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Diabetes mellitus is associated with declines in physical function among men with and without HIV

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Abstract

Objective: To determine the longitudinal relationships between abnormal glucose metabolism and physical function in persons with HIV (PWH) and without HIV.

Design: Prospective cohort study of men with or at risk for HIV in four US cities between 2006 and 2018.

Methods: Men with or at risk for HIV from the Multicenter AIDS Cohort Study (MACS) had semi-annual assessments of glycemic status, grip strength, and gait speed. We used linear mixed models with random intercept to assess associations between glycemic status and physical

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function. Glycemic status was categorized as normal, impaired fasting glucose (IFG), controlled diabetes mellitus (DM) (hemoglobin A1C [HbA1C] <7.5%), or uncontrolled DM (HbA1C ≥7.5%).

Results: Of 2,240 men, 52% were PWH. DM was similar among PWH (7.7 %) vs persons without HIV (6.7%, p=0.36) at baseline. PWH had slower gait speed (1.17 m/s vs 1.20 m/s, p<0.01) but similar grip strength (40.1 kg vs 39.8, p=0.76) compared to persons without HIV at baseline. In multivariate models, gait speed decline was greater with controlled DM (−0.018 m/s [−0.032, −0.005], p=0.01) and grip strength decline was greater with controlled (−0.560 kg [−1.096, −0.024, p=0.04) and uncontrolled DM (−0.937 kg [−1.684, −0.190], p=0.01), regardless of HIV serostatus compared to normoglycemic individuals.

Discussion: Abnormal glucose metabolism was associated with declines in gait speed and grip strength regardless of HIV serostatus. These data suggest that improvement in glucose control should be investigated as an intervenable target to prevent progression of physical function limitations among PWH.

Keywords

diabetes mellitus; glycemic status; physical function; grip strength; gait speed; HIV-1

Introduction

While the routine use of antiretroviral therapy (ART) has transformed HIV into a chronic disease, people with HIV (PWH) experience both earlier onset and increased rates of chronic non-infectious aging-related comorbidities compared to the general population[1, 2]. Older PWH experience more rapid declines in physical function compared to persons without HIV [3, 4]. Impaired physical function has been associated with greater risk of adverse health outcomes in PWH including disability, falls, reduced quality of life, and mortality [5-9]. Therefore, insight into mechanisms underlying physical function declines and interventions to prevent functional impairment in this vulnerable population are urgently needed.

Abnormal glucose metabolism has been associated with physical function impairment in the general population[10-14]. Decreased muscle quality and mitochondrial dysfunction have been identified as potential causes of this relationship[15, 16]. Since the incidence and prevalence of diabetes mellitus (DM) have been higher among PWH compared to the general population, these relationships may be particularly relevant in driving physical function impairment among PWH [17, 18]. A cross-sectional study from the Multicenter AIDS Cohort Study (MACS) showed that worse insulin resistance was associated with frailty, a complex phenotype in which gait speed and grip strength are key components, in men with HIV. In this study, insulin resistance was also significantly worse among non-frail men with HIV compared to non-frail men without HIV [19]. A cross-sectional analysis in the Hawaii Aging with HIV-Cardiovascular Disease Study also showed that frailty was significantly associated with increased insulin resistance in PWH[20]. However, no longitudinal studies have compared the relationship between abnormal glucose metabolism and physical function over time in persons with and without HIV.

The purpose of this study was to determine the longitudinal relationship between glycemic status and physical function in men with and without HIV in the MACS. We aimed to better understand the relative contributions of dysglycemia and HIV to observed physical function declines.

Methods

Study participants

The MACS is one of the largest ongoing prospective observational cohort studies of PWH that includes men with HIV and demographically similar men without HIV. Since 1984, 6,972 participants have been recruited from four sites (Baltimore/Washington DC, Chicago, Los Angeles, and Pittsburgh). MACS eligibility criteria and follow-up assessment protocols have been previously described[21, 22]. In brief, MACS participants complete semiannual study visits which include detailed interviews, physical examination, and collection of blood for laboratory testing and storage.

In 2006, semi-annual assessments of physical function (i.e., gait speed and grip strength) were added to the MACS protocol. The present study included all participants who underwent at least two measurements of gait speed and/or grip strength between 2006 and 2018. The MACS protocol has been approved by the institutional review board at each study site. Informed consent has been obtained from all study participants.

