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Vascular Risk Drives Cognitive Decline over 10 Years in People Aging with Well-Controlled HIV

Running head: Cognitive Decline in HIV

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Abstract

Objective: To characterize long-term cognitive trajectories in adults aging with well-controlled HIV and identify baseline predictors of cognitive decline.

Design: Prospective, multicenter longitudinal cohort study with repeated cognitive assessments for up to 10 years.

Methods: Positive Brain Health Now enrolled HIV+ adults aged ≥35 years without dementia and followed at 9–12-month intervals across two study phases (2013–2018; 2019–2024). Cognitive performance was assessed using the Brief Cognitive Ability Measure (B-CAM). Group-based trajectory modeling identified patterns of cognitive change among participants with at least one visit in each phase. Baseline predictors of declining trajectory membership were examined using generalized estimating equations.

Results: Two cognitive trajectories were identified: one stable and one declining. Although no decline was detected during the initial 3-year follow-up, 47% of participants exhibited decline over up to 10 years, with an estimated 0.35–0.5 SD difference in B-CAM scores between trajectories. The strongest baseline predictors of decline were higher cognitive performance (floor effect), higher Framingham Risk Score and peripheral artery disease (OR [95% CI]: 2.84 [1.35–5.98] and 3.07 [2.06–4.57]), and older age, lower education, needing academic support, cannabis use, anxiety, low motivation, detectable plasma HIV RNA, and higher VACS Index 1.0 scores. Nadir CD4 count and HIV duration were not independently associated with decline.

Conclusions: Among adults aging with well-controlled HIV, cognitive decline, when present, progressed slowly and was driven primarily by vascular risk factors, suggesting that, in the current treatment era, vascular comorbidities may play a greater role in cognitive decline than traditional HIV-related factors.

Keywords: HIV infection; Cognitive decline; Longitudinal study; Neurologic complications

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Introduction

With life expectancy of people living with HIV on combination antiretroviral therapy (ART) now near normal, brain health has emerged as a priority. Despite viral suppression, mild cognitive difficulties remain common [1-6] and worsen quality of life. Clarifying the likelihood of cognitive decline and identifying potentially modifiable risk factors are essential to optimizing function and quality of life among people aging with HIV, a goal often referred to as the "fourth 90" of HIV care [7].

In the pre-ART era, studies of cognitive impairment focused primarily on HIV-related factors but with the widespread use of ART, a more complex picture has emerged [8].Cross-sectional studies have identified a variety of biological and psychosocial factors associated with poor brain health in HIV [9-15], but cannot speak to the predictors of cognitive decline or inform the selection of targets for intervention. Longitudinal studies with sufficiently large, well-characterized samples and repeated cognitive assessment are needed to describe patterns of cognitive change over time and identify factors that predict decline. The Positive Brain Health Now study [16] was designed to fill this gap. In this planned analysis, we aimed to estimate the extent of cognitive decline over time and to identify predictors of clinically relevant decline, to inform early identification of individuals at increased risk and prioritize targets for prevention or intervention.

Methods

A cohort of 856 individuals was recruited from five sites across Canada between 2013 and 2016. Participants were eligible if they were aged ≥35 years, had been living with HIV for at least one year, were able to communicate in French or English, and were free from dementia severe enough to preclude informed consent, non–HIV-related neurological disorders likely to impair cognition, psychotic disorders, or substance dependence or abuse within the previous 12 months.

The study took a holistic approach to brain health, assessing a broad range of candidate biological, psychosocial and environmental contributors. At each visit, cognitive performance, questionnaire data, anthropometric measurements, and chart reviews were collected. The study protocol has been published [17] and baseline data have been reported elsewhere [18-23].

The Positive Brain Health Now cohort comprised two sequential measurement periods. During Phase 1 (2013–2018), participants completed up to four study visits over 27 months. Analyses of longitudinal Phase 1 data did not identify a subgroup exhibiting decline on performance-based cognition, indicating that longer follow-up was warranted. Phase 2 began in 2019 and extended follow-up for up to four additional annual visits. The onset of the COVID-19 pandemic disrupted clinic-based assessments and reduced participant retention. The present analysis included the 275 participants with at least one study visit in each phase (the "longitudinal subgroup"). The study

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was approved by the Research Ethics Boards of all participating institutions, and all participants provided written informed consent.

