A5361s

Pitavastatin to Reduce Physical Function Impairment and Frailty in HIV (PREPARE)

A Multicenter Observational Study of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30140

This file contains the current ACTG A5361s protocol, which includes the following document:

- Clarification Memorandum #1, dated 20 August 2021
- Protocol Version 2.0, dated 6 July 2021

Clarification Memo #1 for:

A5361s

Pitavastatin to Reduce Physical Function Impairment and Frailty in HIV (PREPARE)

A Multicenter Observational Study of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 30140

Letter of Amendment Date: 20 August 2021

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CLARIFICATION MEMO

DATE: 20 August 2021

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5361s Protocol Team

SUBJECT: Clarification Memo #1 for Protocol A5361s

This clarification memo (CM) does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this CM with the protocol for reference.

The protocol clarification(s) contained in this memo should be implemented immediately.

The main reason for this CM is to address the missing Principal Investigator signature and signature date fields on the SIGNATURE PAGE of Protocol A5361s, Version 2.0, dated 06Jul2021.

The following is a clarification (noted in bold) to Protocol A5361s, Version 2.0, 06Jul2021, titled "Pitavastatin to REduce Physical Function Impairment and FRailty in HIV (PREPARE)." This will be included in the next version of the A5361s protocol if it is amended at a future date.

The Principal Investigator (PI) signature and signature date fields are missing on the SIGNATURE PAGE on page 2 of the A5361s Version 2.0 protocol document. This oversight is corrected by the addition of the following to this page:

Signed: _____ **Date:** _____
Name/Title

Sites should include these fields on the SIGNATURE PAGE and then obtain PI signature.

A5361s

Pitavastatin to REduce Physical Function Impairment and FRailty in HIV (PREPARE)

A Multicenter Observational Study of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

National Institute on Aging

Non-IND Protocol

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Final Version 2.0
06 Jul 2021

ACTG
AIDS CLINICAL TRIALS GROUP

Pitavastatin to REduce Physical Function Impairment and FRailty in HIV (PREPARE)

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.coreA5361s@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.coreA5361s@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5361s e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Core protocol team.

- Send an e-mail message to actg.coreA5361s@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the Data Manager.
- Electronic CRFs (eCRFs) completion guidelines and participant completed eCRFs can be downloaded from the FSTRF website at **www.frontierscience.org**.
- For transfers, reference the Study Participant Transfer SOP 119 and contact **Mark Byroads** directly.
- For other questions, send an e-mail message to reprieve.dmc@fstrf.org.
- Include the protocol number, PID, and a detailed question.

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For participant registration questions or problems:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

Computer and Screen Problems
Contact the DMC programmers.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.

- Send an e-mail message to actg.coreA5361s@fstrf.org (ATTENTION: **Jhoanna Roa**).

Copies of the Protocol
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Protocol Registration
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Protocol Activation
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Phone Calls
Sites are responsible for documenting any phone calls made to A5361s team members.
- Send an e-mail to actg.coreA5361s@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ART	antiretroviral therapy
BMI	body mass index
CMV IgG	cytomegalovirus immunoglobulin G
DASI	Duke Activity Status Index
HOMA-IR	homeostasis model assessment-estimated insulin resistance
HU	Hounsfield units
IGF-1	insulin-like growth factor 1
IIS	inflammatory index score
IL-6	interleukin-6
IP-10	IFN-gamma-inducible protein 10
LBM	lean body mass
mSPPB	modified Short Physical Performance Battery
NAFLD	non-alcoholic fatty liver disease
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
REAP	Rapid Eating and Activity Assessment for Patients
REPRIEVE	Randomized Trial to Prevent Vascular Events in HIV - REPRIEVE (A5332)
sCD14	soluble CD14
sCD163	soluble CD163
SPPB	Short Physical Performance Battery
sTNFR-1	soluble tumor necrosis factor receptor 1
sTNFR-2	soluble tumor necrosis factor receptor 2
TGF-β1	transforming growth factor beta 1
TNF-α	tumor necrosis factor α