Glycemic status assessment

Fasting serum glucose levels have been measured at each MACS visit since 1999. For this study, participants were categorized as one of four glycemic statuses: normal, impaired fasting glucose (IFG), controlled diabetes mellitus (DM), or uncontrolled DM. Men were categorized as having IFG if they had a fasting blood glucose level between 100-125 mg/dl. DM was defined as self-reported DM as a medical condition, use of anti-diabetic medications, or a fasting blood glucose level of 126 mg/dl or greater for at least two consecutive visits. DM was further dichotomized as controlled or uncontrolled based on hemoglobin A1C (HbA1C) level: HbA1C less than 7.5% was considered controlled and 7.5% or greater on two consecutive visits was considered uncontrolled DM. Diagnosis of DM was treated as an absorbent state, but glycemic status was reassessed for each participant at each MACS follow-up visit.

Physical function assessments

Gait speed was assessed as the faster of two timed 4-meter walk assessments at usual pace[3]. Grip strength was assessed using a hand-held dynamometer[4]. Participants were asked to squeeze the dynamometer “as hard as you can” three times using their dominant hand. The average of these three measures was used for the current analysis.

Other covariates and risk factors

Demographic factors included in the analysis are listed in Table 1. They included age, race, education level, study site, and enrollment year, body mass index (BMI), and use of tobacco, marijuana, alcohol, or intravenous drugs. Liver disease and arthritis were

defined as prior or current self-reported diagnosis. Hypertension was defined as systolic pressure ≥140 mm Hg, diastolic pressure ≥90 mm Hg or self-reported diagnosis of hypertension with use of antihypertensive medications. Kidney disease was defined as estimated glomerular filtration rate < 60 ml/min/1.73 m^2 body surface areas calculated by the CKD-EPI Creatinine Equation. Hepatitis C virus (HCV) infection was defined by a detectable serum HCV antibody or HCV RNA. Hepatitis B virus (HBV) infection was defined as detectable serum hepatitis B surface antigen. Supplemental testosterone use was assessed by self-report. Depressive symptoms were defined as a score of 16 or greater on the Center for Epidemiologic Studies Depression Scale (CESD). For PWH, additional covariates considered were number of years on ART; cumulative exposure (in years) to zidovudine, didanosine, stavudine, efavirenz, or any protease inhibitor; nadir $CD4^+$ T-lymphocyte cell count/mm^3 (CD4); and plasma HIV-1 RNA viral load. Covariates were updated at each visit.

Statistical analysis

Comparison of baseline characteristics were performed using Student *t* tests for normally distributed continuous variables, Wilcoxon rank-sum tests for variables with skewed distributions, and Chi-square test for categorical data.

We used linear mixed models with random intercept to assess the association of glycemic status and physical function. This approach examined within-individual changes in physical function (i.e., grip strength and gait speed) over the time-period of study follow-up, accounting for within-individual correlations. The present analysis included all participants with a minimum of two study visits and had complete data for all covariates of interest. Due to the relatively large portion of missingness (>20%) in testosterone use, last observation carried forward method was used. For the two initial models, physical function (either grip strength or gait speed) was a function of follow-up time, glycemic status, HIV serostatus, and the clinical characteristics and other confounding factors as listed above. To examine whether there was an association between glycemic status and changes in physical function over time, a three-way interaction term of *follow-up time*glycemic status**HIV serostatus was then added to the initial model. Subgroup analyses were also performed among PWH using the same linear mixed model format with addition of HIV specific risk factors, including nadir CD4, current CD4, undetectable HIV-1 RNA (suppressed on assay available at that time) and time on ART (in years). All the analyses were performed using Stata 14.0 SE (StataCorp, College Station, TX).

