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Impact of glycemic status on longitudinal cognitive performance in men with and without HIV Infection: The Multicenter AIDS Cohort Study (MACS)

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Abstract

Objectives—To determine the relationship between glycemic status and cognitive performance in men living with (MLWH) and without HIV infection.

Design—A prospective HIV/AIDS cohort study in four U.S. cities between 1999 and 2016.

Methods—Glycemic status was categorized as normal glucose (NG), impaired fasting glucose (IFG), controlled diabetes mellitus (DM) and uncontrolled DM at each semi-annual visit. Cognitive performance was evaluated using nine neuropsychological tests which measure attention, constructional ability, verbal learning, executive functioning, memory, and psychomotor

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speed. Linear mixed models were used to assess the association between glycemic status and cognition.

Results—Overall, 900 MLWH and 1149 men without HIV were included. MLWH had significantly more person-visits with IFG (52.1% vs 47.9%) and controlled DM (58.2% vs 41.8%) than men without HIV ($p<0.05$). Compared to men with NG, men with DM had significantly poorer performance on psychomotor speed, executive function and verbal learning (all $p<0.05$). There was no difference in cognition by HIV serostatus. The largest effect was observed in individuals with uncontrolled DM throughout the study period, equivalent to 16.5 and 13.4 years of aging on psychomotor speed and executive function, respectively, the effect of which remained significant after adjusting for HIV-related risk factors. Lower CD4+ nadir was also associated with worse cognitive performance.

Conclusion—Abnormalities in glucose metabolism were more common among MLWH than men without HIV and were related to impaired cognitive performance. Metabolic status, along with advanced age and previous immunosuppression, may be important predictors of cognition in the modern antiretroviral therapy era.

Keywords

HIV-1; Cognition; Diabetes Mellitus; Neuropsychological Tests; Male

INTRODUCTION

The use of combination antiretroviral therapy (cART) has transformed human immunodeficiency virus (HIV) infection into a chronic illness and has markedly extended survival among people living with HIV (PLWH), often into old age[1]. However, the effect of cART on HIV-associated cognitive impairment is modest [2–4]. The prevalence of cognitive dysfunction among PLWH continues to be high [2, 5–7], and the etiology is not clear. Hypotheses include, but are not limited to, immune system integrity and inadequate control of persistent central nervous system (CNS) HIV viral replication[8, 9]. In addition, chronic non-AIDS co-morbidities such as impaired glucose regulation, which is common among PLWH [10], may also play an important role in the pathogenesis of cognitive dysfunction [11].

In the general population, type 2 diabetes mellitus (T2DM) has been associated with impairment in numerous cognitive domains [12–17]. T2DM predominantly affects hippocampal-based declarative memory performance and attention, but psychomotor speed and executive functioning are also affected [13, 18]. The magnitude of cognitive decline depends largely on the duration of T2DM, glycemic control, and antidiabetic agent use [19–25]. It has been reported that a 1% higher glycated hemoglobin (HbA1c) value is associated with significantly lower performance on psychomotor speed, executive functioning and memory[26].

In PLWH, the prevalence of T2DM is up to 14%[10], compared to 9.4% in the U.S. population[27] and associations between glycemic status and cognition have also been reported [28]. For example, in a prospective cohort enriched with older HIV-infected

individuals, diabetes was associated with a five-fold increased odds of HIV-associated dementia (HAD) compared to non-diabetics and this association remained significant after multivariable adjustment [29]. In the Women's Interagency HIV Study (WIHS), greater insulin resistance was associated with poorer performance on Symbol Digit Modalities Test (SDMT), on Stroop Color-Naming (SCN) and on Stroop Interference in unadjusted analyses [30]. Similar results were found using adjusted models in a more recent study of the same cohort[31]. In addition, the authors reported that women with T2DM had worse performance on measure of psychomotor speed and manual dexterity testing than women without T2DM [31].

Despite evidence suggesting that glycemic status is associated with cognition in PLWH and without HIV, previous cross-sectional studies were limited in their ability to investigate longitudinal glycemic status with regard to trajectories of cognitive function over time [29, 30, 32]. In some cases, assessment of cognitive domains was not comprehensive [33, 34] and glycemic status was not adequately characterized[30, 31]. The purpose of the present study was to determine the longitudinal relationship between glycemic status and cognition using data from Multicenter AIDS Cohort Study (MACS), one of the largest ongoing cohorts of the natural and treated history of HIV among gay/bisexual men. The MACS has followed a neuropsychological (NP) sub-cohort for over 29 years, allowing for determination of the neurological and neurocognitive consequences of HIV over time [35]. We hypothesized that: 1) glycemic status is associated with cognitive performance among men living with HIV (MLWH) and without HIV; 2) the magnitude of this effect varies by cognitive domains; 3) the duration of T2DM is associated with accelerated cognitive decline and; 4) HIV-specific risk factors affect cognition in MLWH.