SCHEMA

A5361s
Pitavastatin to REduce Physical Function Impairment and FRailty in HIV (PREPARE)

DESIGN	A5361s is a prospective, observational study of muscle strength and function among HIV-1 infected adults who are receiving pitavastatin or placebo as part of REPRIEVE (A5332) and are also enrolled in A5333s **or enrolled in REPRIEVE (A5332) only**. All participants will undergo physical function testing on an annual basis for **up to 60** months. In addition, data from evaluations done on REPRIEVE (A5332) and A5333s will be used. Computed tomography (CT) scans will be re-analyzed for the degree of fatty muscle infiltration, and serum/plasma samples will be analyzed for changes in biomarkers. The primary study objective is to determine whether pitavastatin can slow or prevent the decline in physical function of adults aging with HIV infection.
DURATION	**Up to 60** months
SAMPLE SIZE	600 participants
POPULATION	Ambulatory participants enrolled in both REPRIEVE (A5332) and the Mechanistic Substudy (A5333s) **OR ambulatory participants that are newly enrolling to** REPRIEVE (A5332) at **A5333s** ACTG sites. **It is desired that a substantial proportion of study participants will be enrolled in the Mechanistic Substudy of REPRIEVE (A5333s).**

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Measures of physical function will remain stable or show a slowed decline among participants assigned to pitavastatin compared to participants assigned to placebo.

1.1.2 Participants assigned to pitavastatin will have a greater decline in systemic markers of inflammation and immune activation compared to participants assigned to placebo.

1.1.3 Participants assigned to pitavastatin will have a greater reduction in fatty infiltration of the skeletal trunk muscles compared to placebo.

1.1.4 A decrease in inflammation/immune activation and a reduction in skeletal trunk muscle fat infiltration will be associated with a higher level of physical function among HIV-infected adults.

1.2 Primary Objectives

1.2.1 To determine whether pitavastatin can slow or prevent the decline in physical function of adults aging with HIV infection.

1.2.2 To evaluate mechanistic pathways through which pitavastatin affects physical function.

1.3 Secondary Objectives

1.3.1 To characterize muscle function and muscle attenuation and their association with clinical characteristics and risk factors (such as age, comorbidities, level of physical activity, inflammation/immune activation, lipids) in virologically suppressed HIV-infected older population at low cardiovascular risk.

1.3.2 To determine the effects of pitavastatin on muscle fat attenuation over 24 months.

1.3.3 To determine the relationship between changes in inflammation/immune activation and skeletal trunk muscle fat infiltration with change in physical function over **60** months.

1.3.4 To determine the impact of pitavastatin versus placebo on self-reported physical activity or sedentary time.

1.3.5 To assess the impact of muscle symptoms on the effect of pitavastatin versus placebo on physical function.

1.3.6 To determine whether changes in muscle fat attenuation are independent of lipid changes and changes in homeostasis model assessment-estimated insulin resistance (HOMA-IR).

1.4 Exploratory Objectives

1.4.1 To determine whether the impact of pitavastatin on physical function or fat infiltration is affected by baseline vitamin D levels.

1.4.2 To determine whether the impact of pitavastatin on physical function or fat infiltration is affected by sex hormones (total and free testosterone) or menopausal status.

1.4.3 To determine the effects of pitavastatin on physical function by subgroup (race, sex, CD4 count, physical activity, baseline physical function, duration of antiretroviral therapy [ART], and inflammation).

1.4.4 To evaluate the effects of the COVID-19 pandemic on physical function.

2.0 INTRODUCTION

2.1 Background

Evidence of Impaired Physical Function and Frailty Is Present in Middle-Aged Adults Aging with HIV. With combination ART, longer life expectancy is changing the demographics of the HIV epidemic, and nearly half of those living with HIV in the United States are now 50 years or older [1]. However, even with long-term, effective ART, impairment in physical function and frailty are more common than expected in HIV-infected populations and have been associated with an increased risk of falls, hospitalizations, and mortality [2,3]. Furthermore, the combination of both HIV infection and impaired physical function is associated with a greater risk of mortality than the presence of HIV infection or impaired function alone [4,5]. The aging HIV-infected population, therefore, is an emerging risk group for the accelerated development of mobility disability, and careful investigation to improve physical function and quality of life in this population is required.