Results

Demographic characteristics

Baseline characteristics for the 1,170 PWH and 1,070 persons without HIV included in this study are shown in Table 1. The mean follow-up time was 8.7 years. Compared to persons without HIV, PWH tended to be younger and were more likely to be non-White, current smokers, have a lower BMI, have a history of cocaine or injection drug use, use supplemental testosterone, or to have liver disease, kidney disease, depression, and HBV or HCV. PWH were less likely to have a college education, a history of marijuana use, or hypertension. At baseline, persons without HIV were more likely to have IFG

or uncontrolled DM, but PWH were more likely to have controlled DM. Baseline mean HbA1cfor each glycemic category by HIV serostatus is shown in Table 2. No statistically significant difference in grip strength by HIV serostatus was noted at baseline. Gait speed was significantly lower in PWH at baseline (p=0.001).

Grip strength

Compared to persons with normal glycemic status, men with controlled (β −0.560 kg, p=0.040) or uncontrolled DM (β −0.937kg, p=0.014) had significant declines in grip strength (Table 3). IFG and HIV serostatus were not significantly associated with grip strength. Other characteristics significantly associated with change in grip strength included current smoking status, older age, higher BMI, depression and HCV infection. No grip strength decline over time was observed by glycemic status in both PWH or persons without HIV (Figure 1 and Supplemental Table 1).

Because the finding that HIV serostatus was not associated with grip strength differed from prior analysis in the MACS[4], we performed several sensitivity analyses. In analyses restricted to participants over the age of 40 or 45 years old, the effect of HIV serostatus on grip strength remained non-significant. When glycemic status was removed from the model, HIV did have a significant effect on grip strength decline (β - 0.719 kg, 95% CI: −0.011, −1.428, p=0.046, data not shown).

Gait speed

In our multivariate linear mixed model, men with controlled DM had significant declines in gait speed compared to men with normoglycemia (β −0.018 m/s, p=0.007). Men who had uncontrolled DM or IFG also demonstrated gait speed declines compared to those with normoglycemia, but these associations did not reach statistical significance. HIV serostatus was not significantly associated with gait speed. Other characteristics significantly associated with changes in gait speed included obesity, black race, smoking, kidney disease and depression. No gait speed decline over time was observed by glycemic status in both PWH or persons without HIV (Figure 1 and Supplemental Table 1).

Since HIV serostatus had previously been associated with gait speed decline in the MACS[3], we performed additional sensitivity analyses. In analyses restricted to participants over the age of 40 or 45 years old or when glycemic status was removed from the model, the effect of HIV serostatus on gait speed remained non-significant (data not shown).

Analyses restricted to PWH

In a subgroup analysis restricted to PWH, uncontrolled DM (β −1.874 kg, p<0.001) but not IFG or controlled DM was found to be associated with grip strength decline, as shown in Table 4. Longer time on ART was associated with improvement in grip strength (β 0.183 kg per year of ART, p=0.001), but greater cumulative exposure to didanosine (ddI) was associated with decline in grip strength (β −0.227 kg per year of ddI, p=0.041). No significant associations between glycemic status and gait speed were noted among PWH. Greater cumulative exposure to zidovudine (AZT) was significantly associated with gait speed decline (β −0.005 m/s per year of AZT, p<0.001).

Discussion

Our data support the hypothesis that abnormal glucose metabolism is associated with similar declines in physical function among men with and without HIV. In the current study, IFG was not significantly associated with change in physical function, but DM was associated with declines in both gait speed and grip strength compared to participants with normoglycemia.

We found an effect of glycemic control on the relationship between DM and grip strength, with uncontrolled DM having a greater effect on grip strength decline than controlled DM (−0.937 kg vs −0.560 kg). In these models, the effect of controlled and uncontrolled DM on grip strength decline were equivalent to 4.34 and 7.26 years of aging, respectively. We similarly found that the effect of controlled DM on gait speed decline was equivalent to 6 years of aging. These findings suggest that DM is a more significant risk factor than advancing age for declines in physical function among men with and without HIV.

These findings are consistent with findings of prior studies conducted in the general population identifying DM as a risk factor for sarcopenia that can accelerate age-related declines in skeletal muscle mass and function[23-25]. Few studies have considered glycemic status beyond DM as a risk factor for physical function declines. A recent study of community-dwelling older adults without HIV found that uncontrolled DM (HbA1C ≥7%) was associated with increased risk of weak grip and that glycemic control modified this relationship[26]. DM and its associated complications can have myriad effects on physical function. Decreased insulin signaling in persons with DM can cause dysregulated protein turnover which can ultimately lead to decreases in muscle mass[27]. Moreover, insulin resistance is associated with mitochondrial dysfunction[28], increased oxidative stress[29], and chronic inflammation[30, 31] that can contribute to reduced skeletal muscle mass, strength, and function[32, 33]. Chronic hyperglycemia can also increase advanced glycation end products that accumulate in skeletal muscle thereby increasing muscle stiffness and leading to reduced physical function[34, 35]. In addition, diabetic neuropathy leads to wasting and weakness of distal skeletal muscles[36, 37] and increased intermuscular adipose tissue, which is associated with decreased muscle strength and function[38].

