., dementia).

While there is a newly FDA approved immunotherapy drug (Aducanumab) available that has been associated with a reduction in Aβ-PET signal, clinical trials did not find evidence that the reduction slows cognitive and functional decline (Krudys, 2020). Therefore, future clinical research is necessary to validate Aducanumab's clinical efficacy and effectiveness at different stages of AD. Alternatively, it may be possible to prevent or delay progression to dementia with early lifestyle modifications to minimize known risk factors for AD. Vascular diseases and dementia syndromes have several shared risk factors including hypertension, type 2 diabetes, smoking tobacco, and poor diet, which can be prevented or managed with lifestyle changes as

recommended by the World Health Organization (2019). Furthermore, receiving a timely diagnosis is valuable for access to specialty care (e.g., neurology, memory clinics, caregiver support programs), symptom management, acquisition of compensatory strategies, enhancing quality of life, maintaining functional independence, and planning for the future (Sherman et al., 2017).

In a clinic-based population study of 970 patients with dementia (AD, vascular dementia, and AD with cerebrovascular disease), a shorter time between symptom onset and initial medical visit was significantly related to longer survival, regardless of dementia syndrome (Bruandet et al., 2009). Additionally, three recent case reports on AD in PWH have reported the risk of delayed diagnosis of AD, detailed complications determining etiology of cognitive impairment, and underscored the clinical need for predispositional markers to indicate AD (Turner et al., 2016). Identifying risk factors for AD and understanding clinical presentation is critical for improving diagnostic accuracy and providing appropriate clinical care that may help protect against worse cognitive and physical health outcomes in older PWH (Ritchie et al., 2015; Sperling et al., 2011).

1.3 Evidence that APOE-ε4 Status is Associated with AD and HAND.

AD has high heritability and there is a well-established genetic component to risk for neurodegenerative diseases such as AD (Corder et al., 1993; Henderson et al., 1995; Poirier et al., 1993). The apolipoprotein ε4 (APOE-ε4) allele is a genetic marker associated with increased amyloid deposition in cerebral vessels, medial-temporal lobe tau, and development of plaques in AD (Strittmatter & Roses, 1996; Vidal et al., 2000; Weigand et al., 2020; Wisniewski & Drummond, 2020). Among HIV- samples, APOE-ε4 has been associated with lower baseline neurocognitive functioning (Mungas et al., 2010) as well as declining performance in verbal

memory (word list immediate recall), executive function, confrontational naming, and visuo-spatial abilities (Bretsky et al., 2003; Mungas et al., 2010; Turana et al., 2015). In a longitudinal study of "relatively high functioning" older adults aged 70 to 79 part of the MacArthur Successful Aging Study, APOE-ε4 carriers showed cognitive decline in confrontational naming and visuo-spatial abilities. Furthermore, APOE-ε4 carriers were twice as likely to have declines in global neurocognitive function after 7 years compared to noncarriers (Bretsky et al., 2003).

The role of APOE-ε4 in neurocognitive impairment among PWH has been less clear. While there is ample evidence linking APOE-ε4 to accelerated HIV disease progression and increased susceptibility to infections (Mahley et al., 2009); the heritability for AD pathology cannot be fully explained by APOE-ε4 status (Daw et al., 2000; Huang et al., 2004). There are discrepant findings in the literature regarding the influence of APOE-ε4 on cognitive performance among PWH as well as whether APOE-ε4 is associated with a higher susceptibility to HAND. Several studies have found no association between APOE-ε4 status and HAND diagnosis (Becker et al., 2015; Joska et al., 2010; Morgan et al., 2013). Conversely, numerous studies have shown that having at least one APOE ε4 allele is associated with decreased cognitive performance, reduced brain white matter integrity, brain atrophy, and Aβ42 plaques in PWH (Chang et al., 2011; Chang et al., 2014; Spector et al., 2010; Wendelken et al., 2016). Moreover, a recent meta-analysis of 20 studies among PWH showed evidence that APOE-ε4 is a risk genotype for HIV-associated cognitive impairments in the domains of verbal fluency, learning, executive function, and memory (Mu et al., 2022).

The contradictory findings across the literature may be, in part, attributable to an age dependence of the APOE-ε4. Limitations of previous studies are that study samples were comprised of individuals younger than expected to show neurocognitive deficits (Becker et al.,

2015; Joska et al., 2010; Morgan et al., 2013). In a sample of 249 PWH (mean age = 43 years), results revealed no association between APOE-ε4 status and cognitive functioning in the total sample; however, the older (≥ 50 years) APOE-ε4 carriers performed worse on executive functioning and processing speed tests and showed a significantly higher risk (odds ratio = 13.14) for diagnosis of HAND compared with the age-matched noncarriers (Panos et al., 2013). The pattern of cognitive impairment, atrophy, white matter integrity damage, and plaque deposition suggests exacerbation of HIV-related pathology (Soontornniyomkij et al., 2012; Wendelken et al., 2016), indicating that the APOE-ε4 allele may contribute to a higher risk of developing HAND. Considering, APOE- ε4 status has been suggested to accelerate HIV disease progression (Kuhlmann et al., 2010) and evidence that the neurocognitive effects of APOE-ε4 manifest later in age (Panos et al., 2013; V Valcour et al., 2004), further investigation of the effects of APOE-ε4 on neurocognitive trajectories among aging PWH is warranted.

1.4 Evidence that Family History of Dementia is Associated with HAND and AD in PWH

Family history of dementia (FHD) is considered an inexpensive proxy for genetic markers (Liu et al., 2017) as it is commonly assessed via self-report measures (Reid et al., 2009). It is conceptualized as a composite factor of both known and unknown genetic risks for AD as well as environmental factors (e.g., socioeconomic status) (Borenstein et al., 2006; Donix, Ercoli, et al., 2012; Gatz et al., 2006). In persons without HIV, first-degree family history of dementia is associated with a higher risk for developing the disease compared to those without family history of dementia (Cannon-Albright et al., 2019; Donix, Ercoli, et al., 2012; Mayeux et al., 1991; Scarabino et al., 2016).

Longitudinal research studies have shown that a parental family history of AD related to lower baseline neurocognitive performance, particularly in the domains of processing speed,

executive functioning, and memory (Donix, Ercoli, et al., 2012). Although limited studies have investigated the interactive or combined effects of family history of dementia and APOE-ε4 status, few studies suggest associations between first-degree family history and APOE-ε4 both independently and synergistically with brain anatomy (Donix et al., 2010; Donix, Ercoli, et al., 2012; Donix, Small, et al., 2012; Yi et al., 2018). Another longitudinal study found that FHD was associated with an increased risk of AD only among APOE-ε4 carriers, suggesting a gene-environment interaction (Huang et al., 2004).

Limited studies have investigated FHD within the context of aging and HIV (Donix, Small, et al., 2012); however, one study suggests that PWH who are FHD+ have significantly worse global neurocognitive function compared to PWH who are FHD- (Moore et al., 2011). Considering the cross-sectional design of the previous study, it is unclear whether the association reflects a link between FHD and HAND or to the early stages of AD.

1.5 Middle age: a critical time for AD

Middle age is a critical time in which brain changes (i.e., AD pathology and medial-temporal lobe atrophy) that are associated with cognitive decline in older age, begin to emerge (Ritchie et al., 2015; Sutphen et al., 2015; Villemagne et al., 2011). Longitudinal research studies have found that the onset of these brain changes occur several years before cognitive impairment in AD (Okonkwo et al., 2014; Singh-Manoux et al., 2012). Studies investigating cognitive trajectories beginning in midlife have shown that subtle differences in cognition can help predict AD progression several years later (Clark et al., 2016; Kremen et al., 2014). Furthermore, research suggests that midlife risk factors (e.g., hypertension, type 2 diabetes mellitus, obesity, lower physical activity) are associated with future cognitive decline, suggesting that midlife represents a critical period in aging in which middle-age adults at a higher risk for AD (e.g.,

APOE-ε4+, FHD+) should be carefully monitored and assessed for AD symptoms and pathology (Bangen et al., 2013; Rovio et al., 2005; Schubert et al., 2019; Whitmer et al., 2005).

In the HIV literature, the majority of aging research has focused on PWH in midlife; however, this will change as aging trends are predicted to continue (Centers for Disease Control and Prevention, 2018). In PWH, age-associated comorbidities appear 5-10 years earlier and increase risk for neurocognitive impairment related to HAND and AD (Centers for Disease Control and Prevention, 2018). Due to the neurotoxic effects of HIV (Everall et al., 1999; Garden et al., 2002; Masliah et al., 1997; Nath, 2002), as well as medical comorbidities and possible accelerated brain aging (Cohen et al., 2015; Kuhn et al., 2018; David P Sheppard et al., 2017), PWH also may have less brain reserve (Foley et al., 2012; Milanini et al., 2016; Morgan, Woods, Smith, et al., 2012) to compensate for accumulating neurodegenerative pathology (Horvath & Levine, 2015; Kuhn et al., 2018). Therefore, cognitive deficits indicative of AD trajectory may appear earlier in PWH (Cohen et al., 2015). Taken together, examining PWH in mid-life is advantageous as it could identify those with early signs of AD cognitive trajectories.

1.6 Specific Aims and Hypotheses

This project aims to investigate the relationships between FHD, APOE-ε4 status and neurocognitive decline in middle- to older-age (aged 35-69 years) PWH. The specific aims of this study are:

Aim 1. To determine whether FHD and APOE-ε4 status is associated with worse global- and domain-specific neurocognition among middle-to-older age adults living with HIV. *Hypothesis 1a:* Neurocognition will be worse in the FHD+ group as compared to the FHD-group. *Hypothesis 1b:* Neurocognition will be worse in the APOE-ε4+ group compared to the APOE-ε4– group. *Hypothesis 1c:* There will be an interactive effect of FHD and APOE-ε4

status such that neurocognition will be worst in the FHD+/APOE-ε4+ group then the FHD+/APOE-ε4–, FHD-/APOE-ε4+, and FHD-/APOE-ε4– groups.

Aim 2. To compare longitudinal (up to 15 years) neurocognitive trajectories between FHD and APOE-ε4 status groups to determine whether neurocognitive trajectories are predicted by FHD and APOE-ε4 status. *Hypothesis 2:* Global- and domain-specific neurocognition will worsen more rapidly in FHD+/APOE-ε4+ group followed by the FHD+/APOE-ε4–, FHD-/APOE-ε4+ groups; and be most stable in the FHD-/APOE-ε4– group.

Aim 3. Examine if demographic (e.g., sex); neuropsychiatric (e.g., depression), substance use (e.g., alcohol use), daily functioning factors (e.g., employment); comorbidities (e.g., traumatic brain injury, Hepatitis C) and HIV disease characteristics (e.g., plasma viral load) impact neurocognitive trajectories by FHD and APOE-ε4 status.

2. METHODS

The proposed study will retrospectively analyze de-identified cross-sectional and longitudinal data from individuals enrolled in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) program (HHSN271201000036C). In accordance with CHARTER policy, I have received formal approval to use the deidentified longitudinal data for the proposed study (NNTC Request Number: R705).

2.1 Participants

To evaluate Aims 1, 2 and 3, the proposed study will include baseline and follow-up neuropsychological data of PWH enrolled in CHARTER from 2002-2020. CHARTER recruited a wide-range of ages. Therefore, to study the effect of aging with HIV, the age range for the current study will be restricted to participants that were aged 45 or older at the time of baseline evaluation. The proposed study will include 283 PWH between ages 45-69 at the baseline evaluation. The average age of participants is 50 years old, 40% are non-Hispanic white, 50% are Black/African American, and 78% are male. While the majority of participants are male, this is reflective of the current demographics of people with HIV in the United States (Centers for Disease Control and Prevention, 2017). All participants completed a blood draw and comprehensive neuropsychological-, neuromedical-, and neuropsychiatric evaluation. HIV serostatus was determined by enzyme-linked immunosorbent assay (ELISA) with a confirmatory Western Blot. Inclusion criteria for the current study will be completion of 2-20 CHARTER study visits occurring in 6-month follow-up intervals (mean visits = 7). Participants were drawn from six participating sites: Johns Hopkins University, Mt. Sinai School of Medicine, University of California San Diego, University of Texas Medical Branch, University of Washington, and

Washington University in St. Louis. All CHARTER study procedures were approved by local Institutional Review Boards, and all participants provided written informed consent.

2.2 Participant Characterization and Inclusion/Exclusion Criteria

Participant inclusion criteria were broad and did not exclude on the basis of comorbid conditions that may impact cognitive function. CHARTER recruited PWH that broadly reflect the geographic and sociodemographic diversity of HIV patients at university-affiliated treatment centers across the U.S. Participants were screened based on Frascati criteria for HIV-associated Neurocognitive Disorders (HAND) guidelines for classifying comorbidity burden (Antinori et al., 2007; Heaton et al., 2010). Developmental and neuromedical histories of each participant were extensively reviewed by Dr. Robert K. Heaton, and re-reviewed by an independent CHARTER clinician investigator (Dr. David Clifford), to determine the extent to which non-HIV-related comorbidities confounded the interpretation of neurocognitive functioning. To focus the current analyses most directly on effects of HIV and aging, participants with severely "confounding" (Antinori et al., 2007; Heaton et al., 2010) comorbidities will be excluded from this project. This decision is further supported by a recent CHARTER paper showing that those with severe "confounding" comorbidities had overall worse brain integrity, but those with moderate comorbidities (i.e., "contributing" comorbidities) had fairly equivalent brain abnormalities as those with mild comorbidities (i.e., "incidental" comorbidities) (Saloner et al., 2019).

CHARTER exclusionary conditions included history of severe learning disability (e.g., <70 on the WRAT-IV)(Wilkinson, 1993), diagnosis of a psychotic (e.g. schizophrenia) or mood disorder with psychotic features, major neurological conditions that may impair neurocognitive functioning (e.g., stroke), and evidence of intoxication by illicit substances (except marijuana) by

positive urine toxicology screen or Breathalyzer test for alcohol on the day of testing (Heaton et al., 2010). Additionally, individuals with an estimated duration of HIV disease <5 years were excluded to ensure the study sample reflects participants with chronic HIV.

2.3 Neuropsychological Evaluation

At each study timepoint, participants completed a standardized battery of neurocognitive tests designed to provide a comprehensive assessment of neurocognitive domains most affected in HIV: verbal fluency, executive functioning, processing speed, learning, delayed recall, attention/working memory, and motor skills. In cross-sectional analyses, individual raw scores were converted into demographically adjusted (i.e., age, sex, education, race/ethnicity) T-scores, which were averaged within each domain across the entire battery to derive mean global- and domain-specific T-scores (A Antinori et al., 2007; RK Heaton et al., 2004; Heaton et al., 2003). In longitudinal analyses, raw test scores from the follow-up visit were transformed into practice-effect corrected T-scores using published norms for change (Cysique et al., 2011). A global deficit scores (GDS) was derived by converting T-scores for each domain into an averaged deficit score, ranging from 0 (no impairment) to 5 (severe impairment). Participants with a GDS greater than or equal 0.5 were considered neurocognitively impaired, and those with a GDS less than 0.5 were deemed cognitively unimpaired (Blackstone et al., 2012)

2.4 Family History of Dementia

All participants completed self-report assessments capturing FHD. Participants enrolled in CHARTER completed a free-response question capturing FHD of a first-degree (i.e., biologic parent, sibling, or offspring) and second-degree (i.e., biologic grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) relative. A follow-up question assessed whether the FHD was from the maternal or paternal side of the family. A dichotomized, family history of Alzheimer's

disease and any type of dementia variable (yes/no) will be included in analyses for the proposed project (Moore et al., 2011).

2.5 APOE-ε4 Status

As part of the neuromedical examination for CHARTER, participants underwent a blood draw for which plasma and serum are collected and peripheral mononuclear blood cells are stored. For the CHARTER Host Genetics projects, DNA was extracted from peripheral mononuclear blood cells using standard procedures. Rs7412 and rs429358 (which define the APOE-ε4 isoform) were genotyped using TaqMan predesigned SNP genotyping assays. (Applied Biosystems; Foster City, California) (Morgan et al., 2013). As described above, CHARTER participants with confounding comorbidities that may explain neurocognitive performance have been excluded (Heaton et al., 2010).

2.6 Neuromedical Evaluation

Participants completed a standard HNRP neuromedical evaluation at baseline including: 1) current and nadir CD4 counts; 2) CDC HIV staging; 3) HIV RNA measured in plasma; 4) estimated duration of HIV infection; 5) current ART regimen; 6) comorbid conditions (e.g., hepatitis C co-infection, diabetes); and 7) routine clinical chemistry panels (e.g., glucose, lipids) (R. Heaton et al., 2010). Additional details on the standardized CHARTER neuromedical assessment can be found in Heaton et al. (2010). These variables will be reported in order to characterize the study sample, and some variables may be covariates in the statistical analyses (see Data Analytic Approach).