Inflammation Contributes to Physical Function Impairments and Frailty. In the geriatric literature, the well-described frailty phenotype is regarded as a terminal state of loss of functional homeostasis that leaves a person unable to effectively recover from various stressors and is associated with poor health outcomes, including excess mortality [6]. Frailty and physical function impairments in elderly persons have been associated with excess inflammation and markers of immune senescence. Interleukin-6 (IL-6), a pro-inflammatory cytokine released systemically by T cells and macrophages, has been associated with low physical function [7] and low appendicular muscle mass [8]. In animal models, IL-6 infusion-induced peripheral muscle wasting in healthy rats [9]; ablation of IL-6 through a genetic knock-out [10] or IL-6 receptor antibody [11] completely abolished muscle wasting, indicating a direct role in muscle catabolism. In healthy young

men, IL-6 infusion suppressed skeletal muscle protein synthesis [12]. Clearly, inflammatory pathways are involved in the maintenance of muscle health, and excess inflammation detrimentally affects muscle quality and function.

These very derangements in inflammatory biomarkers have been well characterized in HIV infection: persistent, low-grade inflammation and immune activation [13] are strongly associated with a heightened risk for cardiovascular disease [14-16], osteoporosis [17], anemia [18], physical function impairments, and frailty [7], among other non-AIDS events and mortality [19,20]. This pro-inflammatory state is thought to be multifactorial, driven in part by low-level HIV replication and/or co-infection with other pathogens such as cytomegalovirus (CMV) [21]. Prior and ongoing work by our team has shown a strong relationship between systemic inflammation and physical function impairment in HIV-infected individuals, as detailed in the Preliminary Data section. Given the long-term consequences of chronic inflammation, there is an urgent need to understand the causes and to develop interventions that attenuate the effects of inflammation and immune activation in people living with HIV.

The Need to Determine Statin Effects on Functional Impairment. Statins are the most widely prescribed class of drugs worldwide [22]. The anti-inflammatory effect of statins has generated interest in the use of statin therapy to attenuate the low-grade inflammation and immune activation in treated HIV-infection [23-25]. Most recently, in the SATURN-HIV trial, HIV-infected adults randomized to rosuvastatin had significant reduction in markers of inflammation and immune activation compared with placebo [26]. Among persons with chronic inflammation, the reduction in inflammatory markers with statin therapy is an attractive target for prevention of physical function impairment, ultimately to decrease progression to disability and frailty. In cancer cachexia models in which loss in muscle mass and function are driven by chronic inflammation, simvastatin attenuated loss of lean body mass (LBM) [27]. In a murine model, atorvastatin delayed motor dysfunction and muscle weakness, attenuated the loss of motor neurons, and increased biceps muscle weight by nearly 30% compared with vehicle (placebo), suggesting benefit at the level of both the muscle and the motor neuron [28].