Compared to persons without HIV, many studies have found a higher prevalence of DM among PWH [17, 18]. In addition to traditional risk factors, HIV-related factors increase risk for development of type 2 DM. PWH experience systemic inflammation related to chronic HIV infection that has been associated with incident DM[39]. Various antiretroviral agents can also cause mitochondrial toxicity, body composition changes (e.g., decreased subcutaneous adipose tissue and increased visceral adipose tissue), and excess hyperglycemia that contribute to insulin resistance and development of DM[40].

We hypothesized that excess DM risk among PWH may contribute to and exacerbate accelerated physical declines previously described in this population. In our model restricted to PWH, uncontrolled DM was associated with a significant decline in grip strength. Although we did not find a significant HIV interaction in our models, we did find that the effect of uncontrolled DM on grip strength decline was 2 times greater in our model

restricted to PWH than in our analysis of all MACS participants (−1.87 kg vs −0.937 kg); these findings may reflect poorer diabetes control among some PWH, or could suggest that the adverse effects of uncontrolled DM on physical function, particularly grip strength, may be heightened among PWH.

In our study, HIV serostatus was not an independent risk factor for declines in grip strength or gait speed among MACS participants; this finding contrasts with prior analyses from the MACS that indicated HIV was associated with faster declines in both grip strength and gait speed[3, 4]. The study populations analyzed in these prior studies were slightly different: analyses of gait speed and grip strength trajectories were restricted to men aged 40 and older for gait and 50 and older for grip. In addition, follow-up time for previous analyses of gait and grip continued through 2013 and 2014, respectively, compared to through 2018 in the current study. However, in our sensitivity analyses restricted to men over the ages of 40 or 45 years old at baseline, the effect of HIV on physical function remained non-significant. Of note, these prior models of gait speed and grip strength did not include DM or glycemic status. When glycemic status was removed from our current models, HIV serostatus did have a significant effect on grip strength but not gait speed. These findings suggest that glycemic status is an important mediator of grip strength decline among PWH.

Our findings indicate that interventions to prevent and improve control of DM may help to attenuate physical function declines in PWH and persons without HIV. Optimized glucose control and use of certain diabetes medications have been associated with better functional outcomes among elderly individuals without HIV[46]. Previous studies demonstrated that use of insulin sensitizers, such as metformin or thiazolidinediones, attenuated muscle loss and declines in physical function among older men and women with DM[47, 48]. Dipeptidyl peptidase 4 (DPP4) inhibitors, which increase insulin secretion, have the potential to restore insulin signaling in skeletal muscle[57]; cross-sectional and observational studies have noted an association between their use and greater muscle mass and strength[58, 59]. However, the risks and benefits of such medications and intensive glucose management must be evaluated further, particularly in older PWH who are at increased risk for geriatric syndromes such as polypharmacy and falls [60-62]. Non-pharmacologic therapies, such as diet and exercise-based interventions, can prevent development of DM[63], improve glucose control in individuals with known DM[64, 65], and can increase physical function in older adults with and without DM[66-69]. Exercise-based interventions have resulted in significant improvement in physical function among PWH[70] and warrant further evaluation among persons living with both HIV and diabetes.