METHODS

Study Participants

A total of 6,972 MACS participants have been recruited from four sites: Baltimore / Washington DC, Chicago, Los Angeles, and Pittsburgh over three waves of enrollment (4,954 men were enrolled in 1984–1985, 668 men in 1987–1991, and 1350 men in 2001–2003)[36, 37]. Eligibility criteria and follow-up procedures for the MACS have been described in detail previously [36, 38]. The current study included all participants who were active in the MACS between April 1999 and Oct 2016. Individuals whose primary language was not English or had any of the following conditions: a major neurologic or psychiatric illness, clinical stroke, dementia, learning disability, major head injury, or brain opportunistic infection were excluded from the analysis. In addition, 72 men who became HIV infected during follow-up were excluded. The MACS protocol was approved by the institutional review board at each site. Informed consent was obtained from all participants.

During semi-annual visits, interviewer-administrated questionnaires were completed. Clinical assessment and biological specimens were obtained for laboratory determination of HIV/AIDS disease biomarkers. Reactive enzyme-linked immunosorbent assays (ELISAs), which were confirmed by Western blot tests, were used to determine HIV serostatus. Plasma HIV-1 RNA levels were measured using the Roche Ultrasensitive RNA polymerase chain reaction (PCR) assay (Hoffman-LaRoche, Nutley, NJ, USA) with a lower detection limit of

50 copies/mL. T-lymphocyte cell subset numbers and percentages were quantified using standardized flow cytometry[39]. For the purpose of analysis, the index visit was defined as the first visit at which participants had both metabolic assessment and neuropsychological evaluation.

Impaired fasting glucose and T2DM assessment

Fasting serum glucose was measured at each semi-annual visit beginning in April 1999, under the fasting protocol, which has been described previously [10]. Men were categorized as having impaired fasting glucose (IFG) if they had a fasting blood glucose level between 100 mg/dL -125 mg/dL. Self-reported T2DM was assessed using the following questions: "Have you seen a doctor or other medical practitioner for any condition since your last visit? If yes, was there a diagnosis for your condition?" Current T2DM medication use was determined from a report of all medications used since the previous visit. Men were categorized as having T2DM if they: 1)self-reported T2DM as a medical condition or 2) took anti-diabetic medications or 3) fasting blood glucose level ≥ 126 mg/dL for two consecutive visits. T2DM was further dichotomized as controlled T2DM and uncontrolled T2DM if HbA1c< 7.5% and HbA1c≥7.5% confirmed at two consecutive visits, respectively. Men who were not categorized in any of the groups above were considered to have normal glucose level (NG). Glycemic status was assessed for each individual at each follow-up visit.

Neuropsychological Evaluation

Primary neurocognitive tests were the Symbol Digit Modalities Test (SDMT)[40] and the Trail Making (TM) Test Part A and B[41]. Part A of the TM Test is a test of attention, motor speed, and visuospatial tracking[34]. Part B of the TM Test has all of the cognitive demands of TM Part A, with an addition of a set-shifting component, which tests executive functioning. The TM Test is sensitive to aging effects among the elderly[42]. The SDMT evaluates psychomotor speed, associative learning, and incidental learning, and has demonstrated reliability independent of age, gender, and socio-economic status [43]. The full neuropsychological battery included the 1) Grooved pegboard (non-dominant hand) (GPN), a sensitive measure of manual dexterity[44]; 2) Rey Auditory Verbal Learning Test (RAVLT)[45], immediate and delayed recall trials, assessing auditory learning and memory; 3) Rey-Osterrieth Complex Figure[46], immediate and delayed recall trials, assessing visual learning memory; and 4) the Stroop Test-Interference Trial (SIT)[47], a measure of response inhibition, considered an executive function. The TM and SDMT tests have been administered at each semi-annual visit since Oct 1, 1991, and the full battery of neuropsychological tests every 2 years since Oct 1, 2005. These 9 tasks were selected to be sensitive to most major areas of cognitive functioning. The validity/reliability of the above neuropsychological tests among PLWH have been reported in the previous studies[48, 49].