*Table **2.1-1**. Systematic Review of Statins on Physical Function*

Design		*N*	*Dur.*	*Effect*	*Ref*
Positive Effect	RCT	64	6 mos	Statins improved lower extremity blood flow in healthy adults	[29]
	RCT	86	6 mos	Statins increased walking distance in PAD	[30]
	RCT	354	12 mos	Statin-users with improved pain-free walking time, self-reported walking ability; no change in max walking time	[31]
	RCT	68	6 mos	Significantly improved 6-min walking time in statin arm only in CHF	[32]
	RCT	144	24 mos	Significantly greater LBM gain in statin arm, no difference in self-reported physical activity	[33]
	RCT	83	12 mos	EX +/- lovastatin; significantly greater METS and exercise time in statin arm only	[34]
	RCT	15	20 wks	Cerivastatin versus placebo in heart failure patients; significantly improved 6-min walking distance	[35]
	RCT	125	6 mos	Pravastatin versus placebo in COPD; improved exercise time and dyspnea with pravastatin	[36,37]
	RCT	64	12 wks	Atorvastatin versus placebo in cardiomyopathy; improved 6-min walking distance in atorvastatin group	[38]
	OBS	756	n/a	Statin users had better timed chair stands than non-statin users	[39]
	OBS	641	n/a	Better physical function, faster gait speed and velocity among statin users with or without PAD	[40]
	OBS	5,777	n/a	Less decline in chair rise among oldest women on statins	[41]
	OBS	544	n/a	Less decline in lower extremity performance among PAD patients on statin	[42]
	OBS	49	12 wks	REx +/- statin use (pravastatin/lovastatin but not atorvastatin/simvastatin) greater gains in LBM	[43]
	OBS	3422	n/a	Statin use associated with improved disability scores on discharge from rehab	[44]
Null Effect	RCT	420	6 mos	No change in strength/endurance but increase in CK in statin arm	[45]
	RCT	41	12 mos	Cross-over RCT of pravastatin +/- tocopherol; no significant quality of life differences	[46]
	RCT	26	8 wks	No sign change with atorvastatin in resting energy expenditure, V02, or RER	[47]
	RCT	16304	Up to 5 yrs	From JUPITER, no difference in self-reported fatigue or muscle weakness in rosuvastatin versus placebo	[48]
	CT	26	12 wks	Statin users and non-users completed 12 wks EX; similar gain in V02 max, workload, muscle strength; similar changes in mitochondrial density and function	[49]
	CT	22	8 wks	Statin users/non-users completed 8 wks EX; similar gains in V02 max and exercise time	[50]
	OBS	25378	n/a	Longer duration low-potency statin associated with reduced frailty; no effect with other potency	[51]
	OBS	2005	n/a	No detrimental effect of statins on gait speed; 22% lower risk of decline among low-dose statins only	[52]
	OBS	1665	7 yrs	No association between statin use and institutionalization or death	[53]

	OBS	749	N/a	No difference in swim distance, sessions, or time among master swimmers with or without statin use	[54]
	OBS	317	6 mo	Statin-users and non-users had increase in physical function but not different	[55]
	OBS	28	n/a	No difference in muscle function measures between statin-users or non-users	[56]
Negative Effect	RCT	37	12 wks	EX +/- simvastatin. Greater LBM; attenuated V02 response in statin arm. *Strength was not reported.*	[57]
	RCT	1016	6 mo	Randomized simvastatin, pravastatin or placebo; lower self-reported energy/greater fatigue in statin arm	[58]
	OBS	18	n/a	No difference in mass, power, or strength; increased expression of mRNA linked to mitochondrial apoptotic signaling in statin myalgia arm compared with non-statin users	[59]
	OBS	774	n/a	Statin use predicted increased fall risk score and decreased leg strength.	[60]
	OBS	6966	n/a	Statin users tended to have lower self-reported physical function & self-rated health	[61]
	OBS	3280	n/a	Loss of LBM between age >60 and <75 yrs was greater in the statin (10.9%) than non-statin (8.5%) group.	[62]
	OBS	4137	n/a	Statin users self-reported less moderate or vigorous physical activity	[63]
	OBS	2207	n/a	Longer-duration statin associated with worsened self-reported physical function	[64]

PAD, peripheral artery disease; EX, exercise; CHF, congestive heart failure; LBM, lean body mass; COPD, chronic obstructive pulmonary disease; RER, respiratory exchange ratio; RCT, randomized controlled trial; CT, controlled trial; OBS, observational study