Measures

Cognition was assessed using the Brief Cognitive Ability Measure (B-CAM), a computerized battery developed by our group to provide an easy-to-use, open-access measure of cognition across the full range of cognitive ability typical of adults living with HIV. Tasks included: simple reaction time, verbal learning and recall (8 words), a version of the Corsi block test of spatial working memory (forward and back) [24], mini Trail-Making test B, Eriksen flanker task [25], 2-back working memory task (shapes) [26], phonemic verbal fluency [27], Tower of London [28], digit-symbol coding test, and incidental memory for faces [29]. A total score reflecting the underlying unidimensional construct of cognition was created with Rasch analysis, an approach previously applied to cognitive measurement in HIV [30, 31] and other populations [32-35]. Using RUMM2030 (version 5.4), raw scores from individual cognitive tasks across all visits over 10 years (n = 3717) were fitted to the Rasch model. Items were calibrated according to difficulty rather than grouped into traditional cognitive domains. The resulting continuous score provides a robust measure of overall cognitive ability suited to assessing meaningful change over time. Over the study period, the B-CAM was refined by removing less informative tasks and adding measures of higher-level performance. The Rasch model expresses cognitive ability on a logit scale, where 0 represents the average performance, positive values indicate above-average ability, and negative values indicate below-average ability. This approach allows each participant's score to be estimated from whatever tasks were completed at a visit. An abbreviated version of the B-CAM with automated scoring is available at: https://bcamtest.org/public/study/23.

Potential predictors of cognitive decline were selected based on the existing literature on cognitive impairment or decline in people with well-controlled HIV or in older adults in the general population. These include: demographic variables (age, sex, education, ethnicity), HIV-related factors (time since diagnosis, current and nadir CD4 count, CD8 count, CD4/CD8 ratio, plasma HIV RNA), comorbidities (vascular: self-reported heart disease or angina, hypertension, peripheral vascular disease (PVD), Framingham Risk Score, diabetes, hyperlipidemia, apolipoprotein B; other: thyroid problem, kidney disease, hepatitis C infection/liver problem, numbness), lifestyle factors (use of tobacco, cannabis, alcohol, BMI, waist-to-hip ratio, level of physical activity, satisfaction with sleep), medication-related factors (taking prescribed benzodiazepines, opioids or medication for depression/anxiety, anticholinergic burden[36], sedative burden[36]), psychosocial and environmental factors (depression, anxiety, motivation, loneliness, stigma), general health indicators indicators (hemoglobin, eGFR, VACS Index V1.0, C-reactive protein (CRP), calcium, FIB-4, physical function index and vitality from the RAND-36 [37]), and personal/family history (cognitive reserve, family history of cardiac disease and dementia, history of head trauma, educational history- failing a grade, needing special help with class, prior diagnosis of learning disability or attention deficit disorder). A comorbidity score was created based on items forming

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the Charlson Index [38], excluding HIV, dementia and stroke (both study exclusion criteria); it included self-reported myocardial infarction, PVD, history of a cerebrovascular accident with minor or no residua, lung disease, peptic ulcer, liver disease, diabetes, chronic kidney disease and cancer.

Statistical analysis

Descriptive statistics, regression modelling and imputation for missing data were done using SAS software version 9.4. Means, standard deviations (SD), medians, percentiles and proportions were determined from the information collected at initial assessment.

Longitudinal B-CAM data from up to 10-years of follow-up were analyzed using group-based trajectory models (GBTM) [39]. To identify trajectories of cognitive change, scores were centered on each participant's mean, allowing the model to focus on change over time. Each participant was assigned to a trajectory group based on their highest posterior probability (pp), with model adequacy indicated by average pp >0.7 in all groups [40, p88]. Analyses were conducted in SAS 9.4 using the developers' GBTM module.

Logistic regression was used to identify baseline predictors of membership in the declining trajectory. To account for clustering by recruitment site, generalized estimating equations (GEE) were used with a binomial distribution and log link. Analyses were performed on all baseline variables, and those with a p-value < 0.10 in either unadjusted or age- and sex-adjusted models were carried forward into a multivariable model. For this final model, missing baseline data were replaced using simple imputation informed by longitudinal data from up to four Phase 1 visits. Predictors were sequentially removed and replaced until all remaining variables were significant at $p < 0.05$. Age, sex, education, and baseline B-CAM scores were retained as adjustment variables.

Given that odds ratio (Ors) may overestimate effect sizes when the outcome is not rare, relative risks (RR) were calculated to quantify the association between baseline predictors and B-CAM decline. Variables with 95% confidence intervals (CI) that excluded 1 were retained in the final model.