2.7 Data Analytic Approach

Findings will be considered significant at $p<0.05$. Effect sizes will also be examined and reported rather than fully relying on p-values. Statistical assumptions will be checked prior to all

testing. JMP Pro version 17.0.0 (JMP®, Version *<17.0.0>*. SAS Institute Inc., Cary, NC, 1989-2007) will be used for Aim 1, and R version 3.5.0 will be used to examine Aims 2 and 3. Linear mixed-effects models will be examined with the "lme4" package.

Our primary outcome for all aims is neurocognitive performance. For cross-sectional analyses, we will use demographically-corrected global- and domain-specific *T*-scores. For longitudinal analyses, practice-effect corrected T-scores will be used for each participant, which are adjusted for practice effects and baseline cognition (Cysique et al., 2011). Domain-specific scores will be evaluated irrespective of global results, as specific domains (e.g., memory) may be affected by FHD and APOE-ε4 status.

Aim 1. A 2x2 factorial analysis of covariance (ANCOVA) will be used to model independent and interactive effects of FHD and APOE-ε4 status. Covariates (e.g., demographics, comorbidities, HIV disease characteristics) will be selected by evaluating the bivariate relationships between potential covariates and global and domain-specific *T*-scores. If a potential covariate is significantly associated with cognition, it will be entered as a covariate in the model. Power analysis was conducted using GPower version 3.1.9.7 (Erdfelder et al., 1996). These analyses will be powered ($1-\beta = 0.75$) to detect medium effect sizes ($d = 0.50$), with a two-tailed $\alpha = 0.05$, and up to 5 covariates.

Aim 2. Linear mixed-effects modeling for continuous data will be used to examine change in global- and domain-specific neurocognitive performance. The mixed-model analysis will include random intercepts, a random effect for time (i.e., years since baseline visit), and FHD/APOE-ε4 groups as the predictors of the primary outcomes (i.e., change in neurocognitive performance). Additionally, potential curvilinear effects will be explored to comprehensively understand the nuanced relationship between these genetic and familial risk factors and

neurocognitive decline over time. Covariates will include baseline age, sex, and covariates

identified in Aim 1. Covariates that vary over time (e.g., CD4 count) will be averaged within-

persons across study visits to generate person-mean values. Bonferroni corrections for multiple

comparisons will be applied.

Power analysis was conducted using PowerUpR v1.1.0. These analyses will be powered

$(1-\beta = 0.97)$ to detect small-medium effect sizes ($d = 0.35$), with a two-tailed $\alpha = 0.05$. Multi-

level modeling was selected because it uses all available data and gives heavier weight to

participants with more waves of data. Therefore, this methodology can account for participants

that may have missed a follow-up visit and samples that have a differing number of follow-up

assessments.

Aim 3. Linear mixed-effects modeling will be used to investigate if demographic,

neuropsychiatric, substance use, daily functioning factors, comorbidities, and HIV disease

characteristics impact neurocognitive trajectories, and whether these effects differ by FHD and

APOE-ε4 status. Exploratory variables will be specified as predictors, as well as in models

stratified by FHD/APOE-ε4 group.

2.8 Implications and Relevance

The proposed study represents an important step toward understanding ways in which we

may improve early detection of AD, accurate diagnosis of HAND vs. AD, and protect against

poor cognitive health outcomes in older PWH. Self-report assessment measures are routinely

used in clinical assessment to capture relevant health factors and history that may help elucidate

risk and protective factors of neurocognitive diseases. Family history of dementia is a valuable

and informative genetic-proxy marker that may indicate higher risk for accelerated cognitive

aging among middle- to older age adults; however, the majority of aging/AD studies exclude

PWH. Consequently, it is unclear if aging/AD research on family history of dementia is generalizable to adults with HIV. Considering the heritability of AD pathology may not be fully explained by APOE-ε4 status in PWH, this study directly assesses a void in the HIV and aging literature by examining the genetic and genetic-proxy markers relevant to both AD and HIV.

3. RESULTS

3.1 CHARTER Participant Characteristics

Participant demographic and clinical characteristics are displayed in Table 2. Data presented in Table 2 represents participants' first visit for this analysis. Participants were on average in their early-50s [range = 45 - 69], predominantly male, approximately half reported being African American/Black, and had some college education.

In terms of neurocognitive functioning at baseline, 52% were classified as neurocognitively impaired via Frascati criteria for HAND (A. Antinori et al., 2007; R.K. Heaton et al., 2004). Average T-score for global, executive functioning, working memory, delayed recall, and motor skills was around 44-46. Verbal fluency and processing speed were above the average at a T-score of 49, whereas the average T-score for learning fell below the average at 42.

Table 2. Participant demographic and neurocognitive characteristics (N=280)

	M (SD), n (%)
Demographic Variables	
Age (years)	51.0 (5.1)
Education (years)	13.2(2.6)
Sex (Male)	218 (77.9%)
Ethnicity	
African American/Black	139 (49.6%)
Non-Hispanic White	111 (39.9%)
Hispanic/Latino	25 (8.9%)
"Other"	5 (1.8%)
Baseline Neurocognitive Functioning	
GDS (impaired)	145 (52.0%)
Global T-score	46.2 (5.9)
Verbal Fluency T-score	49.3 (8.2)
Executive Function T-score	45.9 (8.4)
Processing Speed T-score	48.8 (8.7)
Learning T-score	42.2 (7.8)
Delayed Recall T-score	44.7 (8.3)
Working Memory T-score	45.7 (9.0)
Motor Skills T-score	45.4 (9.4)

Note. GDS = global deficit score; GDS $\geq$ 0.5 were considered neurocognitively impaired

With regard to clinical characteristics at baseline (Table 3), approximately 35% of participants had HCV, 47.5% had a history of major depressive disorder, and 73% (206 participants) had a lifetime history of substance use disorder (157 alcohol, 120 cocaine, 78 cannabis, 62 opioid, 25 methamphetamine, 25 sedative, 24 hallucinogen, 10 inhalant, 9 prescription drug, and 7 "other"). At the first study visit, forty-three participants (15.5%) met criteria for current major depressive disorder and fourteen met criteria for a current substance use disorder (9 cocaine, 5 alcohol, 1 cannabis, 1 sedative, 1 other). 22.8% of participants were considered APOE-ε4+ which was defined as having at least one APOE-ε4 allele. Participants that were APOE-ε2/4+ were excluded from Aims 1 and 2. Participants were considered FHD+ if they reported a family history (first- or second-degree relative) of Alzheimer's disease and any type of dementia. 21.8% of participants were FHD+. A chi-square test of independence was performed to examine the relation between FHD and APOE-ε4 status. The association between these variables was not significant, χ^2 (1, N = 283) = 2.403, $p = .121$.

In terms of HIV disease characteristics at baseline, over half of participants (65.0%) had a history of AIDS. The median number of years living with HIV was 12.3 and the median CD4 count was 459. Approximately 80% of participants were on ART and 50% had an undetectable plasma viral load (<50 copies/ml).

Table 3. Participant clinical characteristics (*N*=283)

	M (SD), median [IQR], n (%)
Comorbid Conditions	
Hyperlipidemia	31 (11.1%)
Hypertension	67 (23.9%)
Diabetes mellitus	31 (11.1%)
Hepatitis C	98 (35.0%)
LT MDD	132 (47.5%)
Current MDD	43 (15.5%)
LT substance use disorder	203 (73.0%)
Current substance use disorder	14 (5.0%)
APOE Genotype	
APOE ε4 (positive)	64 (22.8%)
APOE Genotype	
2/2	4 (1.9%)
2/3	32 (15.3%)
3/3	109 (52.2%)
3/4	50 (23.9%)
4/4	14 (6.7%)
Family History of Dementia	
Family History of Dementia (positive)	61 (21.8%)
HIV Characteristics	
History of AIDS	182 (65.0%)
Current CD4	459 [297 – 653]
Nadir CD4	150 [42 – 283]
Duration of HIV disease (years)	12.3 [7.1 – 16.2]
On ART	223 (78.8%)
Detectable viral load[a]	138 (50.0%)

Note. LT lifetime; MDD = Major Depressive Disorder; ART = antiretroviral therapy
[a]Defined as >50 copies/mL in plasma

Comparisons in participant baseline demographic, clinical, and neurocognitive characteristics by FHD/APOE-ε4 status group are presented in Table 4. In terms of demographics, group differences in age at baseline were significant, with younger PWH in the FHD+/APOE-ε4+ group compared to the other FHD/APOE-ε4 groups (*p* = .029). All psychiatric, medical, and HIV disease characteristics were comparable across groups. Regarding neurocognitive function, proportion of participants classified as cognitively impaired at baseline did not differ by FHD/APOE-ε4 groups. Global T-scores also did not significantly differ

between groups. Results revealed neurocognitive domain level differences that approached

statistical significance in motor skills T-scores. The FHD+/APOE-ε4- had lower motor skills T-

scores (p = .052) compared to the FHD-/APOE-ε4+ groups.

Table 4. Participant baseline demographic, clinical, and neurocognitive characteristics by FHD/APOE-ε4 status group

	A FHD-/APOE ε4- n=174	B FHD-/APOE ε4+ n=45	C FHD+/APOE ε4- n=42	D FHD+/APOE ε4+ n=19	p value	Group dif.
Demographics						
Age (years)	50.7 (4.9)	52.4 (4.6)	51.8 (6.4)	48.6 (2.9)	**.029**	D < B
Education (years)	13.1 (2.8)	13.0 (2.2)	13.2 (2.6)	13.8 (2.3)	.738	
Sex (male)	141 (81%)	35 (78%)	31 (74%)	11 (58%)	.125	
Ethnicity (Non-Hispanic White)	73 (42%)	9 (20%)	21 (50%)	8 (42%)	.121	
# of visits	5.9 (4.7)	7.2 (5.4)	6.6 (5.2)	6.2 (5.4)	.433	
Years followed by study	5.8 (4.8)	4.2 (3.7)	5.5 (4.5)	3.7 (3.6)	.061	
Comorbid Conditions						
Hyperlipidemia	20 (11.5%)	6 (13.3%)	4 (9.5%)	1 (5.3%)	.891	
Hypertension	40 (23.0%)	13 (28.9%)	10 (23.8%)	4 (21.1%)	.856	
Diabetes mellitus	17 (9.8%)	8 (17.8%)	5 (11.9%)	1 (5.3%)	.409	
Hepatitis C	61 (35.1%)	18 (40.0%)	12 (28.6%)	7 (36.8%)	.736	
LT MDD	80 (46.2%)[a]	22 (48.9%)	21 (50.0%)	9 (50.0%)[b]	.959	
Current MDD	27 (15.6%)[a]	7 (15.6%)	8 (19.1%)	1 (5.6%)[b]	.671	
LT SUD disorder	127 (73.4%)[a]	34 (75.6%)	29 (69.1%)	13 (72.2%)[b]	.916	
Current SUD disorder	9 (5.2%)[a]	2 (4.4%)	1 (2.4%)	2 (11.1%)[b]	.551	
HIV Characteristics						
History of AIDS	110 (63%)	32 (71%)	30 (71%)	10 (53%)	.398	
Detectable plasma viral load[c]	88 (51%)	20 (47%)	20 (48%)	9 (47%)	.953	
Current CD4 count	446 [297-640]	504 [324-693]	489 [293-680]	444 [283-607]	.765	
Nadir CD4 count	157 [37-295]	110 [33-272]	110 [51-251]	193 [54-400]	.529	
Years of HIV disease	11.8 (6.0)	11.4 (5.7)	11.7 (6.3)	11.2 (7.4)	.962	
ART Status	135 (78%)	40 (89%)	34 (81%)	12 (63%)	.120	
Neurocognition						
Cognitive Impairment	79 (45%)	15 (33%)	22 (52%)	8 (42%)	.327	
Global T-score	46.2 (5.8)	47.6 (5.2)	44.9 (6.6)	45.3 (6.3)	.176	
Verbal Fluency T-score	49.4 (8.4)	49.8 (8.1)	47.7 (8.2)	51.2 (7.0)	.429	
Executive Function T-score	46.4 (8.1)	46.8 (9.4)	44.5 (9.4)	42.4 (9.9)	.132	
Processing Speed T-score	48.5 (8.6)	50.9 (8.7)	48.5 (9.2)	46.9 (8.7)	.293	
Learning T-score	42.0 (7.6)	44.7 (7.2)	41.4 (8.3)	40.3 (8.7)	.099	
Delayed Recall T-score	45.1 (8.3)	44.0 (7.2)	44.0 (8.9)	43.9 (10.0)	.743	
Working Memory T-score	45.6 (8.7)	47.2 (9.2)	44.2 (9.9)	46.1 (8.6)	.481	
Motor Skills T-score	45.6 (9.5)	47.8 (8.9)	42.2 (9.8)	45.8 (7.9)	**.052**	C <B

Note. [a]n=173; [b]n=18; Values presented as Mean (SD), n (%), or median [IQR]. LT=lifetime; MDD = Major Depressive Disorder; SUD = Substance Use Disorder; ART = antiretroviral therapy
p-values were calculated using Wilcoxon Signed-Rank Tests for non-normally distributed continuous outcomes or t-test for normally distributed continuous outcomes. Chi-squared statistics were used for dichotomous outcomes
[c]Defined as >50 copies/mL in plasma

3.2 Aim 1: To Determine if FHD and APOE-ε4 status are Associated with Neurocognition

Separate independent *t*-tests were used to examine group differences in neurocognitive outcomes by FHD status and APOE-ε4 status. Mean differences in global T-scores by FHD status trended towards significance, such that participants with FHD ($M = 45.02$, $SD = 6.43$) had lower global T-scores compared to participants with no FHD ($M = 46.57$, $SD = 5.70$; $t(281) = -1.83$, $p = .0689$). Results revealed significant mean differences in executive function T-scores (FHD+: $M = 43.84$, $SD = 9.56$; FHD-: $M = 46.54$, $SD = 7.93$; $t(281) = -2.25$, $p = .0252$) and motor T-scores (FHD+: $M = 43.32$, $SD = 9.34$; FHD-: $M = 46.08$, $SD = 9.37$; $t(278) = -2.04$, $p = .0427$) with lower scores among FHD+ participants compared to FHD- (Figure 2). Mean differences in motor skills T-scores by APOE-ε4 status approached significance (APOE-ε4+: $M = 47.16$, $SD = 8.58$; APOE-ε4-: $M = 44.92$, $SD = 9.62$; $t(278) = 1.68$, $p = .095$), with higher scores among APOE-ε4 carriers. No other differences in neurocognitive outcomes by APOE-ε4 status were detected (ps > 0.182).
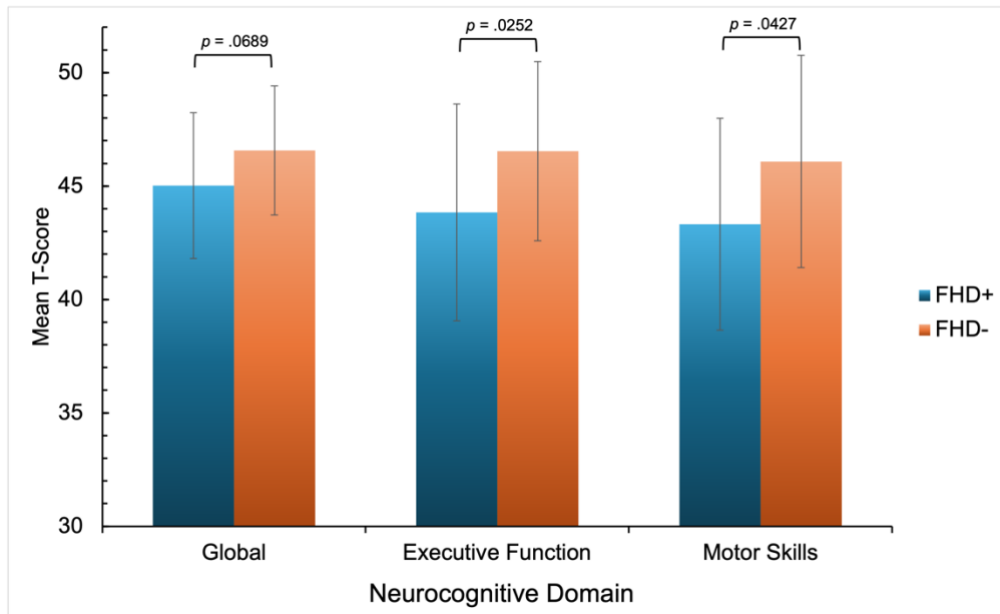
Figure 2. Mean differences in global and domain-specific neurocognitive T-scores by FHD

Results of a 2x2 factorial analysis of covariance (ANCOVA) examining the independent and interactive effect of FHD and APOE-ε4 status on neurocognition are shown in Table 5. Demographic variables, comorbid conditions, and HIV disease characteristics in Tables 2 and 3 were considered as covariates. These potential covariates were included in the models if they were associated with the specific cognitive outcome at $p < 0.10$ in bivariate analyses. There were no significant interactions between FHD and APOE-ε4 status on neurocognitive outcomes, although the interaction on learning T-scores trended towards significance ($p = .063$). Rather, main effects were found for FHD status on global cognitive functioning and learning, with participants with a FHD exhibiting significantly lower global T-scores (b = -0.900, $p = .0593$) and learning T-scores (b = -1.308, $p = .0360$) compared to those without FHD. Effect sizes were small (0.013, 0.016). Of note, there were no main effects of APOE-ε4 status.