To understand the clinical impact of statins, we performed a systematic review (Table **2.1-1**). A PubMed search using ("Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Medical Subject Heading {MeSH}] or **"**statins**"**) AND (**"**frailty**"** or **"**sarcopenia**"** or "muscle strength" or "physical function" or "physical performance") with human and English filters yielded 59 articles. A separate search for ("Hydroxymethylglutaryl-CoA Reductase Inhibitors" **[**MeSH**]** AND **"**exercise**"** [MeSH]) yielded 186 articles. We augmented the search using the reference lists from relevant studies and prior systematic reviews. Each abstract was reviewed and full articles were reviewed if the abstract was potentially relevant. Both observational and clinical trials reporting any measures of physical function were reviewed. As detailed in Table **2.1-1**, prior clinical studies among HIV-uninfected populations have found that randomized or observed statin therapy was associated with increased total walking distance or time [30,32,34-38], self-reported walking ability [31], and improved chair rise time [39]. Statin use among adults initiating resistance exercise was associated with a greater gain in LBM compared with those not using statins [43]. Furthermore, as detailed in Preliminary Data, our SATURN-HIV study showed that HIV-infected participants assigned to low-dose rosuvastatin had significantly greater LBM at 96 weeks compared with placebo [33].

In contrast to the positive benefits of statins on physical function and muscle mass described above, myalgias are one of the most commonly reported and well-recognized

side effects of statin therapy. Although estimates vary, the prevalence of subjective myalgias or weakness with statin treatment is reportedly as high as 20% in clinical practice, and myalgias are a major cause of statin non-compliance and discontinuation [65]. While data suggest that myalgias are not associated with a decrease in physical function [45,59,66,67], *observational* cohort studies have reported lower strength [60], physical activity [63], and lean mass [60,62] among participants using statins. To our knowledge, the only *randomized, placebo-controlled study* to demonstrate a negative effect of statins was a small study of an aerobic exercise intervention with (N=18) or without (N=19) simvastatin; the simvastatin arm demonstrated an attenuated aerobic response to exercise training, but a significant increase in LBM (no increase in placebo arm); no measures of strength were reported [57]. A separate randomized, placebo-controlled trial reported negative impact on energy and fatigue, but no objective measures were reported [58]. A large trial specifically designed to assess the impact of statins on skeletal muscle function randomized 468 healthy participants to atorvastatin versus placebo and found no significant differences in strength or endurance between arms; however, effects were assessed after only 6 months of therapy [45]. The authors concluded that the findings “should prompt studies examining the effects of more prolonged, high-dose statin treatment on muscular performance.”

Muscle Fat, a Measure of Muscle Quality and Statins. With increasing age comes deterioration of muscle mass and quality. One key component of muscle quality is the amount of fatty infiltration, which increases with age and, as we have shown, is more pronounced in HIV-infected persons. Fatty infiltration of the muscle has been independently associated with impairments in muscle strength, chair rise time, and gait speed [68-70] and thus, is an important potential target for interventions aimed at improving physical function. Skeletal muscle lipid accumulates as the result of increased circulating fatty acids, enhanced fatty acid uptake, and decreased mitochondrial oxidation, among other mechanisms. Excess free fatty acids accumulate within the muscle as lipid droplets are converted to molecules involved in signaling pathways that may contribute to insulin resistance, inflammation, or production of reactive oxygen species [71-73]. A strong correlation between intramyocellular and intrahepatic lipid content has previously been reported and linked to excess visceral fat, as well as insulin resistance [74,75]. Although the effects of statins on *muscle fat* have not been reported, in animal and human models of non-alcoholic fatty liver disease (NAFLD), several statins have demonstrated decreases in both hepatic steatosis and decreased fibrosis [76-79]. In a rat model of NAFLD, pitavastatin treatment led to smaller hepatocyte lipid droplet size, reduced hepatic triglycerides, reduced hepatic expression of TNF-α and transforming growth factor (TGF)-β1 mRNA, and reduced expression of fibrogenesis markers [77]. Similarly, among NAFLD patients on atorvastatin, significant improvements were seen in NAFLD index scores, liver-to-spleen density ratio, and transaminases, with improvements attributed in part to a reduction in TNF-α [76]. We therefore hypothesize that statin therapy will similarly improve fatty infiltration of the muscle and that the reduction in muscle fat will be associated with improvement in measures of physical function and reduced inflammation.