To better understand the significance of baseline plasma HIV RNA >50 copies/mL and determine whether it reflected isolated or persistent viremia, individual viral load records were reviewed for the 269 participants with available baseline data. An additional analysis used a threshold of HIV RNA ≥200 copies/mL as this value is commonly used in clinical guidelines to distinguish low-level viremia from virologic failure, and to guide clinical management. To assess whether baseline viremia was more strongly associated with trajectory membership than viremia occurring later during follow-up, separate odds ratios were estimated for detectable viremia at baseline and for detectable viremia at any study visit, each compared with never detectable viremia.

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To facilitate interpretation, continuous variables were rescaled to clinically meaningful units: age per decade; Framingham Risk Score per 10 units; Hospital Anxiety and Depression Scale (HADS) [41] anxiety subscale per 4 points (approximately the baseline SD); and Veterans Aging Cohort Study Index (VACS) V1.0 [42] (scored 0-100) per 5 points, reflecting roughly the interquartile range. Categorical variables are interpreted relative to the reference category.

Results

Table 1 presents key demographic and clinical factors at initial assessment of the 856 participants who began in Phase 1, and of the longitudinal subgroup who had at least one visit in Phase 2 of the study (n=275). Those who completed an intial assessment were mostly men, on average 53 years of age, had been living with HIV for 17 years and were aviremic, with a few exceptions. While they were not immunosuppressed, the average nadir CD4 count was low (median <200 cells/μL). The characteristics of the longitudinal subgroup did not differ substantially from those of the original cohort.

Figure 1 shows the trajectories of centered B-CAM scores, with each time point reflecting the deviation from that person's average B-CAM score across visits. Group-based trajectory modeling (GBTM) identified two distinct trajectories with good fit: 53.5% of participants were classified into a non-declining ("stable") trajectory with a mean posterior probability of 0.84, while 46.5% were classified into a declining trajectory with a mean posterior probability of 0.80. Model adequacy was further supported by the close agreement between the observed and expected proportions of participants assigned to each trajectory. Over time, the 2 groups separated such that by year 6, the groups different by 0.5 SD, generally considered clinically meaningful in behavioral and health research because it reflects a change beyond normal day-to-day variability in performance. Applying this benchmark, a decline of 0.37 or more in B-CAM score is likely to be clinically relevant.

Table 2 presents the results of the multivariable analysis identifying predictors of membership in the declining trajectory, ordered by the magnitude of the OR. Values for all the tested predictors are shown in Table S1 Supplemental Digital Content, Supplemental Digital Content, http://links.lww.com/QAD/D936.

The variable with the greatest effect was B-CAM score at initial assessment: Compared with participants in the lowest quartile at initial assessment, those in the higher three quartiles had 3.48-fold greater odds of belonging to the declining trajectory, corresponding to a 71% greater probability of classification into the declining group (RR = 1.71). This pattern is expected and primarily reflects a floor effect. The next most important predictors were presence of peripheral vascular disease and Framingham Risk Score, both indicators of systemic vascular pathology. These were followed by current cannabis use, older age, absence of university education, and a history of requiring special academic support, with more modest contributions from plasma HIV

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RNA >50 copies/mL, lack of self-reported plans or goals for the future, higher HADS anxiety scores, and higher VACS V1.0 scores.

Among the 269 individuals with baseline viral load data, most participants with detectable baseline viremia were receiving ART (decliners: 9/11, non-decliners: 3/4). Baseline viral loads were generally low, with 8/11 decliners and 3/4 non-decliners having values between 50-199 copies/mL. Table 2 shows the odds ratio for baseline HIV RNA ≥ 200 copies/mL: although numbers were small, both baseline viral loads 50-199 copies/mL and ≥ 200 copies/mL (n=3) were associated with cognitive decline. Detectable viremia at baseline was typically isolated, with recurrent episodes during follow-up observed in 2 decliners and 1 non-decliner. As shown in Table 2, detectable viremia >50 copies/mL at any time during follow-up (n=43 person-visits among 1775) was associated with trajectory membership, and a similar magnitude of association was observed for HIV RNA ≥200 copies/mL detected at any visit (n=24 person-visits).