Other Covariates and Risk Factors

Age (<40, 40–50 and >50 years old), race (White, Black and Other) and education (college degree versus less than college) were demographics selected. Depressive symptoms were defined using the Center for Epidemiologic Studies Depression Scale (CES-D) >16; hypertension was defined as diastolic BP ≥90 or systolic BP ≥140 or (self-reported/clinical diagnosis of hypertension and use of medications); hypercholesterolemia was defined as

fasting TC≥200 mg/dl or LDL≥130 mg/dl or HDL<40 mg/dl or triglycerides≥150 mg/dl or use of lipid lowering medications with self-reported/clinical diagnosis in the past; hepatitis C virus (HCV) infection was considered present if a participant's serum HCV antibody and HCV RNA (COBAS AmpliPrep TaqMan HCV Assay) were positive; intravenous drug users (IVDU) and cocaine use were determined based on questions "Took/used drugs with a needle since last visit?" and "Used crack or any form of cocaine since last visit?", respectively; Body Mass Index (BMI) was calculated using weight (kg) / [height (m)]^2: < 18.5 is considered underweight; 18.5-<25 is normal; 25.0-<30 is overweight; and ≥30.0 is obese. Participants were asked if they currently smoke at each visit and former smokers would be those who answered yes and then no at a later visit. All covariates were updated by participants at each follow-up visit.

Statistical Analysis

Comparisons of baseline characteristics, stratified by HIV serostatus, were performed using Student *t* tests for normally distributed continuous variables, Wilcoxon rank-sum tests for variables with skewed distributions, and chi-square tests for categorical data. All NP test scores were transformed and summarized as z-scores with adjustment for learning effect, age and education. A higher z-score indicated better cognitive performance.

The association of glycemic status with cognition was examined using linear mixed models with random intercept allowed. This approach assessed within-individual changes in neuropsychological test scores from baseline to the end of the study period, accounting for within-person correlations. The analysis used all person-visits for three primary outcomes: (1) SDMT; (2) TMT-A; and (3) TMT-B and six secondary outcomes from the tests in the full battery of neuropsychological tests. For the initial models, the performance of each NP test was a function of follow-up time, glycemic status, HIV serostatus and potential confounders. The interaction of *follow-up time*glycemic status* was then added to examine if there was an association of glycemic status and changes in cognitive performance over time. In order to assess the effect of cumulative exposure to glycemic impairment on cognition, the DM group was further categorized according to the percentage of time under observation during which DM was uncontrolled. This analysis used the same linear mixed model format from the initial model. Lastly, subgroup analysis was performed among MLWH to examine the role of nadir CD4+ T cell count (<200, 200–500, >500 cells/mm^3), undetectable HIV RNA and time on cART (in years), with the same covariate adjustments from the initial model. Analyses were performed using Stata 14.0 SE (StataCorp, College Station, TX).

RESULTS

Demographic characteristics

In total, 1149 MLWH and 900 men without HIV were included, with a mean follow-up of 13 (±4) years. Compared to men without HIV, MLWH tended to be younger, were more likely to be Black, obese, current smokers, cocaine users, infected with HCV, to have reported hypertension, depressive symptoms, hypercholesterolemia, but less likely to have college education (Table 1). At baseline, MLWH were also more like to have abnormalities in glucose metabolism than the men without HIV, though no statistically significant

differences in IVDU status, glucose level, use of DM medications and DM duration were found by HIV serostatus.

Cognitive Performance Test Results

At baseline, except for TMT-A, RAV-sum of learning trails, RAV-delayed recall and GPN, MLWH demonstrated significantly poorer performance on all NP tests than men without HIV (Table 2). Longitudinally, linear mixed models indicated that factors associated with lower performance in all nine NP tests included being Black, the presence of depressive symptoms, IVDU and current smoking, while other risk factors including education, cocaine use, hypercholesterolemia, HCV infection, BMI and older age differed in their associations across cognitive domains (Table 3).

Psychomotor Speed and Attention

TMT-A, SDMT and GPN primarily evaluate psychomotor speed and attention (Table 3). Men with uncontrolled T2DM had significantly worse performance on TMT-A (Coef.= −0.137, $p<0.001$) and SDMT (Coef.=−0.121, $p=0.001$) compared to men with NG, regardless of HIV serostatus, equivalent to the effect of 3.9 years and 8.8 years of aging (derived from coefficient estimation of age parameter) on psychomotor speed and attention, respectively. Men with controlled T2DM (Coef.=−0.219, $p<0.001$) and IFG (Coef.=−0.027, $p=0.014$) also had worse NP scores on GPN and SDMT, respectively, than men with NG. However, no associations were observed on the following: IFG on both TMT-A and GPN, controlled T2DM on SDMT and TMT-A and uncontrolled DM on GPN. Current smoking, Black race and IVDU were associated with worse performance, while being overweight/obese seemed to have a protective effect on cognition regardless of HIV serostatus. Further analysis with the interaction has shown a significant cognitive decline in IFG, controlled and uncontrolled T2DM compared to NG on TMT-A. A similar pattern was also found among both controlled and uncontrolled T2DM compared to NG on SDMT and GPN (data not shown).