Table 5. Results of 2 x 2 factorial ANCOVA examining independent and interactive effects of FHD and APOE ε4 status on neurocognitive T-score outcomes

Outcome: Global Cognition	F	p-value	η_p^2
FHD x APOE-ε4 status	0.307	0.580	0.001
APOE-ε4 status	0.557	0.456	0.002
FHD	3.587	**0.059**	0.013
Age	0.274	0.601	0.001
LT substance use disorder	4.130	**0.043**	0.015
Nadir CD4	6.122	**0.014**	0.022
Outcome: Verbal Fluency			
FHD x APOE-ε4 status	0.582	0.446	0.002
APOE-ε4 status	1.914	0.168	0.007
FHD	0.199	0.656	0.001
Sex	5.135	**0.024**	0.019
Hepatitis C	0.939	0.333	0.004
LT substance use disorder	2.171	0.142	0.008
ART status	0.009	0.924	0.000
Detectable viral load	7.553	**0.006**	0.028
Outcome: Executive Function			
FHD x APOE-ε4 status	0.285	0.594	0.001
APOE-ε4 status	0.378	0.550	0.001
FHD	2.557	0.111	0.010
Sex	4.251	**0.040**	0.016
Ethnicity	4.072	**0.008**	0.044
Hepatitis C	0.035	0.852	0.000
LT substance use disorder	2.561	0.111	0.010
Current CD4	1.436	0.232	0.005
Nadir CD4	0.360	0.549	0.001
Outcome: Processing Speed			
FHD x APOE-ε4 status	1.794	0.182	0.006
APOE-ε4 status	0.108	0.743	0.000
FHD	1.757	0.186	0.006
Education	3.967	**0.047**	0.014
Outcome: Learning	F	p-value	η_p^2
FHD x APOE-ε4 status	2.890	0.090	0.010
APOE-ε4 status	0.250	0.617	0.001
FHD	4.440	**0.036**	0.016
Nadir CD4	4.405	**0.037**	0.016
Outcome: Delayed Recall			
FHD x APOE-ε4 status	0.042	0.838	0.000
APOE-ε4 status	0.006	0.937	0.000
FHD	0.228	0.634	0.001
Sex	3.012	0.084	0.011
Ethnicity	1.474	0.223	0.016
Hepatitis C	1.850	0.175	0.007
ART status	4.689	**0.031**	0.017

Table 5, continued

Outcome: Working Memory	F	p-value	η_p^2
FHD x APOE-ε4 status	0.042	0.838	0.000
APOE-ε4 status	1.050	0.307	0.004
FHD	1.089	0.298	0.004
Current substance use disorder	2.497	0.115	0.009
Current CD4	0.437	0.509	0.002
Nadir CD4	1.236	0.267	0.005
Outcome: Motor Skills			
FHD x APOE-ε4 status	0.030	0.864	0.000
APOE-ε4 status	2.633	0.106	0.010
FHD	3.136	0.077	0.012
Education	0.952	0.330	0.003
Ethnicity	1.861	0.137	0.021
Hypertension	3.464	0.064	0.013
Diabetes mellitus	4.134	**0.043**	0.016
LT MDD	0.126	0.723	0.000
Current MDD	1.783	0.183	0.007
Nadir CD4	3.080	0.080	0.012

Note. Bolded values are significant at $p<0.05$.

3.3 Aim 2: To Examine if FHD and APOE-ε4 status Predict Neurocognitive Trajectories

In terms of participant follow-up data, participants underwent an average of 6.2 follow-up neuropsychological and neuromedical visits, with a range from 2 to 18 visits. Average number of follow-up visits did not differ by FHD/APOE-ε4 status. Participants were followed for an average of 5.4 years, with a range of 0.4 to 15.8 years. Over half (57%; $n = 159$) of participants were followed for between zero and five years, approximately 21% ($n = 59$) for five to ten years, 22% ($n = 62$) for 10-15 years, and less than 1% ($n = 1$) for over 15 years. There were no statistically significant differences by FHD/APOE-ε4 group in average number of years followed. Notably, 68% ($n = 13$) of participants in the FHD+/APOE-ε4+ group were followed for between zero to five years, with only one participant followed for over ten years. At the last follow-up visit, participants were on average 56.2 years old ($SD = 6.8$).

Regarding HIV disease characteristics over time, 64 (31%) participants had a consistently undetectable viral load (<50 copies/ml; not including 73 counts of missing data) across study

visits. Of the 117 participants with at least one timepoint in which they were virally detectable, these participants were virally undetectable in plasma at 57% of visits (median = 442 copies/mL, IQR = 296 – 627). 186 (70%) participants were on ART across all study visits, and 16 (6%) participants were not on ART across all study visits (not including 15 counts of missing data). For participants with variable ART use, they were, on average, on ART for 64.2% of visits (range: 6% - 94%). 29 participants converted to AIDS.

Regarding comorbid conditions, 32% (59 of 185; not including 95 counts of missing data) of participants were diagnosed with hyperlipidemia at least once; 42% (79 of 185) were diagnosed with hypertension at least once, and 21% (38 of 185) were diagnosed with diabetes at least once. 57 participants (31%) were consistently HCV-positive (not including 95 counts of missing data) across study visits. 215 of 270 participants met criteria for any lifetime substance use disorder during the study (excluding 2 counts of missing data; 166 alcohol, 126 cocaine, 86 cannabis, 67 opioid, 32 sedative, 28 methamphetamine, 24 hallucinogen, 11 inhalant, 9 prescription drug, and 7 "other").

In terms of covariate selection, age and sex were included as covariates in all models. Demographic variables, comorbid conditions, and HIV disease characteristics in Tables 2 and 3 were considered as covariates. These potential covariates were included in the models if they were associated with the cognitive outcome at $p<0.10$ in bivariate analyses and were retained in the models if they remained associated with the outcome at $p<0.10$. See Table 6 for covariates.

Table 6. Covariates by cognitive outcome

Cognitive Outcome	Additional Covariates
Global	LT substance use disorder Nadir CD4*
Verbal Fluency	Hepatitis C LT substance use disorder ART status* Detectable viral load
Executive Function	Ethnicity* Hepatitis C* LT substance use disorder Current CD4 Nadir CD4*
Processing Speed	Education
Learning	Nadir CD4
Delayed Recall	Ethnicity* Hepatitis C ART status
Working Memory	Current substance use disorder Current CD4* Nadir CD4*
Motor Skills	Education Ethnicity* Hypertension* Diabetes mellitus* LT MDD Current MDD* Nadir CD4

Note. *Indicates the covariates remained associated to the outcome in the full model and were thus included in the models

Global Cognition. The intercept-only model was used to calculate the intraclass correlation (ICC; random intercept variance/total variance) for global neurocognitive function. The value derived was 0.795 (i.e., 36.45/(36.45 + 9.42)), suggesting that approximately 80% of the total variance in global T-scores is attributed to between-person differences. In the random slopes and random intercept model with no additional covariates, the average slope was 0.112, indicating that, on average, the global T-score increased by 0.112 every year. The standard error of the slope was 0.036.

Results of the random slopes and random intercept model including covariates (i.e.,

baseline age, sex, nadir CD4), are presented in Table 7. None of the years since baseline by

FHD/APOE-ε4 status cross-level interactions were significant ($ps > .392$). Follow-up analyses

were conducted to examine whether FHD and APOE-ε4 status independently predict global

cognitive T-scores, covarying for factors included in primary analyses. Results revealed no

significant interactions between FHD and time ($p = .3368$) and APOE-ε4 and time ($p = .6640$).

Table 7. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated
with change in global cognitive performance

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.114	[0.026, 0.201]	.0118
Baseline age	-0.074	[-0.211, 0.063]	.2926
Sex			
- Male	(reference)	(reference)	
- Female	-0.216	[-1.767, 1.325]	.7852
Baseline Nadir CD4	0.004	[-0.0001, 0.008]	.0594
FHD/APOE-ε4			.0979
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	1.714	[-0.022, 3.646]	.0863
- FH+/ε4-	-1.249	[-3.246, 0.748]	.2255
- FH+/ε4+	-1.201	[-4.025, 1.627]	.4100
FHD/APOE-ε4 x Years since baseline			.6201
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	0.090	[-1.141, 0.294]	.3923
- FH+/ε4- x Years	-0.052	[-0.253, 0.149]	.6158
- FH+/ε4+ x Years	-0.108	[-0.401, 0.183]	.4715

Note. *Value remains statistically significant after Bonferroni correction ($p < .0007$)

Linear mixed-effects models additionally examined the potential curvilinear fit of global

T-scores over time and explored whether curvilinear slopes differed by FHD/APOE-ε4 status,

covarying for demographic variables included in primary analyses. Results revealed a significant

quadratic effect of time (i.e., years since baseline x years since baseline) on global T-scores ($b =$

-0.032, $SE = 0.006$, $p < .001$). The interaction between the quadratic effect of time and

FHD/APOE-ε4 status (i.e., [years since baseline]^2 x FHD/APOE-ε4) also showed a significant

difference in slope between the FHD-/APOE-ε4- and FHD+/APOE-ε4+ groups (b = -0.005, *SE* = 0.022, *p* = .0127). The curvilinear effect of time on global neurocognition by FHD/APOE-ε4 status is represented in Figure 3.
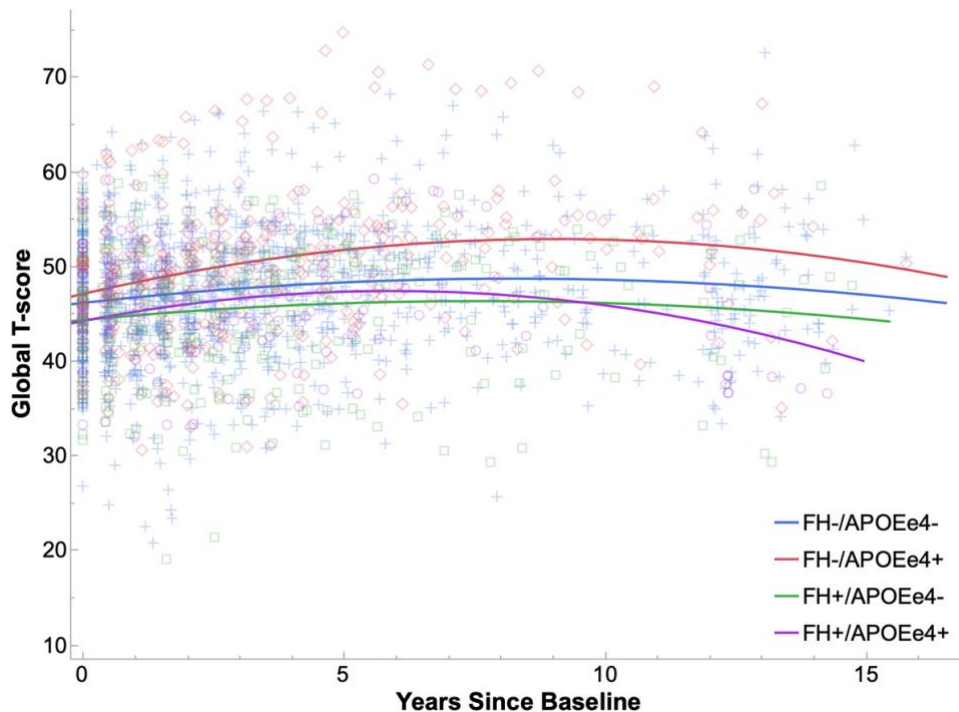
Figure 3. Global neurocognitive performance over time by FHD/APOE-ε4 status

Follow-up analyses explored the potential curvilinear relationships between FHD, APOE-ε4, and global cognitive T-scores, covarying for factors included in primary analyses. Results revealed no significant interactions between the quadratic effect of time and FHD (*p* = .2049). The interaction between the quadratic effect of time and APOE-ε4 status showed a significant difference in slope between APOE-ε4 carriers and non-carriers (b = -0.025, *SE* = 0.013, *p* = .0462).

Verbal Fluency. The intraclass correlation (ICC) for verbal fluency was 0.689 (i.e., 52.27/(52.27 + 23.55)), suggesting that approximately 69% of the total variance in verbal fluency T-scores is attributed to the between-person differences. In the random slopes and random

intercept model with no additional covariates, the average slope was 0.070, indicating that, on average, the verbal fluency T-score increased by 0.070 every year. The standard error of the slope was 0.050.

Results of the random slopes and random intercept model including baseline age, sex, and ART status as covariates, are presented in Table 8. None of the years since baseline by FHD/APOE-ε4 status cross-level interactions were significant ($ps > .1825$). Follow-up analyses explored the independent relationships between FHD, APOE-ε4 status, and verbal fluency T-scores, revealed no significant interactions between FHD and time ($p = .5627$) and APOE-ε4 and time ($p = .4001$).

Table 8. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated with change in verbal fluency

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.031	[-0.092, 0.156]	.6196
Baseline age	-0.109	[-0.281, 0.071]	.2275
Sex			
- Male	(reference)	(reference)	
- Female	0.822	[-2.464, 2.960]	.4027
ART status			
- On	(reference)	(reference)	
- Off	-1.505	[-2.464, -0.542]	.0022
FHD/APOE-e4			.3288
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	0.490	[-2.060, 3.083]	.6978
- FH+/ε4-	-1.943	[-4.607, 0.720]	.1568
- FH+/ε4+	1.620	[-2.138, 5.385]	.4028
FHD/APOE-ε4 x Years since baseline			.5136
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	0.197	[-0.089, 0.483]	.1825
- FH+/ε4- x Years	-0.009	[-0.292, 0.272]	.9483
- FH+/ε4+ x Years	-0.103	[-0.511 - 0.304]	.6225

Note. *Value remains statistically significant after Bonferroni correction ($p < .0007$)

Results of linear mixed-effects models examining the potential curvilinear fit of verbal fluency T-scores over time and interaction between the quadratic effect of time and FHD/APOE-

ε4 status were not significant (ps > .1177). Follow-up analyses examining the potential curvilinear relationships between FHD, APOE-ε4, and verbal fluency T-scores also revealed no significant interactions between the quadratic effect of time and FHD (p = .2509) as well as the quadratic effect of time APOE-ε4 status (p = .1644).

Executive Function The intraclass correlation (ICC) for executive functioning was calculated from the intercept-only model. The value derived was 0.593 (i.e., 52.99/(52.99 + 36.28)), suggesting that approximately 60% of the total variance in executive function T-scores is attributed to the between-person differences. In the random slopes and random intercept model with no additional covariates, the average slope was 0.219, indicating that, on average, the executive function T-score increased by 0.219 every year. The standard error of the slope was 0.057.

Results of the random slopes and random intercept model including baseline age, sex, ethnicity, baseline nadir CD4, and baseline HCV status as covariates, are presented in Table 9. Results revealed a significant cross-level interaction between FHD/APOE-ε4 status group and time (i.e., years since baseline) on executive function performance such that participants in the FHD-/APOE-ε4+ group (b = 0.340, p = .0303) demonstrated higher executive function T-scores over time compared to the FHD-/APOE-ε4- group. This interaction did not remain statistically significant after applying Bonferroni correction (p > .0007) for multiple comparisons. Follow-up analyses were conducted to examine whether FHD and APOE-ε4 status independently predict executive function T-scores, covarying for factors included in primary analyses. Results revealed no significant interactions between FHD and time (p = .4230). In line with primary findings, the interaction between APOE-ε4 and time approached significance (b = 0.2702, p = .0586), such

that individuals with the APOE-ε4 allele showed an incremental increase in executive function

T-scores over time compared to those without the APOE-ε4 allele.