While lifestyle interventions to reduce obesity may be beneficial to prevent DM and its negative effects on physical function, the current study found that elevated BMI had differential effects on gait speed and grip strength. While obesity was associated with significant declines in gait speed, higher BMI class (both overweight and obese) was associated with improved grip strength. Obesity has been linked to gait speed impairment among both PWH and the general population[71, 72]. Individuals with obesity may experience more balance impairment and physical fatigue leading to slower gait. In addition, excess adipose tissue can reduce the ratio of lean to non-lean muscle mass and thereby decrease skeletal muscle quality and function[73]. Some studies in the general

population have suggested that obesity is associated with lower hand grip strength[74, 75], while others have noted that higher BMI is associated with higher grip strength in men[76]. [76]. In men with greater amounts of lean muscle mass, BMI can overestimate obesity[77], which may explain the positive association between BMI and grip strength in our current study. Additional analyses are needed to define more clearly the relationship between body composition and physical function in PWH compared to the general population.

Depression was associated with declines in both gait speed and grip strength. Mood disorders and reduced physical function are known to be highly overlapping and mutually reinforcing syndromes[29, 78].

Among PWH in the current study, longer duration of didanosine and zidovudine use were associated with grip strength and gait speed declines, respectively, while longer duration of ART was associated with grip strength improvement. Both didanosine and zidovudine have been shown to cause mitochondrial toxicity[79] that can contribute to physical function declines[80, 81]. However, neither didanosine nor zidovudine are routinely used in newer ART regimens. Therefore, PWH without didanosine and zidovudine exposure may face less physical function impairment than PWH without such exposures.

Several limitations of this study must be acknowledged. First, MACS participants are all male and a majority are White. Additional studies are needed to determine if similar associations are observed in other demographic groups. In addition, the overall number of men with either controlled or uncontrolled DM was low, which limited the power of our findings. While our statistical models accounted for many of the factors that affect the relationship between glycemic status and physical function, complete data for some confounders (e.g., steroid use) was not available. Furthermore, there was significant missingness in testosterone use data. Also, survivorship bias may exist in this cohort; some MACS participants have been involved in the study for over 20 years, but those with more severe complications of HIV or aging may have been more likely drop out. Moreover, the generalizability of our results to other cohorts of PWH with less exposure to older more toxic ART regimens and shorter duration of HIV is not clear.

As the population of older PWH continues to grow, it is imperative to develop targeted interventions aimed at preserving physical function and independence and promoting resiliency in this population. This study represents the largest longitudinal evaluation to date of the relationship between glycemic status and physical function among men with and without HIV. These data suggest that glycemic control may be an important modifiable risk factor to preserve physical function, regardless of HIV serostatus. Accordingly, efforts to prevent, screen for, and optimally manage pre-diabetes and DM in aging PWH should constitute a priority for clinicians and researchers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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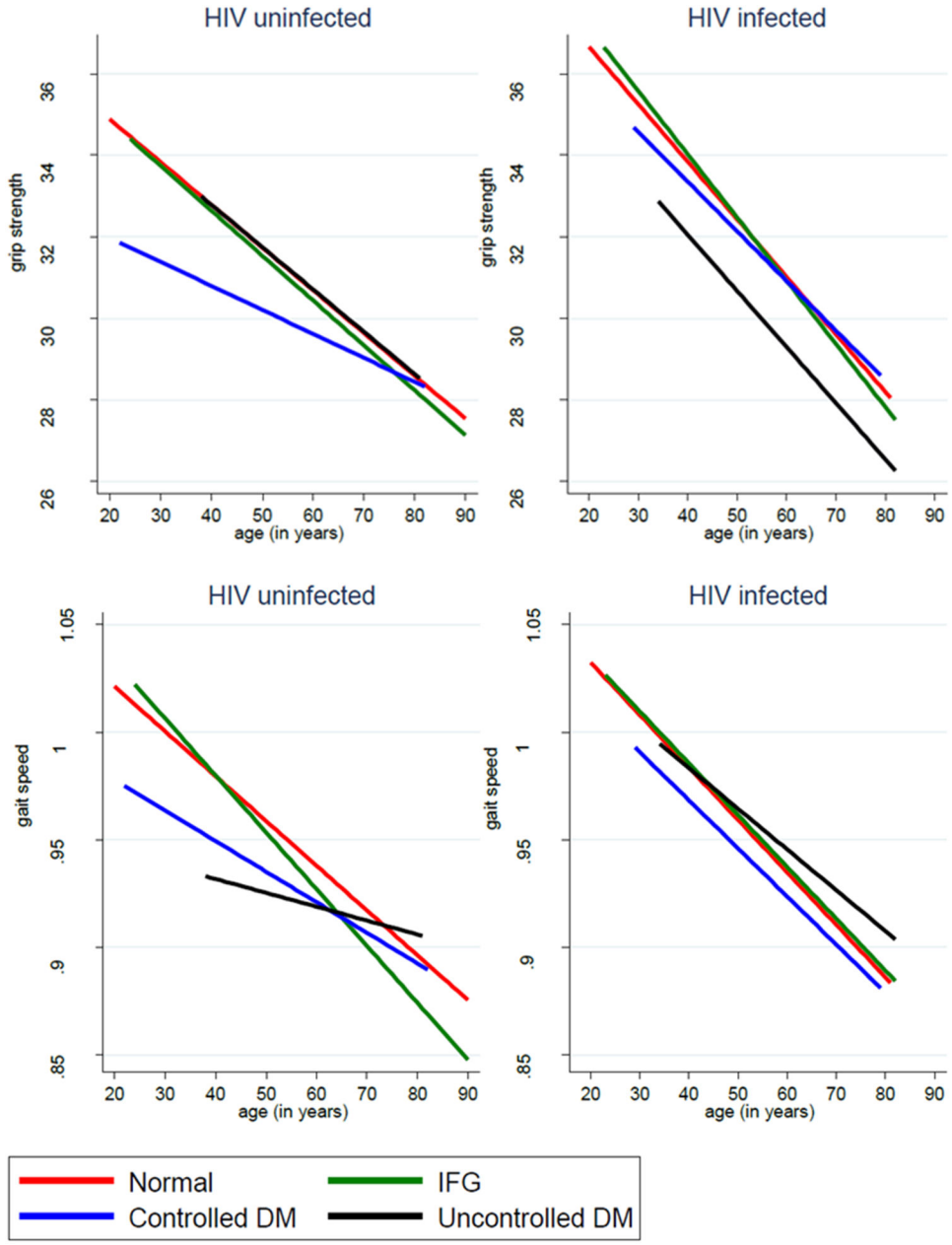