Executive Function

SIT and TMT-B are considered measures of executive function (Table 3). Only men with uncontrolled DM (Coef.=−0.077, $p=0.048$) had significantly poorer executive function, measured by TMT-B, than men with NG, an equivalent effect of 1.8 years of aging. Worse performance was observed for TMT-B but not for SIT in association with current smoking and Black race. Significant cognitive decline over time was observed in both controlled and uncontrolled T2DM compared to NG on TMT-B.

Verbal Learning and Memory

RAVLT (Sum of Learning Trails & Delayed Recall) and RCF (Copy & Delayed Recall) assess verbal learning and visuospatial memory (Table 3). Only men with controlled DM (Coef.=−0.114, $p=0.008$) had worse cognitive performance on RAVLT (Sum of Learning Trails) than men with NG, a difference similar to 9 years of aging on verbal learning and memory, though no significant associations were observed on RAVLT (Delayed recall) or

RCF. Current smoking status, Black race, and IVDU were associated with worse cognitive performance, whereas hypercholesterolemia showed a protective effect on cognition.

T2DM Disease Duration

Among men with DM, disease duration was further categorized as the percentage of time with DM being uncontrolled over the study period (0%, 0-<30%, 30-<70%, 70-<100%, 100%), according to quintiles. The impact of glycemic status on cognition was predominantly seen among men who had uncontrolled T2DM more than 70% of the time (Table 4). Specifically, this effect is equivalent to 16.5 years of aging on psychomotor speed and attention (tested by TMT-A, Coef.=−0.726, p=0.001) as well as 13.4 years of aging on executive function (tested by TMT-B, Coef.=−0.676, p=0.003).

Analysis Restricted to MLWH

Subgroup analysis was performed in regard to three primary NP tests. With additional HIV-related covariates adjusted, the effect of uncontrolled T2DM remained significant on all three tests, SDMT (Coef.=−0.156, p=0.005), TMT-A (Coef.=−0.138, p=0.018) and TMT-B (Coef.=−0.123, p=0.039) (Table 5). Moreover, men with nadir CD4+ T cell counts below 200 cells/mm^3 (Coef.=−0.157, p=0.006) had significantly worse cognitive performance on TMT-A than men with counts above 500 cells/mm^3. However, neither having undetectable HIV-1 RNA nor length of cART showed a significant relationship with cognition.

DISCUSSION

Our data support the hypothesis that abnormalities in glucose metabolism are associated with neuropsychological dysfunction among MLWH and without HIV. Greater cognitive impairment was correlated with poor glycemic control and longer duration of T2DM. In the present study, T2DM was associated with cognitive performance on all the domains. IFG affected psychomotor speed/attention but had a less profound impact on cognition compared to T2DM. Of the nine cognitive tests, the Trail Making Test and SDMT appeared to be affected most, demonstrating an increased risk of psychomotor inefficiency, attention deficits and visuospatial tracking problems. Moreover, our results indicate a significant association between longer T2DM duration and cognitive dysfunction, suggesting that optimization of glycemic control and management of vascular disease risk factors may improve cognitive performance.

Although the affected cognitive domains differ across studies, the magnitude of observed impairment reported in people without HIV in general support our findings[50–56]. Specifically, a systematic review reported that memory, processing speed and cognitive flexibility were most consistently affected by diabetes across studies [57]. Among PLWH, increasing insulin resistance (IR) negatively affected attention and recognition among women after multivariable adjustment [31].

We also found that duration of T2DM was a strong predictor of cognitive performance, which is consistent with literature [20, 21, 58, 59]. A population based case-control study reported that for participants with a duration of DM for 10 years or longer, their odds of having mild cognitive impairment were significantly elevated, 1.8 fold greater, compared to

persons with duration of DM<10 years [59]. Similarly, community-dwelling elderly individuals in the highest HbA1c tertile were found to have significantly poorer overall cognition, semantic categorization and executive functioning, while such an association was not revealed in the lowest HbA1c tertile, which highlighted the importance of glycemic control in reducing the risk of cognitive decline [22].

In the current study, IFG appeared to be less related than T2DM to cognition, as only mild impairment was observed on psychomotor speed among people with IFG, which has been seen in other studies[60, 61]. However, associations reported between IFG and cognition have varied in the literature[62–65]. A pooled cohort analysis that included 8,447 individuals from the general population reported that neither elevated fasting glucose levels nor IR was associated with executive function and memory in older people without a history of DM, while individuals with DM were noted to have cognitive decline[66]. In contrast, an analysis from a 4-year study of postmenopausal women reported that IFG increased the risk of developing cognitive dysfunction approximately twofold [67]. Hence, future studies are warranted to investigate whether there are thresholds for effects of dysglycemia on cognition.