Table 9. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated
with change in executive function

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.159	[0.017, 0.300]	.0293
Baseline age	-0.092	[-0.265, 0.084]	.3025
Sex			
- Male	(reference)	(reference)	
- Female	-1.551	[-3.657, 0.540]	.1524
Ethnicity			.0551
- Non-Hispanic White	(reference)	(reference)	
- Black	1.806	[-0.161, 3.783]	.0763
- Hispanic	-1.489	[-4.441, 1.466]	.3238
- Other	-3.336	[-9.792, 3.146]	.3181
Baseline Nadir CD4 count	0.005	[-0.0002, 0.010]	.0638
Hepatitis C			
- No	(reference)	(reference)	
- Yes	1.531	[0.359, 2.679]	.0101
FHD/APOE-e4			.2560
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	0.589	[-1.898, 3.025]	.6559
- FH+/ε4-	-1.298	[-3.831, 1.235]	.3233
- FH+/ε4+	-3.099	[-6.658, 0.468]	.0943
FHD/APOE-ε4 x Years since baseline			.1362
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	0.340	[0.041, 0.698]	.0303
- FH+/ε4- x Years	-0.081	[-0.401, 0.240]	.6255
- FH+/ε4+ x Years	-0.017	[-0.436, 0.468]	.9419

Note. *Value remains statistically significant after Bonferroni correction ($p < .0007$)

Results of additional linear mixed-effects models examining a curvilinear fit revealed a

significant quadratic effect of time (i.e., years since baseline x years since baseline) on executive

function T-scores (b = -0.026, *SE* = 0.012, *p* = .0316). The interaction between the quadratic

effect of time and FHD/APOE-ε4 status (i.e., [years since baseline]^2 x FHD/APOE-ε4) was not

significant (*p* = .5534). Follow-up analyses examining the potential curvilinear relationships

between FHD, APOE-ε4, and executive function T-scores revealed no significant interactions

between the quadratic effect of time and FHD ($p = .7409$) as well as the quadratic effect of time

APOE-ε4 status ($p = .2832$).

Processing Speed. The intraclass correlation (ICC) for processing speed was calculated

from the intercept-only model. The value derived was 0.760 (i.e., 68.34/(68.34 + 21.57)),

suggesting that approximately 76% of the total variance in processing speed T-scores is

attributed to the between-person differences. In the random slopes and random intercept model

with no additional covariates, the average slope was 0.138, indicating that, on average, the

processing speed T-score increased by 0.138 every year. The standard error of the slope was

0.048.

Results of the random slopes and random intercept model are presented in Table 10. No

additional covariates were retained in the full model after backwards selection. None of the years

since baseline by FHD/APOE-ε4 status cross-level interactions were significant (ps > .0749).

Follow-up analyses examining the independent relationships between FHD, APOE-ε4 status, and

processing speed T-scores, covarying for factors included in primary analyses, revealed no

significant interaction between FHD and time ($p = .6366$). The interaction between APOE-ε4

and time trended towards significance (b = 0.213, $p = .0698$), with APOE-ε4+ showing

incremental increases in processing speed T-scores over time.

Table 10. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated with change in processing speed

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.105	[-0.011, 0.221]	.0789
Baseline age	-0.068	[-0.260, 0.124]	.4900
Sex			
- Male	(reference)	(reference)	
- Female	-0.727	[-2.931, 1.466]	.5200
FHD/APOE-e4			.2987
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	2.293	[-0.427, 5.008]	.1018
- FH+/ε4-	-0.186	[-2.997, 2.624]	.8978
- FH+/ε4+	-1.418	[-5.385, 2.556]	.4875
FHD/APOE-ε4 x Years since baseline			.2722
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	0.249	[-0.021, 0.518]	.0749
- FH+/ε4- x Years	-0.058	[-0.325, 0.208]	.6705
- FH+/ε4+ x Years	0.098	[-0.288, 0.482]	.6223

Note. *Value remains statistically significant after Bonferroni correction ($p < .0007$)

Results of a linear mixed-effects model examining the potential curvilinear fit of processing speed T-scores over time did not reveal a significant quadratic effect of time (i.e., years since baseline x years since baseline) ($p = .1179$). The linear effect of time was significant in this adjusted model ($p = .0079$). Results examining the interaction between the quadratic effect of time and FHD/APOE-ε4 status was also not significant ($p = .3071$). Follow-up analyses examining the potential independent curvilinear relationships between FHD, APOE-ε4, and processing speed T-scores revealed no significant interactions between the quadratic effect of time and FHD ($p = .4257$) as well as the quadratic effect of time APOE-ε4 status ($p = .7809$).

Learning. The intraclass correlation (ICC) for learning was calculated from the intercept-only model. The value derived was 0.620 (i.e., 53.84/(53.84 + 32.93)), suggesting that approximately 62% of the total variance in learning T-scores is attributed to the between-person differences. In the random slopes and random intercept model with no additional covariates, the

average slope was 0.185, indicating that, on average, the learning T-score increased by 0.185 every year. The standard error of the slope was 0.057.

Results of the random slopes and random intercept model including baseline age and sex as well as nadir CD4 as the only covariate retained after backwards selection, are presented in Table 11. None of the years since baseline by FHD/APOE-ε4 status cross-level interactions were significant (ps > .0859). Follow-up analyses examining the independent relationships between FHD, APOE-ε4 status, and learning T-scores, covarying for factors included in primary analyses, revealed no significant interactions between FHD and time (p = .1993) and APOE-ε4 and time (p = .1404).

Table 11. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated with change in learning

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.253	[0.111, 0.393]	.0005
Baseline age	-0.050	[-0.227, 0.127]	.5860
Sex			
- Male	(reference)	(reference)	
- Female	-0.591	[-2.688, 1.518]	.5840
FHD/APOE-e4			.1560
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	2.501	[-0.341, 5.026]	.0555
- FH+/ε4-	-0.915	[-3.548, 1.717]	.4994
- FH+/ε4+	-0.810	[-4.526, 2.902]	.6715
FHD/APOE-ε4 x Years since baseline			.3092
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	-0.152	[-0.475, 0.171]	.3604
- FH+/ε4- x Years	-0.124	[-0.443, 0.194]	.4476
- FH+/ε4+ x Years	-0.406	[-0.866, 0.055]	.0883

Note. *Value remains statistically significant after Bonferroni correction (p < .0007)

Results of additional linear mixed-effects models revealed a significant quadratic effect of time (i.e., years since baseline x years since baseline) on learning T-scores (b = -0.113, *SE* = 0.010, p < .0001). The interaction between the quadratic effect of time and FHD/APOE-ε4 status

showed a significant difference in slope between the FHD-/APOE-ε4- and FHD+/APOE-ε4+ groups (b = -0.093, *SE* = 0.040, *p* = .0207). Follow-up analyses examining the potential independent curvilinear relationships between FHD, APOE-ε4, and learning T-scores revealed no significant interactions between the quadratic effect of time and FHD (*p* = .1600) as well as the quadratic effect of time and APOE-ε4 status (*p* = .2740).

Delayed Recall. The intraclass correlation (ICC) for delayed recall was calculated from the intercept-only model. The value derived was 0.613 (i.e., 54.02/(54.02 + 34.14)), suggesting that approximately 61% of the total variance in delayed recall T-scores is attributed to the between-person differences. In the random slopes and random intercept model with no additional covariates, the average slope was 0.139, indicating that, on average, the delayed recall T-score increased by 0.139 every year. The standard error of the slope was 0.054.

Results of the random slopes and random intercept model including baseline age, sex, and ethnicity as covariates, are presented in Table 12. None of the years since baseline by FHD/APOE-ε4 status cross-level interactions were significant (*p*s > .1253). Follow-up analyses examining the independent relationships between FHD, APOE-ε4 status, and delayed recall T-scores, covarying for factors included in primary analyses, revealed no significant interactions between FHD and time (*p* = .1713) and APOE-ε4 and time (*p* = .8967).

Table 12. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated with change in delayed recall

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.155	[0.022, 0.285]	.0223
Baseline age	-0.002	[-0.177, 0.172]	.9842
Sex			
- Male	(reference)	(reference)	
- Female	-1.337	[-3.459, 0.774]	.2215
Ethnicity			.0002
- Non-Hispanic White	(reference)	(reference)	
- Black	3.270	[1.269, 5.275]	.0012
- Hispanic	-2.534	[-5.489, 0.421]	.0967
- Other	3.354	[-3.225, 9.935]	.3246
FHD/APOE-e4			.4766
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	0.536	[-1.982, 3.045]	.6798
- FH+/ε4-	-1.850	[-4.437, 0.735]	.1673
- FH+/ε4+	-0.777	[-4.424, 2.874]	.6807
FHD/APOE-ε4 x Years since baseline			.3374
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	0.104	[-0.198, 0.407]	.5025
- FH+/ε4- x Years	-0.083	[-0.383, 0.218]	.5930
- FH+/ε4+ x Years	-0.343	[-0.776, 0.091]	.1253

Note. *Value remains statistically significant after Bonferroni correction (*p* < .0007)

Results of linear mixed-effects models examining a curvilinear fit revealed a significant quadratic effect of time (i.e., years since baseline x years since baseline) on delayed recall T-scores (b = -0.063, *SE* = 0.011, *p* < .0001). The interaction between the quadratic effect of time and FHD/APOE-ε4 status (i.e., [years since baseline]^2 x FHD/APOE-ε4) was also significant (*p* = .0312), with a trending difference in slope between the FHD-/APOE-ε4- and FHD-/APOE-ε4+ groups (b = -0.055, *SE* = 0.028, *p* = .0505). Follow-up analyses examining the potential independent curvilinear relationships between FHD, APOE-ε4, and delayed recall T-scores revealed a significant interaction between the quadratic effect of time and FHD (b = 0.057, *SE* = 0.0259, *p* = .0264). The interaction between the quadratic effect of time APOE-ε4 status was not significant (*p* = .0955).

Working Memory. The intraclass correlation (ICC) for working memory was calculated from the intercept-only model. The value derived was 0.722 (i.e., 59.22/(59.22 + 22.77)), suggesting that approximately 72% of the total variance in working memory T-scores is attributed to the between-person differences. In the random slopes and random intercept model with no additional covariates, the average slope was 0.198, indicating that, on average, the working memory T-score increased by 0.198 every year. The standard error of the slope was 0.045.

Results of the random slopes and random intercept model including baseline age, sex, within-person mean CD4, and baseline nadir CD4 as covariates, are presented in Table 13. None of the years since baseline by FHD/APOE-ε4 status cross-level interactions were significant ($ps > .4319$). Follow-up analyses examining the independent relationships between FHD, APOE-ε4 status, and working memory T-scores, covarying for factors included in primary analyses, revealed no significant interactions between FHD and time ($p = .5148$) and APOE-ε4 and time ($p = .7647$).

Table 13. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated with change in working memory

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	0.178	[0.066, 0.290]	.0024
Baseline age	-0.075	[-0.260, 0.109]	.4282
Sex			
- Male	(reference)	(reference)	
- Female	-0.426	[-2.579, 1.724]	.7004
Mean CD4 count	0.002	[0.0005, 0.003]	.0009
Baseline Nadir CD4 count	0.004	[-0.001, 0.010]	.1275
FHD/APOE-e4			.8175
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	1.085	[-1.603, 3.771]	.4335
- FH+/ε4-	-0.506	[-3.297, 2.279]	.7246
- FH+/ε4+	-0.288	[-4.220, 3.649]	.8871
FHD/APOE-ε4 x Years since baseline			.7196
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	0.105	[-0.153, 0.364]	.4319
- FH+/ε4- x Years	-0.020	[-0.279, 0.239]	.8810
- FH+/ε4+ x Years	-0.136	[-0.506, 0.235]	.4778

Note. *Value remains statistically significant after Bonferroni correction ($p < .0007$)

Results of a linear mixed-effects model examining the potential curvilinear fit of working memory T-scores over time revealed a significant quadratic effect of time (b = -0.038, *SE* = 0.009, $p < .0001$). The interaction between the quadratic effect of time and FHD/APOE-ε4 status was not significant ($p = .5574$). Follow-up analyses examining the independent relationships between FHD, APOE-ε4 status, and working memory T-scores also revealed no significant interactions between the quadratic effect of time and FHD ($p = .3709$) as well as the quadratic effect of time and APOE-ε4 status ($p = .6055$).

Motor Skills. The intraclass correlation (ICC) for motor skills was calculated from the intercept-only model. The value derived was 0.716 (i.e., 78.50/(78.50 + 31.09)), suggesting that approximately 72% of the total variance in motor skills T-scores is attributed to the between-person differences. In the random slopes and random intercept model with no additional

covariates, the average slope was -0.187, indicating that, on average, the motor skills T-score decreased by 0.187 every year. The standard error of the slope was 0.057.

Results of the random slopes and random intercept model including ethnicity, hypertension, diabetes mellitus, and current MDD as covariates, are presented in Table 14. None of the years since baseline by FHD/APOE-ε4 status cross-level interactions were significant (ps > .4262). Follow-up analyses evaluating the independent relationships between FHD, APOE-ε4 status, and motor skills T-scores, covarying for factors included in primary analyses, revealed no significant interactions between FHD and time (p = .4855) and APOE-ε4 and time (p = .6861).

Table 14. Linear mixed-effects results examining whether FHD/APOE-ε4 status is associated with change in motor skills

	Estimate	95% Confidence Interval	*p*-value
Years since baseline	-0.179	[-0.323, -0.031]	.0190
Baseline age	-0.045	[-0.254, 0.163]	.6745
Sex			
- Male	(reference)	(reference)	
- Female	-1.322	[-3.795, 1.157]	.3027
Ethnicity			.0008
- Non-Hispanic White	(reference)	(reference)	
- Black	4.450	[2.164, 6.731]	.0002
- Hispanic	0.139	[-3.232, 3.486]	.9363
- Other	-1.653	[-9.465, 6.152]	.6833
Hypertension			
- No	(reference)	(reference)	
- Yes	-2.707	[-5.135, -0.281]	.0322
Diabetes Mellitus			
- No	(reference)	(reference)	
- Yes	-4.552	[-7.835, -1.265]	.0079
Current MDD			
- No	(reference)	(reference)	
- Yes	-1.077	[-2.072, -0.087]	.0334
FHD/APOE-e4			.2920
- FH-/ε4-	(reference)	(reference)	
- FH-/ε4+	1.701	[-1.273, 4.667]	.2702
- FH+/ε4-	-2.053	[-5.094, 0.979]	.1928
- FH+/ε4+	-0.803	[-5.094, 3.495]	.7185
FHD/APOE-ε4 x Years since baseline			.8693
- FH-/ε4- x Years	(reference)	(reference)	
- FH-/ε4+ x Years	-0.016	[-0.347, 0.314]	.9249
- FH+/ε4- x Years	-0.063	[-0.386, 0.257]	.7018
- FH+/ε4+ x Years	-0.190	[-0.652, 0.272]	.4262

Note. *Value remains statistically significant after Bonferroni correction ($p < .0007$)

Results of a linear mixed-effects model examining the potential curvilinear fit of motor skills T-scores over time did not reveal a significant quadratic effect of time ($p = .5421$). The linear effect of time was significant in this adjusted model ($p = .0407$). The interaction between the quadratic effect of time and FHD/APOE-ε4 status (i.e., [years since baseline]^2 x FHD/APOE-ε4) was significant ($p = .0351$), with a difference in slope between the FHD-/APOE-ε4- and

FHD+/APOE-ε4+ groups (b = -0.119, *SE* = 0.041, *p* = .0036). Follow-up analyses were conducted to investigate the independent relationships between FHD, APOE-ε4 status, and motor T-scores. The interaction between the quadratic effect of time and FHD trended towards significance (b = -0.043, *SE* = 0.026, *p* = .0975). The interaction between the quadratic effect of time and APOE-ε4 status also approached significance (b = -0.041, *SE* = 0.024, *p* = .0884).