Figure 1. Physical function over time by glycemic status and HIV serostatus

No significant three-way interactions between physical function, HIV serostatus, and glycemic status over time were noted.

Table 1.

Demographic characteristics of study population by HIV serostatus at baseline

Characteristic	Men without HIV N=1070	Men with HIV N=1170	p-value
Age (years), mean (SD)	49.2 (11.7)	44.8 (10.2)	<0.001
BMI (kg/m^2), mean (SD)	27.1 (5.2)	25.8 (4.6)	<0.001
Race, N (%)			
White	786 (73.5%)	674 (57.6%)	
Black	229 (21.4%)	379 (32.4%)	
Other	55 (5.1%)	117 (10.0%)	<0.001
College education, N (%)	636 (63.8%)	501 (46.0%)	<0.001
Center, N (%)			
Baltimore	278 (26.0%)	282 (24.1%)	
Chicago	159 (14.9%)	276 (23.6%)	
Pittsburgh	314 (29.4%)	283 (24.2%)	
Los Angeles	319 (29.8%)	329 (28.1%)	<0.001
Cohort, N (%)			
1984	633 (59.2%)	364 (31.1%)	
1987	43 (4.0%)	90 (7.7%)	
2001	346 (32.3%)	451 (38.5%)	
2010	48 (4.5%)	265 (22.7%)	<0.001
Smoking status, N (%)			
Never	340 (32.1%)	359 (31.2%)	
Former	463 (43.6%)	409 (35.5%)	
Current	258 (24.3%)	384 (33.3%)	<0.001
History of cocaine use, N (%)	472 (44.4%)	572 (49.1%)	0.027
History of marijuana use, N (%)	800 (75.3%)	815 (70.0%)	0.005
Alcohol use, N (%)			
None	158 (15.0%)	206 (18.0%)	
Low-moderate	621 (58.8%)	629 (54.9%)	
Moderate-binge	277 (26.2%)	310 (27.1%)	0.098
Kidney disease, N (%)	58 (6.9%)	171 (17.6%)	<0.001
Hypertension, N (%)	396 (37.9%)	387 (33.9%)	0.051
Arthritis, N (%)	40 (3.9%)	45 (3.9%)	0.942
Depression (CESD≥16) , N (%)	237 (23.0%)	321 (29.1%)	0.001
Hepatitis B infection, N (%)	10 (0.9%)	42 (3.6%)	<0.001
Hepatitis C infection, N (%)	46 (4.3%)	82 (7.0%)	0.006
Glycemic status, N (%)			
Normal	498 (60.4%)	554 (63.5%)	
IFG	272 (33.0%)	252 (28.9%)	