We found that HIV stage of disease-related factors such as CD4 nadir were more informative than HIV serostatus regarding cognition in the cART era. A prospective cohort study that consisted of 1,525 PLWH demonstrated that the odds of neurocognitive impairment were reduced by 10% for every 5-unit increase in square-root CD4 nadir [68]. Heaton RK *et al.* compared the incidence and characteristics of HIV-associated neurocognitive disorders before and during the cART era and found that low nadir CD4 was associated with neurocognitive dysfunction in both eras, while duration of HIV infection and viral suppression predicted impairment only before the cART era, a finding corroborative of our data[69]. These findings support the importance of early cART initiation for disease avoidance, which may help preserve cognition in the long-term.

Impaired glucose regulation plays a crucial role in the pathogenesis of cognitive decline, along with vascular risk factors, socioeconomic and lifestyle factors and depression. Several studies have demonstrated that pre-DM stage leads to a higher incidence of cognitive impairment[70, 71] or dementia[58, 72] and T2DM increases the incidence of vascular [73–75] and Alzheimer dementia[75–77]. Increased amyloid processing in the setting of hyperglycemia has been proposed as an underlying mechanism[78]. Other potential mechanisms include increased formation of advanced glycation end products, diacylglycerol activation of protein kinase C, and increased glucose shunting in the hexosamine pathway of hyperglycemia, which have been shown to alter function in other organs, but whether similar effects occur in the brain is unclear [79–81].

Multifactorial treatment approaches that target shared causes of diverse vascular disease risk factors, together with lifestyle changes (i.e., weight control, nutrition education)[82, 83], may be necessary to prevent cognitive decline. A review has recommended that lifestyle intervention in middle-aged persons should be implemented along with medication for glycemic control to prevent cognitive decline[84]. For persons with a long-standing T2DM, maintaining good glycemic control may modulate the effect of DM on cognition.

To our knowledge, this report represents the largest and most comprehensive evaluation to date of the relationship between glycemic status and cognitive function among MLWH and without HIV. Strengths of our study are its prospective design and long follow-up period with repeated measurement of cognitive function using a sensitive test battery and repeated measures of covariates that allowed us to adjust for a broad array of potential confounders. Our study had several limitations. First, the MACS cohort includes only male participants; additional studies are needed to determine if similar results are observed in women with and without HIV. Since multiple, inter-related factors contribute to cognitive performance, understanding the causal pathway of T2DM to cognitive impairment warrants future studies. Further, survivorship bias may have existed in the cohort; some MACS participants have been studied for more than 20 years, while those who suffered from more severe HIV-related comorbidities may have been more likely to have dropped out. Lastly, the prevalence of T2DM was high in our cohort, possibly due to extensive ART treatment experience, especially exposure to toxic older ART drugs, and more prolonged untreated HIV infection prior to ART initiation. The generalizability of our results to other cohorts with less treatment experience and shorter HIV infection duration is unclear.

In conclusion, abnormal glucose regulation is associated with worse cognitive performance among both MLWH and without HIV. Glucose-mediated processes and duration of diabetic disease appear to be crucial, and therefore optimization of glycemic control appears to be an important goal for the maintenance of cognitive performance, along with control of other chronic vascular disease risk factors and lifestyle changes. The optimal timing of interventions aimed at improvements in glycemic control cannot be ascertained with precision from these data, but such interventions may be more effective when initiated in midlife than at a more advanced age.

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Table 1

Demographic characteristics of study population by HIV serostatus at baseline

Characteristics	HIV uninfected N=900	HIV infected N=1149	P-value
Number of person-visits, Median (IQR)	11 (5, 18)	10 (5, 18)	<0.001
Follow-up time, yrs, Mean (SD)	6.8 (4.4)	6.8 (4.5)	0.42
Age, %			
< 40 yrs	33.1	45.0	
40–50 yrs	36.9	39.8	
> 50 yrs	30.0	15.2	<0.001
Race, %			
White	64.9	51.7	
Black	28.2	37.1	
Others	6.9	11.2	<0.001
College education, %	79.3	69.4	<0.001
Depressive Symptoms, %	23.9	30.1	0.002
CD4+ T cell count nadir, mm^3, %			
< 200	-	30.8	
200–500	-	51.6	
≥ 500	-	17.6	-
Undetectable HIV-1 RNA, copies, %	-	57.0	-
Hypertension, %	30.7	26.5	0.040
Hypercholesterolemia, %	63.9	76.6	<0.001
HCV infection, %	5.9	9.9	0.001
Intravenous drug users (IVDU), %	1.8	2.2	0.52
Cocaine use, %	13.4	17.8	0.007
BMI, %			
Underweight or Normal	41.0	50.0	
Overweight	38.0	37.5	
Obese	21.0	12.5	<0.001
Smoking Status, %			
Never	28.4	27.2	
Former	37.3	31.6	
Current	34.2	41.2	0.003
Glucose, Median (IQR), mg/Dl	91 (84, 99)	92 (85, 100)	0.85
HbA1c, Median (IQR), mmol/mol	5.2 (4.9, 5.5)	5.1 (4.7, 5.5)	<0.001
Glycemia status, %			
Normal	75.7	72.4	
IFG	17.3	19.7	
Controlled DM	4.7	6.8	
Uncontrolled DM	2.3	1.1	0.015
Diabetic medication, %	3.2	3.7	0.53