Measurement of Fatty Infiltration of the Muscle. While muscle biopsy remains the gold standard to measure muscle fatty infiltration, this invasive technique is associated with

increased risk of site infection, morbidity, and cost. Computed tomography (CT) can distinguish different tissue types by tissue density or attenuation; with a greater infiltration of adipose tissue indicated by lower attenuation (lower Hounsfield units [HU]). Skeletal muscle fat attenuation by CT scan is strongly correlated with muscle fiber lipid content obtained by biopsy [80] or estimated by MRI (r=0.97) [81] and has been associated with decreased physical function in the general population [69,70,82,83] .

2.2 Rationale

With several studies suggesting benefits of statins on physical function and others showing potential harm or null effect, the evidence regarding the effects of statin therapy on physical function is mixed. As shown in Table **2.1-1**, the effect of statin therapy may vary by statin potency. Effects of statin therapy may also vary by disease characteristics of the population (i.e., chronic inflammation) and the duration of follow-up. Pitavastatin has a potent effect on reduction in markers of systemic inflammation in HIV-uninfected populations [64,84] and a lower incidence of muscle complaints in comparison to other statins from multiple clinical trials [85-87]. We hypothesize that the effect of statins may also depend on the point in the physical function trajectory when therapy is introduced; frailty is the end result of multiple insults, and targeting inflammation in an already frail or nearly frail individual is unlikely to alter the frail state. Thus, a true state of equipoise exists, providing strong rationale for a careful examination of this endpoint in a relatively high-functioning, HIV-infected population within the setting of a randomized clinical trial.

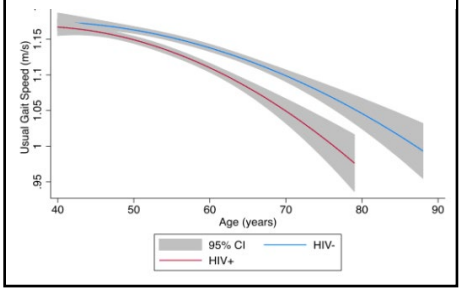
As CT images are already obtained in the Mechanistic Substudy of REPRIEVE (A5333s), we have the unique opportunity to determine whether statin therapy can decrease fatty infiltration of the muscle in participants without additional testing or radiation.

The REPRIEVE (A5332) trial provides an unprecedented opportunity to investigate the impact of statins on physical function, in the setting of a large, randomized, double-blind intervention of HIV-infected adults, with available imaging, biomarkers, and established infrastructure. The proposed PREPARE study will fill a major gap in the understanding of statin's effects on physical function among HIV-infected adults who, despite successful ART, continue to have heightened inflammation. No other randomized controlled trial including physical function outcomes has examined statin effects past 1 year, although statin therapy is typically prescribed for a decade or more. If statins reduce the risk of cardiovascular disease among otherwise healthy HIV-infected adults, as the REPRIEVE (A5332) study is designed to evaluate, then the risk-benefit of statin therapy becomes of particular importance and relevance to a large population. The potential benefits or harms of statin therapy on physical function over time should be thoroughly evaluated to best inform the decision to treat, particularly with the burden of an additional medication in an aging population. Results of this study will provide key insights into the longitudinal relationships between inflammation and physical function, and test a potential intervention to prevent physical function impairments and improve quality of life, results expected to extend beyond those aging with HIV to all older adults with inflammatory conditions.

Physical Function Impairments Are Frequent Among HIV-Infected Adults. Members of our team have identified impairments in physical function and frailty across several cohorts [88]. Among middle-aged HIV-infected men and women on effective ART in Colorado, a team led by Dr. Erlandson found that 50% had difficulty rising from a chair five times [89], and 20% met criteria for low muscle mass [90]. In the ALIVE Cohort, we found that more than one-third of participants had impairments on the Short Physical Performance Battery (SPPB), as defined by a score of ≤10 [4]. In both of these cohorts, the repeated (five times) chair rise was consistently the SPPB measure with the greatest impairment. Additionally, frailty, a clinical indicator of marked vulnerability to stressors, was present in between 8–15% of HIV-infected adults in a Washington University HIV Clinic [91], the Study to Understand the Natural History of HIV (SUN) [92], the ALIVE Cohort [5,93], and the Colorado cohort [88,89]. In an ongoing, multicenter longitudinal ACTG study of 1016 HIV-infected adults aged 40 and older, we have found that 6% of participants were frail and 38% were pre-frail [**94**]. Although impairments in physical function and frailty have been well described in cross-sectional observations, few studies have described changes over time.