Exploratory Analyses. Exploratory follow-up analyses were conducted to investigate cognitive trajectories. Time was categorized into three groups: 0-5 years (*n* = 159), 5-10 years (*n* = 59), and 10-18 years (*n* = 63), based on the distribution of data and ability to represent initial, midline, and latter performance. A series of ANOVAs with follow-up Tukey's HSD were used to examine differences in global- and domain-specific T-scores by time-group in the total sample. Results showed higher global T-scores in the 5-10 (*M* = 49.4, *SD* = 7.5) compared to the 0-5 (*M* = 46.4, *SD* = 6.7, *p* = .018) year group. Learning T-scores were higher in the 5-10 (*M* = 49.3, *SD* = 8.7) group compared to the 10-18 year group (*M* = 44.8, *SD* = 11.8, *p* = .024). In terms of the other domains, results showed higher T-scores in the 5–10-year group compared to 0-5 year group in verbal fluency, executive functioning, processing speed, and working memory (*ps* <.001). There were no significant differences in mean recall *(p* = 458) motor skills T-scores by time-group (*p* = .836).

Curvilinear effects of time on significant domain-specific neurocognitive performance by FHD/APOE-ε4 status are represented in Figure 4. Exploratory analyses investigated the latter years (10–18-year group) of the trajectories that showed significant curvilinear patterns and differences in slope by FHD/APOE-ε4 status (global, learning, recall, motor skills). Preliminary results showed higher global T-scores in the FHD-/APOE-ε4+ group (*M* = 51.5, *SD* = 8.7) compared to the FHD+/APOE-ε4+ group (*M* = 42.2, *SD* = 7.7; *p* = .006); higher learning T-

scores in the FHD-/APOE-ε4- group ($M = 46.8$, $SD = 10.0$) compared to the FHD+/APOE-ε4+ group ($M = 33.1$, $SD = 14.8$; $p = .0007$); and higher motor T-scores in the FHD-/APOE-ε4+ group ($M = 48.4$, $SD = 11.7$) compared to the FHD+/APOE-ε4+ group ($M = 37.1$, $SD = 7.3$; $p = .034$). While group differences did not reach statistical significance in recall, raw score differences between the -/- and +/+ groups was 7.7.

Importantly, these exploratory analyses do not account for multiple evaluations per participant and are greatly limited by small sample sizes in the 10–18-year group (number of evaluations = 11). A more robust statistical methodology is necessary to further explore the quadratic pattern of cognitive trajectories and evaluate meaningful differences by FHD/APOE-ε4 group.
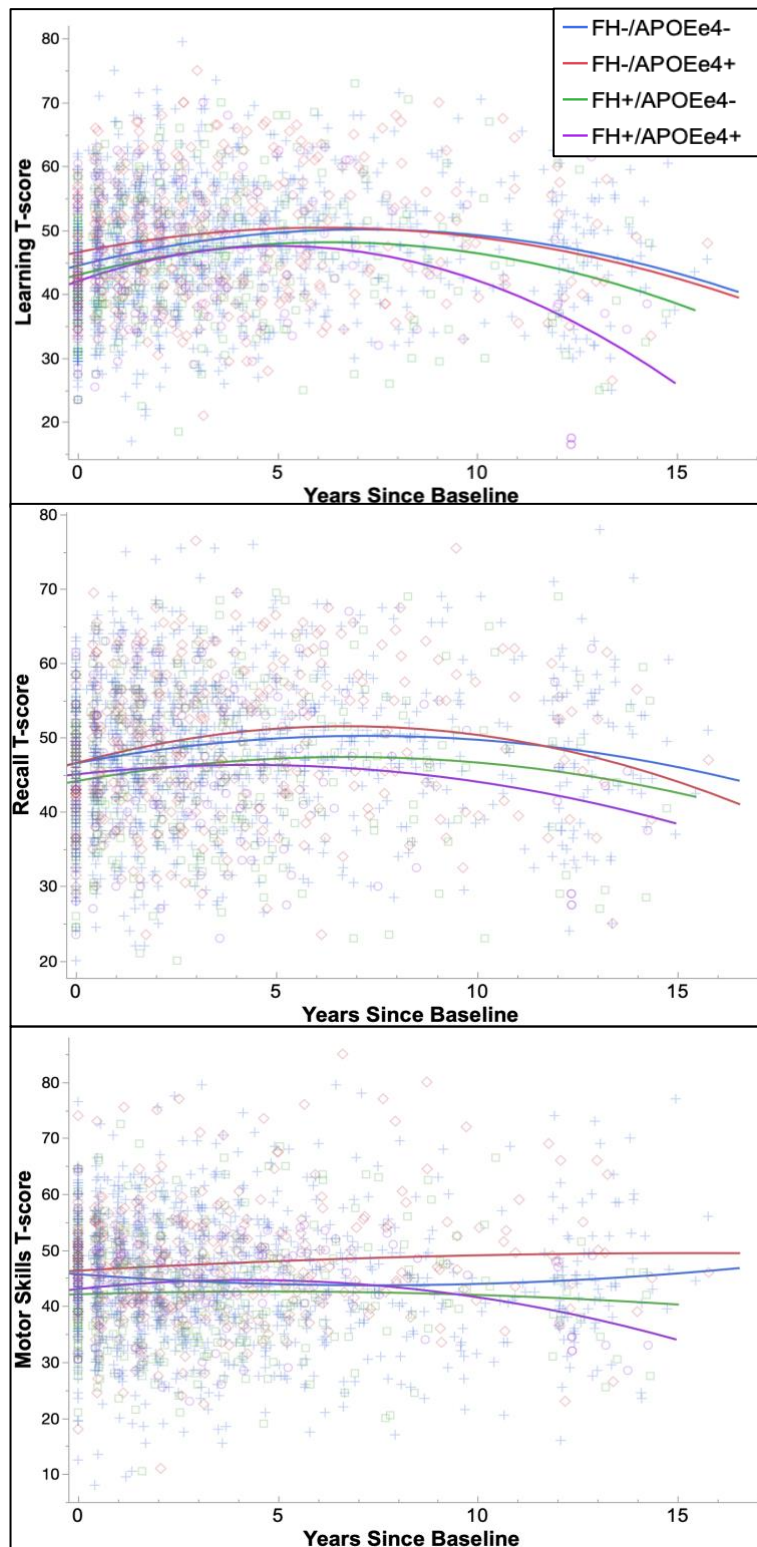
Figure 4. Domain-specific neurocognitive performance over time by FHD/APOE-ε4 status

3.4 Exploratory Aim: To Examine if Exploratory Factors Predict Neurocognitive Trajectories by FHD/APOE-ε4 Status

For this aim, separate linear mixed effects models examined if exploratory factors including demographic, neuropsychiatric, substance use, daily functioning factors, comorbidities, and HIV disease characteristics impact neurocognitive trajectories, and whether these effects differ by FHD and APOE-ε4 status. Age was included as a covariate in all models. Certain neuropsychiatric, medical comorbidities, and HIV disease characteristics that vary over time were examined at baseline and as time-varying factors to capture the cumulative effect of these variables on cognitive functioning, given that long-term exposure to hypertension, for instance, may lead to structural changes in the brain and vascular damage, which could contribute to cognitive decline over time. Considering that the examination of domain-specific outcomes was exploratory, no corrections for multiple comparisons were applied. Exploratory variables included in analyses are displayed in Table 15.

Table 15. List of exploratory predictor variables

Exploratory Variable Domains	Variables Included in Analyses
Demographic	Sex Education* Ethnicity
Neuropsychiatric	Lifetime Major Depressive Disorder* Current Major Depressive Disorder
Substance Use	Lifetime Substance Use Disorder* Current Substance Use Disorder
Daily Functioning	iADL Dependence*
Comorbidities	Hypertension* Hyperlipidemia* Diabetes Mellitus* Hepatitis C*
HIV Disease Characteristics	History of AIDS Current CD4 Nadir CD4* ART Status* Detectable Viral Load

Note. *indicates predictor variables modeled separately as baseline and time-varying values

Global Cognition. Linear mixed-effects models examining the independent relationships between each predictor (predictor x years since baseline) and global T-score revealed a significant interaction between ethnicity and time on global cognition ($p = .001$) with incrementally higher global T-scores over time among participants that identified as Black compared to White ($b = 0.257$, $SE = 0.072$, $p = .0005$). Notably, results showed a significant main effect for Black ethnicity ($b = 2.313$, $SE = 0.732$, $p = .002$), indicating a consistent difference in global T-scores between participants that identified as Black and participants that identified as White.

Results of linear mixed-effects models examining three-way interactions between each predictor, FHD/APOE-ε4 group, and time on global cognition revealed significant findings across exploratory predictor variables. There was a significant three-way interaction between education, time, and group ($p = .031$), such that as time since baseline increased, the impact of education on global T-scores became more pronounced in the FHD+/APOE-ε4+ group ($b = 0.290$, $SE = 0.117$, $p = .0139$) compared to the FHD-/APOE-ε4- group. The interaction between baseline hypertension, time, and group was significant ($p = .0276$), with steeper declines in global T-scores in the FHD+/APOE-ε4- group ($b = -0.470$, $SE = 0.174$, $p = .0129$). The interaction between baseline diabetes, time, and group was significant ($p = .0269$). Follow-up analyses showed that diabetes at baseline predicted steeper declines in the FHD-/APOE-ε4+ group ($b = -0.565$, $SE = 0.266$, $p = .042$). Time-varying hyperlipidemia predicted steeper declines in global cognitive performance in the FHD+/APOE-ε4+ group ($b = -0.803$, $SE = 0.233$, $p = .0009$). Lastly, time-varying lifetime MDD status was associated with worsening global T-scores both in the FHD-/APOE-ε4- ($b = -0.209$, $SE = 0.079$, $p = .009$) and FHD+/APOE-ε4+ ($b = -0.812$, $SE = 0.258$, $p = .002$) groups.

Verbal Fluency. Linear mixed effects models examining the independent relationship between each predictor (predictor*years since baseline) and verbal fluency T-score revealed a significant interaction between sex and time, with steeper declines in verbal fluency T-scores over time among participants that identified as female compared to male (b = -0.313, SE = 0.116, p = .0076). Results also showed steeper declines in verbal fluency in participants who were not currently on ART compared to participants on ART (b = -0.619, SE = 0.166, p < .001). Detectable viral load (modeled as time-varying) was a significant predictor of poorer verbal fluency over time (b = -0.242, SE = 0.103, p = .0193). Diabetes diagnosis at baseline trended towards statistical significance (b = -0.334, SE = 0.176, p = .0595), with greater declines among participants with diabetes compared to those without. iADL dependence at baseline also trended towards significance (b = -0.183, SE = 0.101, p = .0716), with steeper declines among participants characterized as iADL dependent at baseline evaluation.

Results of investigating three-way interactions between each predictor, FHD/APOE-ε4 group, and time on verbal fluency revealed significant relationships. The impact of education at baseline on verbal fluency trajectories was more pronounced in the FHD+/APOE-ε4+ group (b = 0.672, SE = 0.172, p = .0013). The interaction between time-varying lifetime MDD, FHD/APOE-ε4 status, and time trended towards significance (p = .0550), with steeper declines in verbal fluency performance over time in the FHD+/APOE+ group (b = -1.266, SE = 0.475, p = .009).

Executive Function. There was a positive relationship between education, years since baseline, and executive function performance indicating that as education level increases, executive function T-scores increase over time since baseline assessment (b = 0.385, SE = 0.195 p = .0496).

Results of linear mixed effects models investigating three-way interactions between each predictor suggest that the impact of education at baseline on executive function trajectories was more pronounced in the FHD+/APOE-ε4+ group (b = 0.507, *SE* = 0.171, *p* = .0096). The interaction between baseline hypertension, time, and group on executive function T-scores was significant (*p* = .0368). Follow-up analyses stratified by FHD/APOE-ε4 group showed that hypertension at baseline predicted worsening executive function performance in FHD+/APOE-ε4- group (b = -0.681, *SE* = 0.289, *p* = .0283). No lifetime SUD diagnosis was associated with steeper declines in executive function performance in the FHD+/APOE-ε4+ group (b = -1.260, *SE* = 0.433, *p* = .014). The interaction between ART status (modeled as time-varying), time, and group on executive function T-scores was significant (*p* = .0373), such that there were steeper declines in T-scores in participants who were not on ART in the FHD+/APOE-ε4+ group (b = -1.414, *SE* = 0.587, *p* = .0192).

Processing Speed. There was a significant interaction between ethnicity and time on processing speed (*p* = .017) with incrementally higher processing speed T-scores over time among participants that identified as Black compared to White (b = 0.278, *SE* = 0.099, *p* = .006). Results also showed steeper declines in processing speed among participants who reported lifetime SUD at baseline visit (b = -0.229, *SE* = 0.100, *p* = .0242) and over time (time-varying lifetime SUD status; b = -0.229, *SE* = 0.103, *p* = .0288). There was a positive relationship between CD4 count, years since baseline, and processing speed performance indicating that as CD4 count increases, processing speed T-scores increase over time since baseline assessment (b = 0.0003, *SE* = 0.0001 *p* = .0369). Results trended towards significance between ART status and time, with steeper declines in processing speed in participants who were not currently on ART compared to participants on ART (b = -0.275, *SE* = 0.158, *p* = .0819).

The impact of baseline education on processing speed performance over time trended towards significance in the FHD+/APOE-ε4+ group (b = 0.309, SE = 0.164, p = .0799). The interaction between ethnicity, time, and group trended towards significance (p = .0642), with follow-up analyses by FHD/APOE-ε4 status indicating steeper declines among participants identifying as "other" in the FHD-/APOEε4+ group (b = -0.441, SE = 0.315, p = .0197). Hyperlipidemia (modeled as time-varying) predicted higher processing speed T-scores in the FHD+/APOE-ε4- group (b = 0.591, SE = 0.268, p = .0301), and steeper declines in the FHD+/APOE-ε4+ group (b = -1.207, SE = 0.374, p = .002). The interaction between iADL status (modeled as time-varying) approached significance, such that iADL status was associated with steeper declines in processing speed T-scores in the FHD+/APOE-ε4- group (b = -0.446, SE = 0.240, p = .0653).

Learning. Linear mixed effects models revealed a significant interaction between ethnicity and time on processing speed (p = .0002) with incrementally higher processing speed T-scores over time among participants that identified as Black compared to White (b = 0.504, SE = 0.112, p < .001). Results also showed steeper declines in learning performance among participants with hyperlipidemia over time (b = -0.524, SE = 0.124, p < .001), hypertension (b = -0.265, SE = 0.114, p = .0210), lifetime MDD (b = -0.399, SE = 0.108, p = .0003), current SUD (b = -0.566, SE = 0.246, p = .0202), and undetectable viral load (b = -0.401, SE = 0.121, p = .001).

Results suggested that the impact of education at baseline evaluation on learning performance over time trended towards significance in the FHD+/APOE-ε4+ group (b = 0.363, SE = 0.176, p = .0503). The interaction between hyperlipidemia (modeled as time-varying), time, and group was significant (p = .0450) such that hyperlipidemia was associated with steeper declines in learning T-scores in the FHD+/APOE-ε4+ group (b = -1.700, SE = 0.387, p = .0004).

The interaction between time-varying lifetime MDD, time, and FHD/APOE-ε4 status, trended towards significance on learning ($p = .0776$) with worsening learning performance in the FHD+/APOE-ε4+ group (b = -1.434, $SE = 0.464$, $p = .0058$). Current SUD was associated with worsening learning T-scores in the FHD+/APOE-ε4+ group (b = -1.479, $SE = 0.387$, $p = .0002$). AIDS status at baseline predicted steeper declines in learning T-scores in the FHD+/APOE-ε4- group (b = -0.866, $SE = 0.365$, $p = .0231$). The impact of nadir CD4 count at baseline evaluation on learning T-scores over time approached significance ($p = .0689$). Follow-up analysis showed a positive relationship in the FHD+/APOE-ε4+ group, indicating higher nadir CD4 count is associated with higher learning T-scores over time (b = 0.002, $SE = 0.0009$, $p = .0553$).

Recall. There was a negative relationship between education, years since baseline, and recall performance indicating that as education level increases, recall T-scores decrease over time since baseline assessment (b = -0.055, $SE = 0.021$ $p = .0098$). Results also revealed lower T-scores over time among participants that identified as Hispanic (b = -0.628, $SE = 0.166$, $p = .0002$), non-Hispanic White (b = -1.005, $SE = 0.492$, $p = .0436$), and "Other" (b = -0.571, $SE = 0.105$, $p < .001$) compared to Black. Notably, there was a significant main effect for Hispanic and White ethnicities, suggesting a consistent difference in recall T-scores between ethnicities. The interaction between sex and time trended towards significance, with steeper declines in recall T-scores among participants that identified as male compared to female (b = -0.229, $SE = 0.126$, $p = .0696$). A significant interaction was found between HCV at baseline and years since baseline (b = 0.381, $SE = 0.115$, $p = .0011$), with better performance associated with HCV infection at baseline. Results also showed steeper declines in recall performance among participants with a lifetime history of MDD (b = -0.239, $SE = 0.104$, $p = .0225$).