Characteristics	HIV uninfected N=900	HIV infected N=1149	P-value
Diabetes duration, Mean (SD), yr	6.9 (4.4)	7.4 (4.9)	0.18

Table 2

Unadjusted performance of NP Tests by HIV serostatus at baseline

NP Tests	HIV uninfected Mean (SD)	HIV infected Mean (SD)	P-value
Psychomotor speed, attention			
Symbol Digital Test (SDMT)¤	53.7 (12.8)	51.5 (12.4)	<0.001
Trail Making Test Part A (TMA) ξ	25.8 (10.3)	26.3 (11.3)	0.25
Executive functioning			
*Trail Making Test Part B (TMB)*ξ	59.1 (31.2)	64.9 (35.4)	<0.001
Stroop-Interference, seconds ξ	109.4 (29.0)	114.9 (29.5)	0.004
Verbal learning and memory ¤			
Rey Auditory Verbal (RAV)-Sum of learning Trails	49.7 (10.8)	49.7 (10.6)	0.95
Rey Auditory Verbal (RAV)-Delayed Recall	9.8 (3.4)	9.8 (3.3)	0.91
Rey Complex Figure (RCF)-Copy	32.6 (4.3)	31.5 (4.9)	<0.001
Rey Complex Figure-Delayed Recall	21.1 (7.6)	19.5 (7.8)	0.001
Motor slowing			
Grooved Pegboard-Non-dominant hand ξ	73.8 (16.7)	74.1 (17.4)	0.79

ξTime-related NP tests: less time indicates better cognitive performance.

¤Higher score indicates better cognitive performance.

Table 3

Relationship between Glycemic Status and Cognition, Results from Linear Mixed Models[ξ, μ]

Factors	Psychomotor speed, attention			Executive functioning	
	SDMT	TMT-A	GP-Non-dominant hand	TMT-B	Stroop-Interference
	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)
Time since baseline, yr	.004*** (.00, .01)	.007*** (.00, .01)	−.050*** (−.06, −.04)	.005*** (.00, .01)	−.010** (−.02, −.00)
Age					
40 yrs	Ref	Ref	Ref	Ref	Ref
40–50 yrs	−.069 (−.16, .02)	−.252*** (−.34, −.17)	.136* (.03, .25)	−.289*** (−.37, −.21)	.170** (.06, .28)
≥ 50 yrs	−.328*** (−.44, −.22)	−.717*** (−.82, −.62)	.070 (−.07, .21)	−.808*** (−.91, −.71)	.033 (−.11, .18)
College education	.085 (−.01, .18)	.020 (−.07, .11)	−.028 (−.14, .09)	.001 (−.09, .09)	.046 (−.07, .17)
Race					
White	Ref	Ref	Ref	Ref	Ref
Black	−.081 (−.17, .01)	−.202*** (−.29, −.12)	.107 (−.01, .22)	−.098* (−.18, −.01)	.097 (−.02, .21)
Others	−.128 (−.27, .02)	.010 (−.12, .14)	.361*** (.19, .53)	−.102 (−.23, .03)	.025 (−.15, .20)
HIV infection	−.080 (−.16, .00)	.065 (−.01, .14)	−.010 (−.11, .09)	.017 (−.06, .09)	−.086 (−.19, .02)
Glycemic status					
Normal	Ref	Ref	Ref	Ref	Ref
IFG	−.027* (−.05, −.01)	.000 (−.02, .02)	−.036 (−.10, .03)	−.010 (−.03, .01)	.033 (−.04, .11)
Controlled DM	.013 (−.03, .05)	−.010 (−.05, .03)	−.219*** (−.32, −.12)	.006 (−.03, .05)	−.016 (−.12, .09)
Uncontrolled DM	−.121** (−.19, −.05)	−.137*** (−.21, −.06)	−.162 (−.35, .03)	−.077* (−.15, −.00)	−.069 (−.28, .14)
Hypertension	.020 (−.00, .04)	−.017 (−.04, .01)	−.049 (−.12, .02)	.002 (−.02, .03)	−.024 (−.10, .05)
HCV infection	−0.000 (−.10, .10)	−0.004 (−.10, .10)	−.199* (−.37, −.03)	−.027 (−.13, .07)	−.006 (−.18, .17)
IDU	−.128** (−.21, −.04)	−.122** (−.21, −.03)	−.364** (−.59, −.14)	−.067 (−.16, .02)	.117 (−.13, .36)
Cocaine use	.037* (.00, .07)	.013 (−.02, .05)	−.036 (−.13, .06)	.010 (−.03, .05)	−.062 (−.16, .04)
BMI					
Underweight/Normal	Ref	Ref	Ref	Ref	Ref
Overweight	.090*** (.06, .12)	.062*** (.03, .09)	.098* (.02, .17)	.060*** (.03, .09)	.010 (−.07, .09)
Obesity	.095*** (.05, .14)	.088*** (.04, .13)	.061 (−.04, .17)	.115*** (.07, .16)	.001 (−.11, .11)
Depression	−.079*** (−.11, −.05)	−.091*** (−.12, −.06)	−.049 (−.12, .02)	−.069*** (−.10, −.04)	−.087* (−.16, −.01)
Hypercholesterolemia	.023 (−.00, .05)	−.001 (−.03, .02)	−.020 (−.09, .05)	−.017 (−.04, .01)	.002 (−.07, .08)
Smoking status					