Characteristic	Men without HIV N=1070	Men with HIV N=1170	p-value
Controlled DM	33 (4.0%)	57 (6.5%)	
Uncontrolled DM	22 (2.7%)	10 (1.2%)	0.004
Grip strength (kg), mean (SD)	39.8 (8.8%)	40.1 (9.4)	0.760
Gait speed (m/s), mean (SD)	1.20 (0.22)	1.17 (0.22)	0.001
Testosterone use, N (%)	61 (5.7%)	195 (16.7%)	<0.001
Years of ART, mean (SD)	-	5.1 (4.7)	-
Cumulative ART exposure (years), mean (SD)			
AZT	-	2.6 (3.6)	-
DDI	-	0.8 (1.9)	-
d4T	-	1.6 (2.5)	-
EFV	-	1.3 (2.2)	-
Any PI	-	2.9 (3.4)	-
CD4 nadir (cells/uL), N (%)	-	334.7 (212.1)	-
<200	-	300 (25.8%)	
200-500	-	652 (56.1%)	
>500	-	210 (18.1%)	-
Undetectable HIV viral load, N (%)	-	805 (69.6%)	-

ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; d4T, stavudine; DDI, didanosine; DM, diabetes mellitus; EFV, efavirenz; IFG, impaired fasting glucose; PI, protease inhibitor; SD, standard deviation

Table 2.

Baseline hemoglobin A1C [mean (SD)] by HIV serostatus and glycemic status

	Men without HIV N=1070	**Men with HIV N=1170**
Glycemic status		
Normal	5.39 (0.42)	5.29 (0.49)
IFG	5.64 (0.55)	5.39 (0.54)
Controlled DM	6.39 (0.67)	6.15 (0.77)
Uncontrolled DM	9.32 (1.70)	9.32 (2.40)

Table 3.

Association between glycemic status and physical function: results from multivariate linear mixed models

	Grip Strength		Gait speed	
Variables	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Age, years	***-0.129 (−0.166, −0.093)***	***<0.001***	***-0.003 (−0.003, −0.002)***	***<0.001***
Glycemic status				
Normal	Ref		Ref	
IFG	−0.144 (−0.429, 0.140)	0.321	−0.004 (−0.012, 0.003)	0.230
Controlled DM	***−0.560 (−1.096, −0.024)***	***0.040***	***−0.018 (−0.032, −0.005)***	***0.007***
Uncontrolled DM	***−0.937 (−1.684, −0.190)***	***0.014***	−0.007 (−0.026, 0.011)	0.437
HIV infection	0.483 (−0.269, 1.235)	0.208	−0.002 (−0.016, 0.012)	0.773
BMI (class)				
Underweight/normal	ref		ref	
Overweight	***0.720 (0.334, 1.105)***	***<0.001***	−0.008 (−0.017, 0.001)	0.085
Obese	***0.944 (0.406, 1.483)***	***0.001***	***−0.026 (−0.038, −0.013)***	***<0.001***
Race				
White	ref		ref	
Black	−0.975 (−2.003, 0.053)	0.063	***−0.047 (−0.067, −0.028)***	***<0.001***
Other	***−2.935 (−4.484, −1.386)***	***<0.001***	−0.006 (−0.035, 0.023)	0.684
College education	0.243 (−0.347, 0.832)	0.419	***0.024 (0.011, 0.036)***	***<0.001***
Center				
Baltimore	ref		ref	
Chicago	0.331 (−0.752, 1.414)	0.549	***−0.053 (−0.073, −0.033)***	***<0.001***
Pittsburgh	0.925 (−0.081, 1.932)	0.072	***−0.055 (−0.073, −0.036)***	***<0.001***
Los Angeles	−0.932 (−1.968, 0.104)	0.078	***−0.063 (−0.082, −0.044)***	***<0.001***
Cohort				
1984	ref		ref	
1987	1.154 (−0.582, 2.890)	0.193	−0.005 (−0.037, 0.027)	0.775
2001	***2.019 (0.916, 3.122)***	***<0.001***	0.017 (−0.003, 0.038)	0.101
2010	1.370 (−0.219, 2.958)	0.091	−0.010 (−0.041, 0.020)	0.505
Smoking status				
Never	ref		ref	
Former	−0.768 (−1.578, 0.042)	0.063	***−0.025 (−0.040, −0.010)***	***0.001***
Current	***−1.050 (−1.930, −0.169)***	***0.019***	***−0.041 (−0.058, −0.024)***	***<0.001***
History of cocaine use	0.421 (−0.297, 1.139)	0.251	0.009 (−0.005, 0.024)	0.194
History of marijuana use	0.528 (−0.231, 1.286)	0.173	0.014 (−0.001, 0.030)	0.074
Alcohol use status				
None	ref		ref	
Low-moderate	0.121 (−0.318, 0.560)	0.589	***0.012 (0.001, 0.022)***	***0.033***
Moderate-binge	0.074 (−0.454, 0.602)	0.784	0.009 (−0.004, 0.022)	0.161