Results of linear mixed effects models investigating three-way interactions between each predictor, FHD/APOE-ε4 group, and time on recall performance revealed a significant interaction between baseline nadir CD4 count, years since baseline, and group status ($p = .0402$). Follow-up analysis showed a positive relationship between nadir CD4 count and recall over time (b = 0.002, $SE = 0.0009$, $p = .0351$) in the FHD+/APOE-ε4- group.

Working Memory. There was a significant interaction between ethnicity and time on working memory performance ($p = .0447$) with lower T-scores among participants that identified as non-Hispanic White (b = -0.256, $SE = 0.094$, $p = .007$) compared to Black. Results also showed steeper declines in working memory performance among participants with hyperlipidemia (b = -0.212, $SE = 0.102$, $p = .0398$).

None of the exploratory predictors by years since baseline by FHD/APOE-ε4 status cross-level interactions were significant.

Motor Skills. Linear mixed effects models revealed a significant interaction between time-varying hypertension status and time on motor skills performance ($p = .0002$) with incrementally higher motor skills T-scores among participants with hypertension (b = 0.277, $SE = 0.113$, $p = .0150$). Results also showed steeper declines in motor skill T-scores among participants with current SUD (b = -0.576, $SE = 0.242$, $p = .0172$).

Results revealed a significant interaction between hyperlipidemia (modeled as time-varying), time, and group on motor skills T-scores ($p = .0209$). Follow-up analyses stratified by FHD/APOE-ε4 group showed that hyperlipidemia was associated with steeper declines motor skills T-scores in the FHD+/APOE-ε4+ group (b = -0.936 $SE = 0.419$, $p = .0303$). The interaction between diabetes (modeled as time-varying), time, and group was also significant ($p = .0704$), such that no diabetes diagnosis was associated steeper declines motor skills T-scores in

the FHD+/APOE-ε4- group (b = -1.143, SE = 0.391, p = .0051). The interaction between ART status (modeled as time-varying), time, and group was significant (p = .0323). Follow-up analyses showed steeper declines in motor skill T-scores in participants who were not currently on ART (b = -1.213, SE = 0.577, p = .0368) in the FHD+/APOE-ε4- group. A summary of the exploratory results are presented in Table 16.

Table 16. Summary of exploratory results

	GC	VF	EF	PS	LRN	DR	WM	MS
Sex		TS[a]				TS[b]		
Education	+/+	+/+	TS +/+	+/+	+/+	TS		
Ethnicity	TS[c]			TS[c] -/+[d]	TS[c]	TS[c]	TS[c]	
Lifetime MDD	+/+ -/-	+/+			TS +/+			
Baseline Lifetime SUD				TS				
Lifetime SUD			+/+*	TS				
Current SUD					TS +/+			TS
Baseline Hypertension	+/-		+/-					
Hypertension					TS			TS
Hyperlipidemia	+/+			+/-* +/+	TS +/+		TS	+/+
Baseline Diabetes	-/+							
Diabetes								+/-*
Baseline HCV						TS*		
iADL status				+/-				
Current CD4				TS				
Nadir CD4					+/+	+/-		
Baseline AIDS					+/-			
ART Status		TS	+/+	TS				+/-
Detectable Viral Load		TS			TS			

Note. GC=Global Cognition, VF=Verbal Fluency, EF=Executive Function, PS = Processing Speed, LRN = Learning, DR = Delayed Recall, WM = Working Memory, MS = Motor Skills, TS = Total Sample
[a]female < male
[b]male < female
[c]white < black
[d]other < white
[e]hispanic, white, other < black
*indicates relationship is in the unexpected direction

4. DISCUSSION

This is one of the first studies to investigate the independent and synergistic relationships between FHD and APOE-ε4 status both cross-sectionally and longitudinally in middle-to-older age adults with HIV. This study had the potential to validate a proxy for genetic marker of dementia (FHD) as a risk factor for accelerated aging among PWH while also observing whether group trajectories align with those of AD or HAND. This study found a curvilinear trajectory of global cognitive performance over time that significantly differed by FHD/APOE-ε4 status, driven by the domains of executive functioning, learning, delayed recall, and motor skills. In addition, this is the only study to our knowledge that has examined demographic and health predictors of neurocognitive trajectories among PWH and in relation FHD and APOE-ε4 status. This exploratory study revealed clinically relevant predictors of neurocognitive decline among our sample of PWH that may be targeted in interventions as modifiable risk factors. In sum, these findings enhance our understanding of biopsychosocial factors that influence neurocognitive decline in this vulnerable population, and the additive effects of two predispositional risk factors.

4.1 Evaluation of Family History of Dementia, APOE-ε4 status and Neurocognition

Neurocognitive impairment is a prevalent and clinically significant complication among adults living with HIV, with a multitude of contributing factors including genetic predispositions. The first aim of this study was to cross-sectionally evaluate the independent and additive impacts of FHD and APOE-ε4 status on neurocognitive outcomes in middle-to-older-age adults living with HIV. It was hypothesized that global- and domain-specific neurocognition would be worse in the FHD+ group compared to the FHD- group. Somewhat consistent with this first hypothesis, findings indicated trend level associations between FHD and global cognitive functioning. While

this difference did not reach statistical significance, participants with FHD exhibited lower mean T-scores compared to those without FHD, suggesting a potential influence of this environmental/familial risk factor on overall cognitive performance. Notably, significant differences were observed in specific neurocognitive domains, including executive function and motor skills, with individuals having FHD demonstrating poorer performance. These observed deficits are consistent with findings from a previous CHARTER investigation, where impairments in verbal fluency, executive functioning, and motor skills were found only among middle-aged PWH, and not their HIV-negative counterparts (Moore et al., 2011).

As highlighted in the introduction, these domains are also frequently implicated in HIV-related cognitive deficits as they are associated with frontal-striatal impairment (Becker et al., 1995; Heaton et al., 2015; Peavy et al., 1994; Scott et al., 2011; White et al., 1997). A recent meta-analysis showed that older PWH had significantly poorer cognitive performance than HIV-uninfected older adults, particularly within the domains of executive function, processing speed, verbal, recall, and motor/psychomotor skills (Deng et al., 2021). Notably, despite deficits in executive function and motor skills, this study did not observe differences in learning or recall, which are hallmark features of most neurodegenerative processes. While executive function deficits are also common in aMCI and AD (Johns et al., 2012), early executive dysfunction in middle age may be more characteristic of a subcortical profile as in HAND (Walker & Brown, 2018). These cross-sectional results suggest that FHD among PWH may increase risk of HIV-associated impairments in middle age, with a lesser likelihood that these relative deficits represent dementia processes on top of HIV-associated impairments. Importantly, it is possible that these null or modest effects could be amplified with older age, given the age-dependent progression of neurocognitive decline associated with neurodegenerative diseases. Thus, further

longitudinal studies are warranted to elucidate the trajectory of neurocognitive declines in this sample of middle-to-older age PWH, particularly as they age, to inform early and appropriately targeted intervention strategies.

Inconsistent with the second hypothesis, global and domain-specific neurocognitive performance did not significantly differ by APOE-ε4 status in our sample of middle-to-older age individuals with HIV, although motor skills performance trended towards significance. This finding somewhat aligns with previous research, which supports no significant association between APOE-ε4 status and cognitive impairment in middle-age (average age ranging from 30-44) PWH (Becker et al., 2015; Joska et al., 2010; Morgan et al., 2013)(Geffin & McCarthy, 2018). In contrast, several studies have implicated the APOE-ε4 allele as a risk factor for global- and domain-specific cognitive impairment (Chang et al., 2011; Chang et al., 2014; (Mu et al., 2022) Spector et al., 2010; Wendelken et al., 2016). A recent meta-analysis ($N = 20$ studies) assessing the associations between APOE-ε4 and neurocognitive impairment in PWH found that APOE-ε4 was a significant risk factor for developing HAND, as well as specific cognitive impairments in memory, executive function, processing speed, learning, fluency, attention, and motor function (Mu et al., 2022). Panos and colleagues (2013) additionally showed a differential impact by age cohort such that only older (average age of approximately 50) APOE-ε4 allele carriers had higher frequencies of HAND compared with their non-carrier counterparts (average age of 43). In HIV-negative cohorts, individuals as young as 43 who are homozygous carriers of APOE-ε4 have been found to exhibit neurocognitive impairments (Blair et al., 2005; Rawle et al., 2018; Wisdom et al., 2011). Given that HIV infection is thought to accelerate cognitive aging (Aung et al., 2021; Burt et al., 2008), and APOE-ε4 is associated with greater brain atrophy in PWH (Chang et al., 2011), it is reasonable to hypothesize that the impact of APOE-ε4 on

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cognition might manifest at an earlier age in this vulnerable population. As such, there may be additional considerations that may clarify these discrepant findings in the literature and the nuanced associations between APOE-ε4 status, cognitive outcomes, and HIV infection.

The interpretability and generalizability of findings across various studies have been limited by factors such as demographic homogeneity. In terms of race and ethnicity, research in HIV-negative cohorts suggests variability in the relationship between APOE-ε4 and cognition across racial/ethnic groups (Beydoun et al., 2021; Chan et al., 2023; Makkar et al., 2020; Rajan et al., 2019; Sawyer et al., 2009), with one longitudinal study observing more rapid decline in memory among middle-aged participants that self-identified as White, compared African American (Beydoun et al., 2021). Moreover, several differences have been reported between females and males carrying the APOE-ε4 allele irrespective of race (Altmann et al., 2014; Walters et al., 2023), with women showing higher risk of developing AD, earlier disease onset, accelerated progression of the disease, and more severe memory and cognitive decline than men (Neu et al., 2017). These findings have been partially replicated in PWH, with higher risk of global cognitive impairment in female APOE-ε4 carriers (Mu et al., 2022). Given the heightened association between HIV and neurocognitive impairment in women (Sundermann et al., 2018), research investigating the potential differential effect of APOE-ε4 by sex among PWH is warranted. CSF studies suggest a "dose-dependent" effect such that higher levels of CSF APOE in PWH with the APOE-ε4 allele relates to poorer cognitive outcomes (Andres et al., 2011). In sum, the absence of a significant association in this study does not necessarily negate the potential role of APOE-ε4 in neurocognitive functioning among individuals with HIV, as there are several understudied confounders influencing this relationship.

Lastly, we investigated whether the combination of FHD and APOE-ε4 status conferred heightened risk for worse cognitive outcomes among middle-to-older-age adults living with HIV. Drawing from previous literature (Donix et al., 2010; Huang et al., 2004; Small, et al., 2012; Yi et al., 2018), it was hypothesized that individuals with both FHD and APOE-ε4 positivity would exhibit the most pronounced cognitive deficits compared to those with only one or neither risk factor. In the entire sample, no significant interactions between FHD and APOE-ε4 status were detected. Main effects were observed for FHD status, indicating lower global cognitive functioning, and learning scores among participants with FHD, although effect sizes were small. These cross-sectional findings suggest that FHD and APOE-ε4 status do not have additive effects on neurocognition, and rather, may independently influence neurocognitive functioning in individuals with HIV.

There are multiple reasons that may explain these results. First, findings were possibly affected by the modest sample size, with a particularly small ($n = 19$) group of participants in the FHD+/APOE-ε4+ group. Second, it is plausible that factors such as viral load, ART regimen, or comorbidities may mediate or moderate the association between FHD/APOE-ε4 group status and cognitive outcomes. For example, a study by Yang and colleagues (2021) found that among PWH, a history of severe immunosuppression (i.e., low nadir CD4 cell count) exacerbated the effects of APOE-ε4 on memory performance. Nadir CD4 cell counts were relatively low in the current sample, and 50% of participants had a detectable viral load at baseline evaluation. As such, the potential moderating effect of immunosuppression in this sample of middle-to-older PWH warrants further investigation. The presence of comorbidities such as cardiovascular disease have been linked to increased risk of memory decline among PWH who are also APOE-ε4 carriers, with stronger effects in younger women (Makkar et al., 2020). Alternatively, several

covariates emerged as significant in separate models, suggesting that their effects may have superseded the influence of these predispositional risk factors.

4.1.1 Summary of Aim 1. Findings from Aim 1 indicated a trend-level association between FHD and global neurocognitive performance at baseline evaluation, with FHD-positive participants showing poorer performance in specific domains like executive function and motor skills. Notably, these deficits align with those commonly associated with HIV-related cognitive impairments, as opposed to expected early indicators of AD. This study did not find significant differences in neurocognitive performance based on APOE-ε4 status, contributing to a body of literature suggesting a potential age dependent effect of the APOE-e4 on cognitive outcomes in HIV disease. Finally, the combination of FHD and APOE-ε4 status did not have negative additive effects on neurocognition, suggesting independent influences of these predispositional risk factors on cognitive functioning. Research by Donix and colleagues (2012) additionally conclude that there are unique contributions of each risk factor on cognitive performance in people without HIV, highlighting that both factors should be routinely captured in clinical settings and accounted for in neuropsychological evaluations. In summary, although these cross-sectional findings suggest no direct association between these predispositional risk factors and memory deficits indicative of preclinical AD, it is important to note that some participants may still be on an AD trajectory, based on base rates. Conversely, FHD was associated with domain deficits commonly seen in HAND. Further longitudinal analyses are necessary to examine these deficits over time and address remaining questions regarding predictability of HAND and AD.

4.2 Examining Whether Family History of Dementia and APOE-ε4 status Predict

Neurocognitive Trajectories

The second primary aim of this study was to examine the differential impact of FHD and APOE-ε4 status on neurocognitive decline over time. It was hypothesized that global- and domain-specific neurocognition would worsen more rapidly in the FHD+/APOE-ε4+ group and be most stable in the FHD-/APOE-ε4- group.

Results revealed several key findings. First, there was little change in global- and domain-specific T-scores over time. Global cognitive T-scores increased by 0.112 per year. Similarly, verbal fluency, executive function, processing speed, learning, delayed recall, and working memory T-scores exhibited yearly increases ranging from 0.070 to 0.219. Conversely, the T-score for motor skills showed an average decrease of 0.187 per year. None of the cross-level interactions between FHD/APOE-ε4 and the linear effect of time remained significant after correcting for multiple comparisons. Given there was little variability in global- and domain-specific T-scores over time, these results were not surprising.

Notably, the variable representing time exhibited a significant, but subtle in magnitude, quadratic pattern on global cognitive performance as well as several domain-specific cognitive trajectories including executive function, learning, delayed recall, and working memory. These results suggest a non-linear relationship between time and cognitive outcomes, rather than a linear pattern. Further exploration of the data showed a significant increase in global neurocognition within the initial decade of neuropsychological visits, followed by neurocognitive stability. Similarly, there were increases in verbal fluency, executive functioning, processing speed, and working memory during the first ten years, with more stable trajectories thereafter. Moreover, stability was observed in learning within the initial decade, followed by a

decline after ten years that did not fall below baseline scores in the total sample. These exploratory results suggest relatively stable neurocognitive trajectories in our sample of PWH, with some statistically significant levels of improvement observed over the first decade of follow-up assessments. Although certain changes were statistically significant, they may not reflect clinically significant improvement or decline, as T-scores remained within the average range of expected scores. Furthermore, T-scores are adjusted for both practice effects and age, which may explain the initial increase in T-scores as well as any subsequent incremental decline, considering decline did not exceed what would be expected for age. Lastly, it is important to acknowledge that variability in participant follow-up data may have influenced these findings, highlighting the need for further investigation with advanced statistical methodology to adjust for individual differences in follow-up time.

In the HIV and aging literature, studies examining longitudinal trajectories of cognition in PWH have shown variable outcomes, ranging from reports of improvement, cognitive stability over time, and evidence of linear decline (Aung et al., 2021; M.-J. Brouillette et al., 2016; Gott et al., 2017; Heaton et al., 2015). Saloner and colleagues (2022) utilized growth mixture modeling to examine longitudinal neurocognitive classes in a similar sample of CHARTER participants aged 50 and over. Their findings revealed three latent classes, none of which exhibited a decline in global T-score over time: neurocognitive stability, intermediate baseline performance with a u-shaped trajectory, and low baseline performance with a u-shaped trajectory. Other longitudinal studies have observed global cognitive decline among aging PWH, and in the domains of executive functioning, motor function, episodic memory, and processing speed (Baldewicz et al., 2004; M. J. Brouillette et al., 2016; Goodkin et al., 2017; Gott et al., 2017). Another CHARTER study identified four cognitive change phenotypes across data from two neuropsychological

study visits (~6 months apart) that included declines in verbal fluency, executive function, learning and recall, and motor function (Dastgheyb et al., 2019). A more recent investigation of CHARTER data found evidence of neurocognitive decline beyond expected age-related changes among younger (< 60 years) and older (≥ 60 years) PWH (Heaton et al., 2023). Taken together, variability in findings across the literature may be attributed to differences in study sample characteristics, including factors such as demographics (e.g., age, sex, race/ethnicity), HIV-disease severity, and presence of comorbid conditions (Heaton et al., 2015).