Factors	Psychomotor speed, attention			Executive functioning	
	SDMT	TMT-A	GP-Non-dominant hand	TMT-B	Stroop-Interference
	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)
Never	Ref	Ref	Ref	Ref	Ref
Former	−.031 (−.10, .03)	.021 (−.04, .08)	−.086 (−.20, .02)	−.001 (−.06, .06)	.063 (−.05, .18)
Current	−.065 (−.13, .00)	−.085 * (−.15, −.02)	−.200 ** (−.32, −.08)	−.076 * (−.14, −.01)	−.070 (−.19, .05)
New cohort	−.023 (−.06, .01)	−.078 *** (−.11, −.05)	−.033 (−.08, .02)	−.107 *** (−.14, −.07)	.032 (−.02, .08)

Factors	Verbal learning and memory			
	RAV-Sum of Learning Trails	RAV-Delayed Recall	RCF-Delayed Recall	RCF-Copy
	Coef.	Coef.	Coef.	Coef.
Time since baseline, yrs	−.001 (−.01, .00)	.001 (−.00, .01)	−.013 *** (−.02, −.01)	−.028 *** (−.04, −.02)
Age				
40 yrs	Ref	Ref	Ref	Ref
40–50 yrs	−.045 (−.14, .05)	−.039 (−.13, .05)	.111 * (.01, .21)	.028 (−.10, .15)
≥ 50 yrs	−.328 *** (−.45, −.20)	−.223 *** (−.34, −.10)	.170 ** (.04, .30)	.176 * (.01, .34)
College education	−.044 (−.15, .06)	−.094 (−.19, .00)	.039 (−.06, .14)	.242 *** (.11, .37)
Race				
White	Ref	Ref	Ref	Ref
Black	−.171 ** (−.27, −.07)	−.220 *** (−.32, −.12)	−.077 (−.18, .03)	−.224 ** (−.35, −.09)
Others	−.002 (−.15, .14)	−.015 (−.16, .13)	−.064 (−.21, .09)	−.402 *** (−.59, −.21)
HIV infection	−.037 (−.12, .05)	−.075 (−.16, .01)	.077 (−.01, .17)	−.039 (−.15, .08)
Glycemic status				
Normal	Ref	Ref	Ref	Ref
IFG	−.016 (−.07, .04)	−.047 (−.10, .01)	−.043 (−.10, .01)	−.027 (−.10, .05)
Controlled DM	−.114 ** (−.20, −.03)	−.063 (−.15, .02)	−.014 (−.10, .07)	−.107 (−.22, .01)
Uncontrolled DM	−.094 (−.25, .06)	.102 (−.06, .26)	.048 (−.11, .20)	−.049 (−.27, .17)
Hypertension	−.047 (−.10, .01)	.002 (−.05, .06)	−.022 (−.08, .03)	−.030 (−.11, .05)
HCV infection	−.034 (−.18, .11)	−.006 (−.15, .14)	−.102 (−.25, .05)	.217 * (.02, .41)
IDU	−.173 (−.36, .01)	−.249 ** (−.44, −.06)	−.026 (−.21, .16)	−.156 (−.41, .10)
Cocaine use	.047 (−.03, .12)	.050 (−.03, .13)	−.020 (−.10, .06)	−.040 (−.15, .07)
Hypercholesterolemia	.011 (−.04, .07)	−.024 (−.08, .03)	.057 * (.00, .11)	.083 * (.00, .16)
BMI				
Underweight/Normal	Ref	Ref	Ref	Ref