	Grip Strength		Gait speed	
Variables	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Liver disease	−0.648 (−2.217, 0.921)	0.418	−0.028 (−0.062, 0.006)	0.104
Kidney disease	−0.345 (−0.721, 0.034)	0.075	***−0.012 (−0.022, −0.003)***	***0.010***
Hypertension	0.177 (−0.134, 0.489)	0.265	−0.001 (−0.009, 0.007)	0.813
Arthritis	***−0.702 (−1.372, −0.032)***	***0.040***	−0.003 (−0.020, 0.014)	0.745
Depression (CESD⩾16)	***−0.388 (−0.705, −0.072)***	***0.016***	***−0.020 (−0.027, −0.012)***	***<0.001***
Testosterone use	0.379 (−0.235, 0.994)	0.226	−0.005 (−0.019, 0.010)	0.520
Hepatitis B infection	0.782 (−1.573, 3.137)	0.515	−0.034 (−0.079, 0.010)	0.129
Hepatitis C infection	***−2.297 (−3.773, −0.820)***	***0.002***	−0.028 (−0.057, 0.002)	0.063

Table 4.

Association between glycemic status and physical function in men with HIV: results from multivariate linear mixed models

	Grip strength		**Gait speed**	
Variables	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Age, years	***−0.206 (−0.269, −0.143)***	***<0.001***	***−0.003 (−0.004, −0.002)***	***<0.001***
Glycemic status				
Normal	Ref		Ref	
IFG	−0.014 (−0.416, 0.389)	0.946	0.004 (−0.006, 0.015)	0.413
Controlled DM	−0.193 (−0.919, 0.533)	0.602	−0.012 (−0.031, 0.006)	0.186
Uncontrolled DM	***−1.874 (−2.924, −0.824)***	***<0.001***	0.006 (−0.020, 0.032)	0.646
Years of ART	***0.183 (0.073, 0.293)***	***0.001***	0.002 (−0.000, 0.004)	0.078
HIV medications, cumulative years				
AZT	−0.097 (−0.220, 0.026)	0.124	***−0.005 (−0.007, −0.002)***	***<0.001***
DDI	***−0.227 (−0.445, −0.009)***	***0.041***	−0.002 (−0.006, 0.002)	0.396
d4T	−0.020 (−0.233, 0.193)	0.853	−0.003 (−0.007, 0.001)	0.156
EFV	−0.026 (−0.143, 0.092)	0.669	0.001 (−0.001, 0.003)	0.353
Any PI	0.011 (−0.099, 0.122)	0.839	0.002 (−0.000, 0.004)	0.055
CD4 nadir				
<200	Ref		Ref	
200-500	0.341 (−0.874, 1.557)	0.582	0.016 (−0.006, 0.038)	0.160
>500	1.440 (−0.179, 3.060)	0.081	0.016 (−0.014, 0.045)	0.308
Suppressed HIV viral load	0.068 (−0.602, 0.737)	0.843	−0.006 (−0.023, 0.011)	0.490

Models were adjusted for all variables listed in table 3.