Discussion

Among individuals with a median age of 53 years, a median 18-year duration of HIV, and good virological control at baseline in whom no cognitive decline had been detected during the initial 3-year follow-up, fewer than half of the participants exhibited cognitive decline over extended follow-up of up to 10 years. Decline was associated with vascular risk factors, cannabis use, older age, lower educational attainment at study entry and needing special academic support, while detectable plasma HIV RNA, low motivation, anxiety, and higher VACS Index contributed more modestly to risk.

The findings from this large, long-term longitudinal study clarifies the temporal pattern of cognitive change in treated HIV infection: cognition remained largely stable during the first three years of observation (Phase 1), with decline emerging only during longer follow-up. This pattern is consistent with other long-term HIV cohorts. The CHARTER and the HIV Neurobehavioral Research Program (HNRP) cohorts also reported relatively slow cognitive decline, with CHARTER observing an average decline of approximately 0.28 SD over 12 years and HNRP showing meaningful decline only after a median follow-up exceeding a decade [11, 43]. In our cohort, the separation between the declining and stable trajectories corresponded to an estimated difference of approximately 0.35–0.5 SD in B-CAM scores over 10 years (see Figure 1). This magnitude of cognitive decline is likely to be clinically meaningful, being comparable to the difference between individuals working ≥ 15 hours/week versus < 15 hours/week [44].

Shorter studies have also reported minimal cognitive change over 2-5 years. CHARTER and MACS-derived analyses showed stable performance over 3–5 years [45] [46] [47], while cohorts with well-controlled HIV including HAILO [48], NAMACO [49] and COBRA [50], also reported minimal change, with COBRA also demonstrating stability on neuroimaging. Taken together, these studies suggest that in individuals with sustained viral suppression, meaningful, sustained cognition

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decline emerges only slowly. Shorter studies may overinterpret transient variability as decline; our data support multi-year follow-up.

Cognitive decline emerging over this longer time frame was most strongly predicted by poor vascular health. Both the Framingham Risk Score and a history of PVD independently predicted decline, indicating that vascular risk contributes to cognitive trajectories beyond the effect of age alone. Prior evidence for vascular effects on cognition in HIV is largely cross-sectional [51, 52] [53], with limited longitudinal data [54] [11], particularly among aviremic individuals. Our cohort consisted of individuals with sustained viral suppression, providing longitudinal evidence that vascular risk factors are key determinants of cognitive outcomes in well-treated HIV.

The biological plausibility of this association is strong. In HIV, accumulating evidence in HIV links vascular injury—clinical and subclinical—to structural and functional brain changes. Neuroimaging studies associate vascular risk with white matter abnormalities, cerebral small-vessel disease, and reduced brain volumes [55] [56, 57] [58] [59, 60]. Biomarker studies further show that vascular injury markers correlate more strongly with CNS injury than markers of systemic inflammation in virally suppressed individuals [60]. Together, these findings support a role for vascular dysfunction in cognitive decline among aging people with well-controlled HIV and suggest potential intervention targets. For example, the REPRIEVE trial showed that pitavastatin reduces cardiovascular events in low-to-moderate risk people with HIV, leading to guideline recommendations for primary prevention in adults aged 40–75 years. Our findings raise the possibility that statins may also help preserve cognitive function by reducing cerebrovascular injury.

Detectable plasma HIV RNA at any time point was independently associated with cognitive decline after adjustment, with effects observed across both viral load categories (50–199 copies/mL and ≥200 copies/mL). Given that most events were isolated low-level "blips" in treated individuals, this finding is notable. Prior work has similarly suggested that even single episodes of low-level viremia may be detrimental to cognition and are associated with increased CSF/plasma discordance, especially when nadir CD4 counts are low, which is relevant to our sample [61, 62]. Although current guidelines generally define virologic failure at ≥200 copies/mL and do not recommend treatment changes for values below this threshold in isolation, our findings raise the possibility that even transient low-level viremia may reflect biological processes associated with long term cognitive vulnerability. Clarification of this issue may have implications for treatment guidelines. It also underlines the importance of virological control as a brain health intervention.

Most traditional HIV-related markers contributed little to predicting decline, with nadir CD4 count and duration of infection no longer significant after adjustment for age. Similar findings have been reported in cohorts with high levels of viral suppression, including ALLRT [63], MACS [64], NAMACO [65], the Aquitaine and Italian cohort [13, 66], the PIVOT trial participants [67] and a French

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cohort [68]. Earlier treatment-era studies more consistently linked low nadir CD4 counts to cognitive impairment [69] [43, 70-74]. These observations suggest that while immunosuppression was important in early HIV treatment eras, aging-related comorbidities, notably vascular risk, predominate in predicting cognitive outcomes in those on long-term modern ART.