Regarding the primary aim, results were broadly inconsistent with the anticipated hypothesis. None of the cross-level interactions between FHD/APOE-ε4 group and the linear effect of time were significant for global- or domain-specific neurocognition. There was a curvilinear effect of time on global cognitive trajectories showing a significant difference in slope between the FHD-/APOE-ε4- and FHD+/APOE-ε4+ groups. Results suggest that this effect was primarily driven by similar group differences in executive functioning, learning, and motor skills. Additionally, there was a trend level difference between the FHD-/APOE-ε4- and FHD-/APOE-ε4+ groups for delayed recall. Preliminary exploratory findings revealed poorer global, learning, recall, and motor skills performance in the FHD+/APOE-ε4+ group; however, only one participant in the FHD+/APOE-ε4+ group was followed for over ten years, while 47 participants were tracked in the FHD-/APOE-ε4- group. These attrition rates raise concerns regarding power to detect meaningful differences and the possibility of committing a type I or type II error. It is possible that the one participant in the FHD+/APOE-ε4+ group represents an outlier, with significantly lower scores compared to other FHD+/APOE-ε4+ PWH. Alternatively, the one participant may accurately represent performance across PWH with FHD+/APOE-ε4+. Thus, these exploratory results must be interpreted with caution.

Nonetheless, primary findings indicate notable distinctions in trajectory slopes between PWH with both predispositional risk factors and PWH without FHD and the APOE-ε4 allele, suggesting that the co-occurrence of these factors exert deleterious effects on neurocognitive outcomes, specifically for learning, recall, and motor skills. To our knowledge, no study has longitudinally examined cognition in PWH with FHD and limited research has explored the longitudinal effects of APOE-ε4 in PWH. Cross-sectional neuroimaging and neuropsychological studies among APOE-ε4 carrying PWH have observed conflicting results regarding the impact of APOE-ε4 on cognitive trajectories possibly due to the age dependency of APOE-ε4 effects (Geffin & McCarthy, 2018). Longitudinally, Burt and colleagues (2008) found that the APOE-ε4/ε4 genotype was associated with accelerated HIV disease course and progression to death compared to the APOE-ε3/ε3 genotype; however, was not associated with HIV-associated dementia. A study conducted within the Multicenter AIDS Cohort Study, results revealed no association between APOE-ε4 and the time until cognitive impairment onset. Additionally, they observed no interactive effects between APOE-ε4, HIV, age, and cognitive impairment in their cohort of 2204 participants who were initially cognitively intact but presented with potentially confounding conditions at their baseline evaluation.

Follow-up analyses examining the independent effects of FHD and APOE-ε4 status on cognitive trajectories revealed a trend level positive effect of time and APOE-ε4 status on executive function and processing speed. While the APOE-ε4 allele is strongly associated with cognitive deficits and brain atrophy in older adults without HIV, studies in younger adults are mixed. For example, Taylor and colleagues (2017) found that ε4 noncarriers showed worse executive function performance with increasing age compared to the ε4 carriers in their sample of adults aged 20-50. Results also showed a significant quadratic effect of time and APOE-ε4

status on global cognitive trajectories, a significant quadratic effect of time and FHD on delayed recall, and trend-level quadratic effect of both FHD and APOE-ε4 on motor skills. These quadratic results have multiple implications. Firstly, while APOE-ε4 showed protective effects against subcortical processes including executive function and processing speed when time was modeled linearly, there was a curvilinear effect of APOE-ε4 on global cognitive function with worse trajectories among APOE-ε4 carriers. These results suggest that the negative effects of APOE-ε4 heighten with increased age. Next, results suggest the initial null effects of FHD on recall cross-sectionally were amplified with older age, as evidenced by the distinct trajectories between PWH with FHD compared to no FHD longitudinally. Considering delayed recall impairment is a hallmark feature of AD, it is possible that this sample of PWH with FHD may show signs reflecting early AD. Lastly, motor dysfunction is common in PWH and these results suggest that both predispositional risk factors may independently heighten risk of motor decline.

In the broader aging literature, APOE-ε4 has been associated with earlier progressive memory decline, with cognitively healthy APOE-ε4 carriers in their 50s and 60s showing more rapid memory loss and reduced learning efficiency than matched APOE-ε4 noncarriers (Baxter et al., 2003; Caselli et al., 2009; Caselli et al., 2007). FHD has emerged as a predictor of incident dementia, with individuals having FHD experiencing a 39% higher lifetime risk of developing the disease, a risk that escalates to 42% by the age of 70, especially if both parents had AD (Jayadev et al., 2008; Lautenschlager et al., 1996). Although limited, studies exploring the combined influence of FHD and APOE-ε4 on cognitive outcomes generally indicate an additive effect on cognitive decline. A study of 907 cognitively healthy older adults (> 75 years) found a significant relationship between FHD in first-degree relatives and risk of dementia, but only among APOE-ε4 carriers. Interestingly, there was no heightened risk among only APOE-ε4 non-

carriers (Huang et al., 2004). Similarly, Hayden and colleagues (2009) observed steeper declines among participants with FHD and APOE-ε4, compared to participants with only one of the two risk factors in their sample of 2957 adults aged 65 years or older.

As PWH continue to age, potentially into their sixth and seventh decades of life, future research may discover more pronounced effects of FHD and APOE-ε4 in older cohorts. The average age at participants final visits was approximately 56, with a range from 45 to 81. This age range represents a critical time where age-related decline, HAND, and aMCI may intersect. Typical age-related cognitive changes often include declines in processing speed, working memory, attention, and episodic memory; whereas in HAND, longitudinal studies have shown relatively stable patterns of frontal striatal dysfunction including attention deficits, psychomotor slowing, executive dysfunction, and poor learning (Becker et al., 1995; Heaton et al., 2015; Peavy et al., 1994; Scott et al., 2011; White et al., 1997). In aMCI and AD, cognitive changes typically involve progressive memory loss, alongside impairments in other domains including language, executive functioning, and visuospatial abilities (Pini et al., 2016). Additionally, factors such as cardiovascular disease contribute to cognitive decline in this population, further affecting executive function, attention, processing speed, and motor skills (McIntosh et al., 2021; Robinson-Papp et al., 2020). Given the observed cognitive changes in executive function, learning, delayed recall, and motor skills among PWH with FHD and the APOE-ε4 allele, further investigating the temporal onset of domain-specific declines may help elucidate whether cognitive impairment primarily reflects typical aging, HAND, early stages of AD, or a convergence of multiple etiologies.

4.2.1 Summary of Aim 2. Findings from Aim 2 indicated minimal changes in global- and domain-specific T-scores over time. Interestingly, a significant, but subtle, quadratic pattern

was observed in global cognitive performance and several domains, suggesting a non-linear relationship between time and cognitive outcomes. Results did not align with the expected hypothesis, as none of the cross-level interactions between FHD/APOE-ε4 and the linear effect of time remained significant. Although there were significant differences in global and domain cognitive trajectories between the FHD-/APOE-ε4- and FHD+/APOE-ε4+ groups, these results should be interpreted with caution due to limitations in sample size and attrition rates. Considering the high attrition rates in the dually positive group, possibly due to elevated medical and psychosocial burdens affecting follow-up attendance, it is important to consider the potential impact of other cognitive determinants such as individual characteristics, medical comorbidities, and behavioral health factors.

4.3 Evaluation of Exploratory Factors as Predictors of Neurocognitive Trajectories by FHD/APOE-ε4 Status

The exploratory aim of this study was to examine if demographic, neuropsychiatric, substance use, daily functioning, comorbidities, and HIV disease characteristics predict neurocognitive trajectories, and whether there are differences by FHD/APOE-ε4 status. No specific hypotheses were drawn for this investigation. 16 predictors were examined, and these factors were chosen given that they have been previously associated with cognition. The comprehensive analysis of various cognitive domains and their relationship with FHD and APOE-ε4 status revealed intricate patterns of associations.

4.3.1 Relationships between demographic factors and neurocognitive trajectories. First, demographic factors including sex, ethnicity, and education were explored as predictors of global and domain-specific cognitive performance in the full sample of PWH. Ethnicity significantly influenced cognitive performance trajectories, with Black participants exhibiting

higher global cognition, processing speed, working memory, learning, and recall performance

over time compared to non-Hispanic White participants. Female participants exhibited steeper

declines in verbal fluency over time, while males showed steeper declines in recall scores.

Education attainment at baseline showed contrasting associations with cognitive domains: a

positive relationship with executive function performance and a negative relationship with recall

performance. Next, these effects were examined by FHD/APOE-ε4 status revealing that the

influence of education on global cognition became more pronounced in the FHD+/APOE-ε4+

group compared to the FHD-/APOE-ε4- group, particularly driven by the domains of verbal

fluency, executive functioning, processing speed, and learning.

These findings highlight the critical role of demographic factors in influencing cognitive

trajectories among middle-to-older aged adults with HIV. Higher education levels have been

consistently linked to a reduced risk of cognitive decline in HIV and non-HIV cohorts, serving as

a protective factor against age-related cognitive impairment (Bernard et al., 2021; Lovden et al.,

2020). This association is thought to be mediated by the cognitive reserve accumulated through

lifelong learning experiences, which may buffer against the deleterious effects of

neurodegenerative disease and age-related brain changes (Tucker & Stern, 2011). A recent meta-

analysis including 18 studies demonstrated that the risk of HAND in PWH with lower education

attainment was significantly heightened compared to PWH who have higher education levels.

The contrasting effects of education attainment on cognitive domains observed in this study

underscore the complex interplay between socioeconomic factors and cognitive reserve in PWH.

These relationships are even further complicated by interactions with other risk factors for

diminished cognitive reserve, including FHD and APOE-ε4, as findings from the current study

demonstrate a heightened impact of lower education in the dually positive group. Future work

may investigate the longitudinal relationships between additional markers of cognitive reserve (e.g., education quality, literacy, reading grade level), cognitive risk factors, and neurocognitive performance in this sample of PWH (Ryan et al., 2005).

The observed influence of ethnicity on cognitive performance trajectories aligns with previous research in the broader aging literature demonstrating differential cognitive outcomes across racial and ethnic groups within non-HIV and HIV populations (Marquine et al., 2018; Marquine et al., 2016; Zahodne et al., 2016); however, conflicts with extant literature showing poorer cognitive performance among Black relative to White PWH (RK Heaton et al., 2004; Manly et al., 2004; Manly et al., 2002; Manly et al., 2011). Nevertheless, these findings emphasize the importance of considering racial disparities, likely stemming from psychosocial phenomena (e.g., stereotype threat, perceived discrimination, acculturation, low education quality, socioeconomic disparities) when conceptualizing cognitive trajectories (Zahodne et al., 2016).

The observed sex-specific patterns of decline in verbal fluency and recall suggest sex-specific vulnerabilities in certain cognitive domains, which aligns with the existing literature on this topic. Several studies have shown greater cognitive disadvantages in women with HIV compared to men, with specific domain-level differences in memory, learning, processing speed, and motor function (Dreyer et al., 2022; Maki et al., 2018; Rubin et al., 2020; Sundermann et al., 2018). Notably, a systematic review by Rubin and colleagues (2019) showed that few studies have sufficient power to address sex-differences in neurocognitive impairment. Our sample of PWH was 78% male, which could have underpowered our ability to detect additional sex-specific longitudinal effects. Understanding the mechanisms underlying these sex-specific vulnerabilities remains a priority, with possible explanations including differences in cognitive

reserve, biological factors (e.g., hormones, genetic differences), psychosocial factors (e.g., low education, sociodemographic status, trauma, mental health, substance use), and environmental influences (e.g., barriers to healthcare).

4.3.2 Neuropsychiatric factors predicted neurocognitive trajectories by FHD/APOE-ε4 status. Current major depressive disorder (MDD) and lifetime history of MDD were explored as predictors of cognitive trajectories in the full sample of PWH and by FHD/APOE-ε4 status. Participants with lifetime MDD exhibited steeper declines in global cognition, particularly within the FHD+/APOE-ε4+ group. Similar differences by FHD/APOE-ε4 status were found in verbal fluency and learning trajectories, with worsening performance in the FHD+/APOE-ε4+ group. Mental health disorders, particularly depression, are highly prevalent in PWH, with the national prevalence of current depression in PWH reaching approximately one-quarter, and lifetime history of depression at about 42% (Cook et al., 2018; M. G. Nanni et al., 2015; Rubin & Maki, 2019; Yousuf et al., 2020). In our sample of middle-to-older aged PWH, rates of depression were similar to these national estimates, with 15% of the sample reporting current depression, and 47% lifetime depression. Notably, rates of current and lifetime MDD did not differ by FHD/APOE-ε4 status.

There is an established body of literature showing that depression and cognitive impairment frequently co-occur in this population, possibly due to shared neurobiological pathways (e.g., dopaminergic changes, neuroinflammation), common psychosocial determinants (e.g., poverty, stress, trauma), and common behavioral symptoms (e.g., substance use, ART nonadherence) (Maria Giulia Nanni et al., 2015; Rubin & Maki, 2019). Moreover, longitudinal research suggests that the severity and chronicity of depression may be key moderators in the relationship between depression and neurocognition in PWH because they relate to lifetime

neuropsychiatric burden (Bengtson et al., 2018; Liu et al., 2023; Paolillo et al., 2020; Pence et al., 2018). Consistent with our results, several studies examining the relationships between depression and domain-specific cognition over time have shown worsening performance in memory, executive function, psychomotor speed, verbal fluency, and motor function (Baldewicz et al., 2004; Rubin & Maki, 2019).

Fewer studies have investigated associations between depression, neurocognition, FHD and APOE-ε4 status, and findings have been mixed. Harwood and colleagues (2000) showed that current depression was more common in participants with a positive versus negative FHD, and further hypothesized that depression may represent a precursor to the onset of an incipient dementia syndrome among adults with FHD. In terms of APOE-ε4 status, MacAulay and colleagues (2020) observed a significant association between APOE-ε4 status and depression in a sample of cognitively unimpaired, HIV-seronegative participants. In contrast, Bogner and colleagues (2009) did not find a relationship between APOE-ε4 status and depressive symptoms in subgroups of older HIV-seronegative adults. These differing results could be attributable to factors such as differences in sample characteristics or study methodologies. In sum, history of depression is a risk factor for subsequent cognitive decline, particularly within the verbal fluency and learning domains among aging PWH. This relationship is exacerbated by the combined impact of predispositional risk factors, which may independently or synergistically contribute to cognitive decline, potentially reflecting a cumulative dose-environment effect.

4.3.3 Substance use factors predicted neurocognitive trajectories by FHD/APOE-ε4 status. This study examined both current SUD diagnosis and lifetime history of any SUD as predictors of cognitive trajectories. Among the full sample, current SUD was associated with worsening learning and motor skills performance, whereas lifetime SUD at baseline and at study

visits were associated with declines in processing speed. In the FHD+/APOE-ε4+ group, no lifetime SUD diagnosis was significantly associated with worsening executive function, while current SUD was linked to worsening learning performance over time in the same group.

These findings align with a substantial body of literature on the deleterious effects of substance use on cognitive function among people with and without HIV, with novel contributions on the relationship between genetic vulnerabilities and cognitive trajectories in substance using PWH. Among the 73% of participants that reported history of SUD in the current study, over three-quarters were diagnosed alcohol use disorder and over half had cocaine use disorder. Heavy alcohol use history as well as current binge drinking have been independently associated with poorer global- and domain-specific (learning, recall, motor skills) cognitive outcomes, with additive adverse effects of HIV-infection and alcohol use on cognition (Green et al., 2004; Kohli et al., 2020; Paolillo et al., 2022; Rothlind et al., 2005). While mechanisms underlying these effects are poorly understood in older PWH, older adults may be more vulnerable to alcohol-related neurotoxicity due to a reduced capacity to metabolize alcohol, lower total-fluid volume, and reduced physiological capacity to cope with biological stressors (Meier & Seitz, 2008; Strandberg et al., 2018) (Meier & Seitz, 2008; Strandberg et al., 2018). Chronic alcohol use in PWH can lead to structural changes in the brain, including reduced brain volumes in several brain regions crucial for functions like learning, recall, motor skills, processing speed, executive function, attention, and language (Spies et al., 2022). Fewer studies have examined cocaine use and neurocognitive functioning among PWH; however, results suggest that PWH who use cocaine have poorer neurocognitive outcomes, with specific deficits in verbal memory, processing speed, and visuospatial construction (Litvin et al., 2021; Meade et al., 2011). This association may be attributable to several mechanisms including dopaminergic

dysfunction, abnormalities in brain glucose metabolism, and vascular hypoperfusion (Chang et al., 2008; Spronk et al., 2013).