Factors	Verbal learning and memory			
	RAV-Sum of Learning Trails	**RAV-Delayed Recall**	**RCF-Delayed Recall**	**RCF-Copy**
	Coef.	**Coef.**	**Coef.**	**Coef.**
Overweight	.021 (−.04, .08)	.022 (−.04, .08)	−.019 (−.08, .04)	.002 (−.08, .09)
Obesity	.053 (−.03, .14)	.016 (−.07, .10)	.039 (−.05, .13)	.085 (−.03, .20)
Depression	−.051 (−.11, .00)	−.092** (−.15, −.04)	−.019 (−.07, .04)	−.025 (−.10, .05)
Smoking status				
Never	Ref	Ref	Ref	Ref
Former	−.061 (−.16, .03)	−.061 (−.15, .03)	−.078 (−.17, .02)	.008 (−.12, .13)
Current	−.122* (−.22, −.02)	−.071 (−.17, .03)	−.137** (−.24, −.04)	.030 (−.10, .16)
New cohort	.034 (−.01, .08)	.032 (−.01, .07)	−.070** (−.11, −.03)	−.104*** (−.16, −.05)

*< 0.05

**<0.01

***<0.001

ξWe had 2049 men contributed to the analysis of three primary NP tests and 1617 men had information on the full battery of neuropsychological tests.

μAll the NP test were modeled using z-scores and higher z-scores indicated better cognitive performance.

Table 4

Relationship between duration of T2DM and cognition on three primary NP tests among men with DM, results from linear mixed model[ξ, μ]

Factors	SDMT Coef. 95% CI	TMT-A Coef. 95% CI	TMT-B Coef. 95% CI
Time since baseline, yrs	−.014*** (−.02, −.01)	−.010*** (−.01, −.00)	−.015*** (−.02, −.01)
Age			
40 yrs	ref.	ref.	ref.
40–50 yrs	−.166 (−.36, .03)	−.261** (−.44, −.08)	−.247** (−.43, −.06)
≥ 50 yrs	−.438*** (−.67, −.21)	−.712*** (−.93, −.49)	−.818*** (−1.04, −.60)
Glycemic status			
Controlled DM all the time	ref.	ref.	ref.
Uncontrolled DM time<30%	.004 (−.24, .25)	−.043 (−.27, .19)	.016 (−.22, .25)
Uncontrolled DM time 30–70%	−.051 (−.34, .23)	.101 (−.17, .37)	.119 (−.15, .39)
Uncontrolled DM time>70%	−.140 (−.55, .27)	−.098 (−.49, .29)	.024 (−.37, .42)
Uncontrolled DM all the time	−.285 (−.75, .18)	−.726** (−1.17, −.28)	−.676** (−1.13, −.22)
HIV	−.196* (−.36, −.03)	.080 (−.08, .24)	−.047 (−.21, .11)

ξ All models have adjusted for race, college education, depression, hypertension, HCV infection, smoking status, BMI, IVDU, cocaine use, hypercholesterolemia, cohort effect and learning effect.

μ Higher score indicated better cognitive performance.

* < 0.05

** <0.01

*** <0.001

Table 5

Relationship between glycemic status and cognition on three primary NP tests in HIV infected men, results from linear mixed model[ξ]

Factors	SDMT Coef. 95% CI	TMT-A Coef. 95% CI	TMT-B Coef. 95% CI
Time since baseline, yrs	−.010 (−.02, .00)	.006 (−.00, .02)	.008 (−.00, .02)
Age			
40 yrs	ref.	ref.	ref.
40–50 yrs	−.034 (−.17, .10)	−.202** (−.33, −.08)	−.211** (−.34, −.09)
≥ 50 yrs	−.237* (−.42, −.05)	−.621*** (−.79, −.45)	−.704*** (−.87, −.53)
Glycemic status			
Normal	ref.	ref.	ref.
IFG	−.027 (−.06, .00)	−.019 (−.05, .01)	−.024 (−.06, .01)
Controlled DM	.052 (−.00, .11)	−.002 (−.06, .06)	.024 (−.03, .08)
Uncontrolled DM	−.156** (−.26, −.05)	−.138* (−.25, −.02)	−.123* (−.24, −.01)
Nadir CD4+ T cell count			
>500	ref.	ref.	ref.
200–500	.047 (−.03, .12)	−.047 (−.12, .03)	.062 (−.01, .14)
<200	.073 (−.04, .18)	−.157** (−.27, −.05)	.010 (−.10, .12)
Undetectable HIV RNA	−.031 (−.07, .01)	−.014 (−.05, .02)	.020 (−.02, .06)
Time on cART, yrs	.010 (−.00, .02)	−.005 (−.02, .01)	−.010 (−.02, .00)

[ξ]All models have adjusted for race, college education, depression, hypertension, HCV infection, smoking status, BMI, IVDU, cocaine use, hypercholesterolemia, cohort effect and learning effect.

*< 0.05

**<0.01

***<0.001