Cannabis use at baseline was also associated with cognitive decline. Prior evidence in HIV has been inconsistent [11] [75] [65]. In general medical populations, moderate cannabis use typically has limited measurable cognitive effects, while heavy or chronic use is more consistently associated with impairment [76]. Some studies suggest potential anti-inflammatory effects of cannabinoids [77] [78] [79]. Our findings suggest that cannabis may contribute modestly to long-term cognitive decline, though less strongly than vascular risk factors. Baseline assessments were conducted prior to cannabis legalization in Canada; findings may not generalize to contemporary patterns of use following legalization.

Other predictors were associated with cognitive decline. Older age remained a significant risk factor even after accounting for Framingham and VACS scores, with each decade increasing the risk by approximately 35%. Higher educational attainment was protective, consistent with enhanced cognitive reserve. We also observed that a history of requiring special academic support predicted later decline; to our knowledge, this is the first study to report this association in HIV. This variable may represent an easily obtainable clinical marker of cognitive vulnerability.

Mood-related variables also contributed modestly to risk. Higher anxiety scores and lower motivation were associated with cognitive decline. Depressive symptoms have previously been linked to long-term cognitive decline in CHARTER [11], and anxiety and depression frequently co-occur. Whether these symptoms directly contribute to cognitive decline or reflect shared mechanisms remains uncertain. One possible framework for understanding the link between mood symptoms and cognitive outcomes is the concept of vascular depression, with cerebrovascular disease related to late-life mood disturbances as well as cognitive deficits [80], in line with a holistic view of brain health.

The VACS Index 1.0 also predicted membership in the cognitive-decline trajectory, with each one-point increase associated with approximately a 2% increase in risk. The mean difference of roughly five points between declining and stable trajectories therefore corresponds to an approximately 10% greater risk of decline. Although CD4 count and viral load contributed little to the VACS Index in this cohort, other components, including FIB-4 and estimated glomerular filtration rate, capture aspects of liver and vascular health, supporting the role of multisystem health in shaping cognitive trajectories.

Strengths of our study include the long-term follow-up of a contemporary cohort with sustained viral suppression, comprehensive assessment of biological and psychosocial predictors, and use of a modern psychometric instrument (B-CAM) combined with trajectory modeling to capture

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heterogeneity in cognitive change. Some limitations should be acknowledged. Attrition occurred during the COVID-19 pandemic, but the longitudinal subgroup remained broadly comparable to the original cohort, providing some reassurance that pandemic-related selection bias is likely limited and that the observed trajectories are reasonably representative of the overall study population. The number of women was small: our findings may not generalise to women living with HIV. In addition, multiple predictors were tested without formal adjustment for multiple comparisons, and some findings should therefore be interpreted cautiously. Finally, while 47% of participants in the longitudinal subgroup followed a declining trajectory, this also needs to be interpreted with caution. We previously reported that individuals who declined participation in the study were less likely to report cognitive difficulties [81], suggesting that our cohort may overrepresent individuals with baseline cognitive concerns or vulnerabilities.

In summary, in this contemporary cohort with sustained viral suppression, vascular comorbidities emerged as key predictors of later-life cognitive decline. More broadly, our findings that cognition is shaped by multiple interacting risk factors align with multidomain prevention trials in older adults, such as FINGER [82] and MAPT [83], which suggest that integrated approaches targeting vascular risk, lifestyle factors and cognitive health may be required to meaningfully reduce cognitive decline. This suggests that cognitive health could be more systematically integrated into routine HIV care through combined risk assessment (e.g., vascular risk scores), lifestyle counselling, and preventive interventions, including statins when indicated. Overall, these results highlight that people aging with HIV can play an active role in preserving cognitive health through sustained viral suppression, healthy behaviors, and vascular risk reduction. Key uncertainties remain, particularly the potential long-term cognitive relevance of isolated low-level viremia "blips," which warrants further study to inform treatment guidelines. Finally, this study demonstrates that a brief, low-cost computerized cognitive measure can generate robust longitudinal data, supporting its feasibility for integration into large-scale clinical and research settings.