The literature on FHD, APOE-ε4, substance use, and cognition is relatively sparse, with majority of studies examining associations between APOE-ε4, alcohol use, and cognitive outcomes in HIV-negative samples. Slayday and colleagues (2021) found a significant synergistic effect between APOE-ε4 status and heavy alcohol consumption, with worse global cognition and episodic memory among APOE-ε4 carriers in the heavy drinking subgroup. Moreover, a study including 685 patients diagnosed with possible or probable AD found that the presence of an APOE-ε4 allele, history of heavy drinking, or history of heavy smoking was independently associated with earlier onset of AD by 2-3 years. These risk factors were also additive, contributing to a 10-year earlier onset compared to individuals with no identified risk factors (Harwood et al., 2010). Taken together, findings from our current study align with the existing literature and theoretical frameworks that suggest both independent and additive effects of predispositional (i.e., FHD and APOE-ε4) and environmental risk factors (i.e., substance use) on cognitive outcomes.

Of note, although the CHARTER dataset includes variables for individual substance use diagnoses, we relied on a composite "any lifetime substance use" variable for our analyses, limiting our ability to discern which specific substance might have influenced cognitive trajectories. Furthermore, this approach overlooked the consideration of multiple comorbid conditions, such as having multiple substance use diagnoses, thereby potentially amplifying the cumulative impact of substance use history. Additionally, given the common co-occurrence of substance use with neuropsychiatric and vascular conditions, a more nuanced and detailed analysis is needed to explore the specific associations between substance use and cognitive

trajectories, as well as to investigate the contributory effects and interplay among these co-morbid conditions, thus clarifying these remaining questions.

4.3.4 Daily functioning factors did not predict neurocognitive trajectories. iADL dependence at baseline and diagnoses at each study visit were examined as predictors of cognitive trajectories. Participants characterized as iADL dependent at baseline demonstrated slightly worse verbal fluency trajectories. A similar trend-level relationship was observed for processing speed performance, particularly in the FHD+/APOE-ε4- group.

Broadly, functional dependence and cognitive impairment are significant concerns among PWH, as both are associated with declines in overall well-being and quality of life (R. K. Heaton et al., 2004; Nweke et al., 2022). While advances in ARTs have led to improved survival rates and reduced incidence of opportunistic infections, PWH still experience higher rates of functional dependence compared to the general population (Doyle et al., 2013). A recent meta-analysis presented inconsistent findings across studies examining basic ADLs, acknowledging that HAND cases in the modern cART era represent more mild neurocognitive impairment subtypes (Nweke et al., 2022). In terms of iADLs, HAND has been previously associated with dysfunction in several important areas including medication management, financial planning, vocational performance, automobile driving, and shopping (R. Heaton et al., 2004; Hinkin et al., 2002; Marcotte et al., 1999; Morgan, Woods, & Grant, 2012; van Gorp et al., 2007). While our study found a trend-level relationship between iADL dependence and verbal fluency trajectories, previous studies have implicated episodic memory, executive functions, and processing speed in iADL decline (R. K. Heaton et al., 2004; Hinkin et al., 2002; Woods et al., 2008). Nonetheless, there is a well-established relationship between functional and cognitive decline in PWH, and it remains difficult to distinguish whether iADL decline reflects trajectories of HAND or AD, as it

manifests in both conditions at varying degrees. Further research is warranted to examine the variability in magnitude of functional impairment and its association with HAND or AD pathology.

4.3.4 Presence of comorbid conditions predicted neurocognitive trajectories by FHD/APOE-ε4 status. In terms of comorbid conditions, hypertension, hyperlipidemia, diabetes mellitus, and hepatitis C infection (HCV) at baseline and diagnosis at each study visit were explored. Findings among the entire sample of PWH suggest that hypertension diagnosis at study visit was associated with declines in learning scores. Hypertension at baseline was associated with more pronounced declines in global cognition in the FHD+/APOE-ε4+ group, driven by the executive function domain. Hyperlipidemia was associated with accelerated declines in both learning and working memory performance, while exhibiting diverse effects across FHD/APOE-ε4 status including worsening global cognitive, processing speed, learning, and motor skills performance in the FHD+/APOE-ε4+ group and improved processing speed in the FHD+/APOE-ε4- group. Diabetes predicted declines in verbal fluency, specifically in the FHD-/APOE-ε4+ group, whereas no diabetes diagnosis related to worse motor skills in the FHD+/APOE-ε4- group. Finally, HCV diagnosis at baseline was associated with better performance in recall.

Cardiovascular disease is an established risk factor for cognitive impairment in people with and without HIV, and cardiovascular conditions are elevated in PWH (McIntosh et al., 2021; Nakamoto et al., 2011; Wright et al., 2010; Yaffe et al., 2020). In fact, a recent investigation of CHARTER data revealed relationships between several comorbid conditions including diabetes, hypertension, chronic pulmonary disease, and frailty with neurocognitive decline (Heaton et al., 2023). The cognitive impact of cardiovascular disease has been associated

with impaired cerebral blood flow regulation, chronic inflammation, oxidative stress, and subsequent structural and functional changes (e.g., white matter lesions, gray matter atrophy, neuronal dysfunction) in the brain (Mohanta et al., 2023). While cognitive impairments may vary as a function of the underlying etiology, longitudinal studies suggest that deficits in attention, executive functions, psychomotor speed, and processing speed are most common, due to disruption of the frontal and subcortical brain systems (Okonkwo et al., 2010; Schievink et al., 2022). Results from our study are broadly consistent with these established findings, showing notable declines in executive function, processing speed, working memory, learning, and motor skills.

APOE-ε4 has been previously associated with cardiovascular disease, cardiovascular risk factors, and vascular dementia (Schilling et al., 2013; Tai et al., 2016). In a sample of 353 men, aged 69-89 at baseline, Kromhout and colleagues (1996) found a synergistic effect between cerebrovascular disease and APOE-ε4 status on cognitive decline, with the steepest declines among participants with both APOE-ε4 and high cholesterol or diabetes mellitus. Similarly, a study from the Framingham Offspring Cohort Study found that APOE-ε4 modified associations between midlife cardiovascular disease (hypertension, diabetes) and decline in language, verbal memory, attention, and visuospatial abilities (Bangen et al., 2013).

These findings highlight the importance of early detection and effective management of comorbid conditions, especially among middle-to-older age PWH with the APOE-ε4 allele, as well as the negative effects of cardiovascular comorbidities on cognitive trajectories. Early identification and treatment of these modifiable conditions such as hypertension, hyperlipidemia, and diabetes may not only improve cardiovascular outcomes but also contribute to preserving cognitive function. Furthermore, addressing HCV infection may have unexpected cognitive

benefits, as suggested by the association with better recall performance observed in this study. Relatedly, one limitation is the lack of information regarding the within-person management and control of these comorbid conditions overtime. Therefore, it is difficult to understand the extent to which observed cognitive outcomes may be influenced by variations in treatment adherence and control.

4.3.5 HIV disease characteristics predicted neurocognitive trajectories. The analysis of various HIV-related factors revealed significant impacts on cognitive trajectories among this sample of middle-to-older aged PWH. Specifically, higher CD4 counts were associated with improved processing speed. This finding aligns with similar investigations of HIV-disease burden and neurocognitive trajectories in PWH in which lower CD4 nadir related to rapid cognitive decline (Ellis et al., 2022), and CD4/CD8 ratios related to worse motor speed (Le et al., 2023). Moreover, a case control study also found psychomotor slowing among PWH with CD4 levels of 200-499 cells/mm^3, which are slightly lower than CD4 counts within our sample (IQR = 297 – 654) (Ogunrin et al., 2007).

Results also indicated that participants not on ART experienced steeper declines in verbal fluency and processing speed. Furthermore, individuals not on ART exhibited steeper declines in both executive function and motor skills, particularly evident in the FHD+/APOE-ε4+ and FHD+/APOE-ε4- groups, respectively. Findings on whether ART improves cognitive function have been inconsistent, with some studies suggesting potential benefits while others show mixed or no effects. Reviews synthesizing the literature have also found varied results, likely due to differences in study populations, methodologies, and the evolving landscape of HIV treatments (Al-Khindi et al., 2011). In a recent meta-analysis, cross-sectional studies did not demonstrate positive effects of ART on cognitive function, while cohort studies found a notable relationship

between ART and cognitive improvements, particularly among PWH who were in compromised physical health (Gao et al., 2020). Taken together, early ART initiation and ART adherence may improve cognitive outcomes and are particularly important in subgroups with additional environmental and genetic burden.

In conclusion, our findings highlight the protective role of HIV disease characteristics, such as higher CD4 counts, ART adherence, and maintaining an undetectable viral load, against cognitive impairment, especially among PWH with FHD and the APOE-ε4 allele. Considering these findings, it is critical to develop accessible interventions to promote HIV disease management in this vulnerable subgroup, with the goal of mitigating risk of poor neurocognitive outcomes.

4.3.6 Summary of Exploratory Aim. Findings from Aim 3 identified modifiable risk factors that may serve as targets for clinical and psychological intervention to protect against future cognitive decline among middle-to-older aged PWH. PWH face significant barriers to accessing adequate healthcare including stigma, financial constraints, and geographic limitations. Therefore, it is crucial to increase collaborative efforts among healthcare providers, psychologists, and community organizations to develop and implement accessible multifaceted interventions. By leveraging this nuanced understanding of modifiable risk factors, clinicians may adopt a proactive approach to cognitive health management in PWH, which may improve overall quality of life and promote successful aging in this population.

4.4 Limitations and Future Directions

In addition to the limitations discussed above, there are additional limitations that should be considered. First, the demographics of the CHARTER sample must be considered in terms of generalizability of findings. The relatively young age range (i.e., mean age = 50 years; range =

45 – 69) may be too young to expect any negative effects of FHD, APOE-ε4 status, or accumulations of AD pathology. Even at final study visits, the average participant age was 58.5 (range = 45 – 81), which is when we may begin to anticipate neurodegenerative changes. As previously noted, the sample was predominantly male (i.e., 78.1%). While this reflects the current demographics of PWH in the United States (Centers for Disease Control and Prevention, 2018), evidence previously presented suggests sex differences in cognitive impairment among PWH, as well as in HIV-negative APOE-ε4 carriers. Consistent with other studies, our study was likely underpowered to test potential differences by sex and ethnicity (Rubin, Neigh, et al., 2019). Finally, consistent with other CHARTER studies, participants with severe confounding comorbid conditions were excluded from this study which limits the generalizability of our findings to populations with more complex health profiles.

Notably, the prevalence of participants with at least one APOE-ε2 allele (18%) exceeded the general frequencies among North Americans of European decent (8-10%) and among African Americans (11-12%). Considering the lower frequency of the APOE-ε2 allele, it has been relatively less studied compared to the APOE-ε4 allele. However, existing literature suggests that the APOE-ε2 allele is associated with longevity, reduced risk of AD, reductions in amyloid plaque, and greater hippocampal volume in late life. In contrast, it has also been associated with greater white matter hyperintensity burden and certain types of cerebrovascular disorders (Kim et al., 2022). Future research within CHARTER could examine differences in cognitive trajectories and the effects of comorbid conditions across APOE genotypes to understand the differential effects of the ε2 and ε4 alleles in PWH.

A significant limitation in our study was the method by which FHD was captured. The CHARTER study gathered limited information regarding FHD using a free-response question,

without specifying which relative (e.g., first degree or second degree), type of dementia, or the age of onset. This lack of specificity is crucial because not all dementias are hereditary, and understanding the specific family history could provide valuable insights into potential genetic predispositions. Furthermore, it is possible that some participant may have been unaware of their family medical history, potentially resulting in underreporting of FHD. Ideally, a validated instrument would have been employed to diagnose FHD, and corroborating evidence from family members could have been sought to ensure accuracy. Future studies may address this limitation by utilizing a standardized questionnaire that systematically collects information about FHD and neurodegenerative conditions. While this approach will allow for a more comprehensive and accurate assessment, it is important to acknowledge that AD is believed to be caused by both environmental and genetic variations, with a significant percentage of sporadic AD cases rather than familial AD. Therefore, identifying a FHD may inadvertently encompass sporadic forms of the disease, leading to sample inflation and a misrepresentation in testing of true familial AD cases. Genetic testing for variants associated with familial AD may play a role in confirming family history status, however, the full genetic architecture of familial AD remains under investigation.

This study examined a relatively modest sample size. While the overall sample of 283 participants is not necessarily small, when stratified into subgroups based on FHD and APOE-ε4 status, some groups were relatively small (i.e., FHD+/APOE-ε4+ = 19). As highlighted throughout the discussion, this limitation may have limited statistical power to detect meaningful relationships within these specific subgroups. In order to maintain adequate subgroup sample sizes, APOE-ε4 positivity included both heterozygous and homozygous carriers, excluding three participants that were ε2+/ε4+ from Aims 1 and 2. However, this may have impacted our ability

to detect APOE-ε4 effects, given previous findings of a "dose-dependent" relationship with cognition.

There was notable missing data regarding evaluation of comorbid medical, psychiatric, and substance use disorders. This gap could be attributed to inconsistencies in neuromedical assessments across study visits, possibly influenced by time limitations. Despite this, the observed relationships between these factors and cognitive trajectories remained robust enough to retain significance, underscoring their importance even in the presence of missing data.

Future studies should include an HIV-negative comparison group to examine the potential additive impact of FHD, APOE-ε4, HIV-disease on cognitive trajectories. Although utilizing preexisting CHARTER data allowed for a comprehensive longitudinal analysis, this study did not enroll HIV-negative comparison participants, limiting the ability to explore differential relationships by HIV status. Existing literature on FHD and APOE-ε4 has shown worse cognitive outcomes in PWH compared to HIV-negative participants, however these studies have been primarily cross-sectional in design. With an appropriate comparison group, longitudinal studies may assess whether FHD and APOE-ε4 predict HAND versus AD trajectories.

In the current study, linear mixed effects modeling was used to examine longitudinal cognitive trajectories. There are alternate methods of assessing cross-sectional and longitudinal neurocognitive change that have been utilized in other studies among PWH, such as regression-based summary change scores, repeated-measures ANOVA, and multilevel modeling. While these techniques have merit, linear-mixed effect modeling is better equipped to handle data with varying number of timepoints. Results of Aim 2 suggest a curvilinear trajectory of cognitive performance in the larger sample, as well as in various FHD/APOE-ε4 status groups. Future

studies may further investigate this curvilinear pattern using change point analysis. This method offers a more precise quantification of the specific point at which scores shifted from improvement to decline, which could allow for exploration of additional factors (e.g., comorbid conditions, HIV disease characteristics) that may have contributed to cognitive decline.

4.5 Summary and Clinical Implications

This study has several clinical implications. First, it highlights the significance of FHD as a predictor of poorer cognitive outcomes in PWH, underscoring its potential utility in routine clinical assessments. Many studies investigating risk for AD focus on the APOE-ε4 allele, which could reduce awareness for other important risk factors such as FHD. For clinicians, data from the current study could be useful to avoid oversimplifying assumptions about APOE-ε4 genetic risk, and additional closely monitor patients with FHD. Secondly, the presence of both FHD and the APOE-ε4 allele was associated with cognitive change over time, although their ability to distinguish between aMCI and HAND in this sample was limited. Further investigation in older age samples is warranted to examine potential associations between these predispositional risk factors and cognitive decline. Lastly, the study highlights the deleterious effects of neuropsychiatric disorders, substance use disorders, cardiovascular conditions, and poorly controlled HIV-disease on cognitive trajectories, with heightened effects in participants with FHD and at least one APOE-ε4 allele. Effective management of these modifiable health conditions through biopsychosocial interventions is crucial for mitigating the risk of cognitive decline, especially among PWH with additional predispositional burden.

In summary, this study found that FHD and APOE-ε4 status contribute to heightened risk of cognitive decline among middle-to-older age PWH with compounding psychiatric and medical burden. Therefore, increasing accessibility to targeted interventions aimed at managing

these comorbidities is crucial for improving cognitive trajectories and overall well-being in this

vulnerable population.

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