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Table 1: Demographic and clinical factors at initial assessment

	Original cohort	Longitudinal subgroup
	n=856	n = 275
	Mean (SD), [N] or n (%)	Mean (SD), [N] or n (%)
Demographics		
Age (years)	53.0 (8.3) [856]	53.6 (8.1) [275]
Range	35.0 - 81.2	35.1 – 81.2
Male sex	724 (85%)	238 (87%)
Education: University	278 (34%)	107 (39%)
Ethnicity: European descent	561 (73%)	201 (78%)
Language: English	443 (53%)	131 (48%)
HIV-related factors		
Time since diagnosis (years)	16.8 (7.9) [831]	17.3 (8.0) [275]
Current CD4+ T-cells /μL	634 (283) [823]	636 (259) [275]
Median (p25, p75)	610 (440, 780)	620 (463, 780)
Current CD4+ T-cell count < 200 /μL	24 (2.9%)	8 (2.9%)
Nadir CD4+ T-cells /μL	216 (169) [824]	208 (159) [275]
Median (p25, p75)	195 (96, 295)	180 (91, 290)
CD4/CD8 ratio	0.88 (0.49) [821]	0.87 (0.45) [275]
Median (p25, p75)	0.79 (0.56, 1.13)	0.78 (0.57, 1.10)
Plasma HIV RNA: > 50 copies/mL	68 (8%)	15 (5%)
Plasma HIV RNA: ≥200 copies/mL	26 (3%)	4 (1%)
Comorbidities		
Hypertension	204 (25%)	74 (27%)
Peripheral vascular disease	51 (6%)	17 (6%)
Framingham Risk Score	7.0 (5.5) [691]	7.3 (5.5) [275]

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Low: <10	473 (68%)	191 (69%)
Intermediate: 10 to <20	183 (26%)	69 (25%)
High: 20+	35 (5%)	15 (5%)
Diabetes	88 (10%)	32 (12%)
Comorbidity score	1.1 (1.3) [856]	1.2 (1.3) [275]
0	396 (46%)	109 (40%)
1	213 (25%)	81 (29%)
2	132 (15%)	46 (17%)
≥ 3	115 (13%)	39 (14%)
Lifestyle factors		
Tobacco use		
Current	242 (29%) [822]	54 (20%) [267]
Ever	548 (67 %) [822]	168 (61%) [275]
Cannabis use		
Current	292 (35 %) [824]	93 (34%) [275]
Ever	575 (70 %) [824]	182 (66%) [275]
Alcohol use		
None	145 (18%) [821]	42 (16%) [269]
Some	631 (77%)	213 (79%)
Risky	45 (5%)	14 (5%)
Body Mass Index (BMI) (kg/m^2)	26.1 (4.7) [828]	26.0 (4.9) [275]
<18.5	17 (2%)	8 (3%)
18.5 to < 25	362 (44%)	121 (44%)
25 to < 30	311 (38%)	98 (36 %)
30 to < 35	100 (12%)	34(12%)
35 to < 40	28 (3%)	11 (4%)
≥ 40	10 (1%)	3 (1%)

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Level of physical activity		
Vigorous activity	253 (30%) [830]	78 (28%) [275]
Moderate activity	378 (46%)	128 (47%)
Sedentary	199 (24%)	69 (25%)
Medication-related factors		
Anticholinergic burden (0-3)	0.94 (1.56) [820]	0.96 (1.56) [269]
Sedative Burden (0-3)	0.83 (1.37) [820]	0.78 (1.28) [260]
Health status indicators		
Estimated glomerular filtration rate (eGFR): < 60 mL/min/1.73 m^2	68 (8%) [809]	20 (7%) [275]
VACS (V1.0, scored 0-100)	11.4 (8.6) [831]	11.4 (7.8) [275]
Median (p25, p75)	11.0 (6.1, 15.9)	11.0 (7.3, 16.3)
Psychosocial and environmental factors		
HADS depression (0-24, higher is worse)	4.7 (3.8) [831]	4.6 (3.7) [268]
Median (p25, p75)	4 (1,7)	4 (1,7)
HADS anxiety (0-24, higher is worse)	7.2 (4.3) [832]	7.0 (4.1) [260]
Median (p25, p75)	7 (4,10)	7 (4.1)
Cognition		
Perceived Deficits Questionnaire (0-100, higher is worse)	34.1 (17.8) [834]	33.3 (17.0) [273]
B-CAM (range: -2.53 to 4.12)	0.97 (0.75) [771]	1.14 (0.72) [275]

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Table 2: Multivariable odds ratio and relative risk estimates for membership in the declining cognitive trajectory (imputed data n=275)

Predictor at initial assessment	**OR**	**95 % CI**	**RR**	**95 % CI**
B-CAM: 3 highest quartiles vs. lowest quartile	3.48	2.06 to 5.86	1.71	1.44 to 2.02
Peripheral vascular disease	3.07	2.06 to 4.57	1.39	1.23 to 1.56
Framingham Risk Score (per 10 units)	2.84	1.35 to 5.98	1.50	1.20 to 1.87
Current cannabis use	2.53	1.69 to 3.79	1.47	1.23 to 1.76
Age (per 10 years)	2.37	1.59 to 3.54	1.35	1.18 to 1.55
Educational history: needing special academic support vs. not	2.34	1.32 to 4.17	1.28	1.03 to 1.61
No university education	1.94	1.41 to 2.68	1.30	1.18 to 1.43
Plasma HIV RNA: >50 copies/mL [a]	1.80	0.99 to 3.25	1.15	1.07 to 1.24
Motivation: plans and goals for the future: some/a lot vs none	1.45	1.06 to 1.99	1.14	0.98 to 1.32
HADS anxiety (per 4 units)	1.38	1.03 to 1.83	1.14	1.05 to 1.23
VACS V1.0 (per 5 units)	1.25	1.11 to 1.41	1.10	1.05 to 1.17
Post-hoc analyses of viral load				
Plasma HIV RNA at initial assessment				
50-199 copies/mL	2.73	1.00 to 7.48		
≥ 200 copies/mL	6.08	1.48 to 24.97		
Plasma HIV RNA at any visit (n=1775) [b]				
> 50 copies/mL	1.73	1.26 to 2.39		
≥ 200 copies/mL	1.62	1.37 to 1.92		

[a] p=0.053.

[b] adjusted for age, sex and number of visits per person with a viral load value

Note: multivariable model includes sex, which was not predictive

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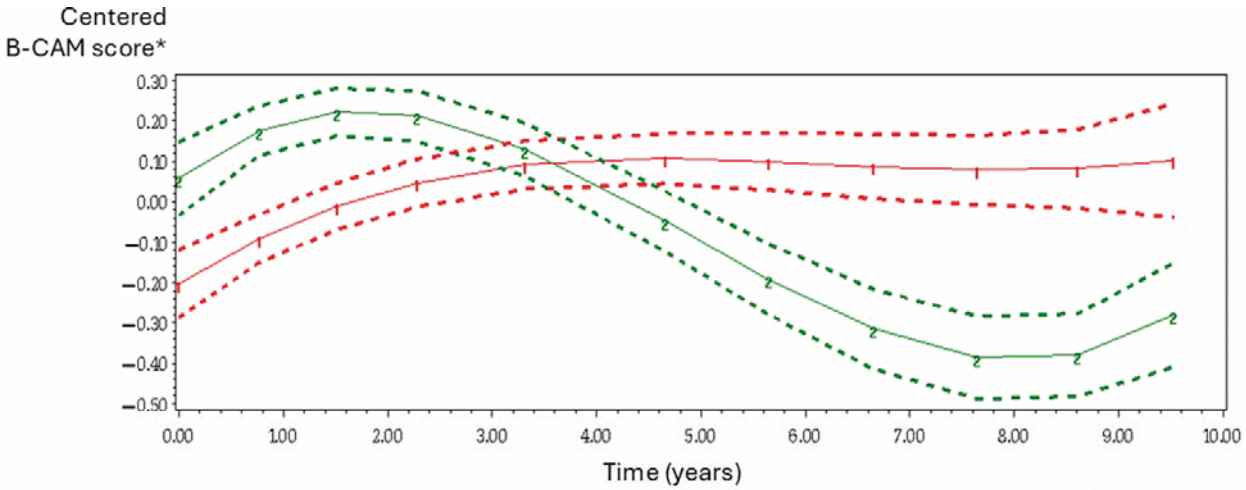
Figure 1: Trajectories of centered cognitive test (B-CAM) scores over 10 years



Trajectory	Theoretical proportions	Assigned proportions (n)	Mean Posterior Probabilities
1. Stable	54.54 %	53.45 % (n=147)	0.84
2. Declining	45.46 %	46.55 % (n=128)	0.80

* Scores centered on each participant's mean. For example, participants in Group 2 began, on average, with B-CAM scores approximately 0.5 points above their own mean across visits.

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