Declines in Physical Function Are More Common Among HIV-Infected Persons. Within the Multicenter AIDS Cohort Study (MACS), we found that decline in gait speed was on average 0.027 m/s per year *greater* in HIV-infected compared with HIV-uninfected men (p<0.001), and this difference intensified with advancing age (p=0.007); Figure 1, with a separation of the trajectories by HIV-serostatus occurring between ages 45 and 50. There was a 57% greater risk of developing clinically slow gait (<1.0 m/s) in HIV-infected compared with HIV-uninfected men (adjusted hazard ratio=1.57, 95% confidence interval 1.28–1.92) [**95**]. Similar differences by HIV-serostatus were seen with longitudinal changes in grip strength in the MACS [**96**].

Figure 1. Usual Gait Speed and Age by HIV Status



Physical Function Impairments and Frailty Are Associated with Poor Outcomes. In our previous studies, slow gait speed and chair rise time were associated with lower quality of life [**94**], impaired balance was associated with a 13-fold greater odds of recurrent falls [3], and poor self-reported physical function was associated with incident diabetes and insulin resistance [**97**]. HIV infection and impaired SPPB had a synergistic effect in the ALIVE Cohort, in which predicted mortality was significantly greater with the combination of both HIV and impaired physical function (HR= 6.03) compared to HIV infection (HR=2.78) or impaired SPPB score alone (HR=2.52) [4,5,93]. Frailty in HIV-infected adults was associated with a greater number of hospitalizations [89,91,**96**]. Similarly, the impact of both HIV infection and frailty had a synergistic effect on mortality (mortality OR= 2.6 with HIV infection; OR=3.3 with frailty; and OR=7.1 with both HIV and frailty) [5,93]. Through our research in multiple cohorts, we have consistently demonstrated that aging with HIV is associated with greater risk of physical function impairments and frailty and that these impairments are associated with morbidity and mortality. Our findings emphasize an urgent need to understand the pathophysiology and develop effective interventions.

Inflammation Is a Major Contributor to Functional Impairment in Persons Aging with or without HIV Infection. Higher IL-6 is closely linked to frailty, disability, and mortality among HIV-uninfected elderly [98-100]; similar relationships are seen with TNF-α [101,102] and neopterin [103], a measure of monocyte activation. In a case-control study, elevated inflammatory markers, particularly a combined inflammatory index of sTNFR-1 and IL-6, were associated with greater odds of low physical function and low appendicular muscle mass [7,104] . In the MACS Cohort, higher inflammation (sTNFR-2) among HIV-infected men was an independent predictor of lower subsequent grip strength [105], and HIV-positivity and the presence of a frailty-related phenotype was associated with increasing inflammation [106]. Similarly, in the ALIVE Cohort, the inflammatory index was predictive of both frailty and mortality [5]. Thus, our preliminary data provides evidence that the inflammatory milieu seen among HIV-infected persons plays a central role in impaired physical function during aging with HIV infection.

HIV Infection Is an Independent Risk Factor for Skeletal Muscle Fat Infiltration. In addition to the association with impaired physical function, low attenuation of skeletal muscle (indicating increased fat infiltration) is associated with metabolic dysfunction, independent of visceral adiposity and body mass index (BMI) [107-110]. Furthermore, low attenuation of thigh musculature is a strong predictor of hip fracture, independent of BMI, percentage body fat, age, race, gender, and bone mineral density [108]. Among younger, HIV-infected persons with lipodystrophy syndrome, low attenuation of the psoas muscle was associated with insulin resistance, while BMI, subcutaneous fat, LBM, and ART were not [111]. In the MACS, we have found decreased attenuation of the mid-thigh muscle bundle in middle-aged HIV-infected men compared to uninfected men, even after multivariable adjustment including visceral and subcutaneous adipose tissue. The decrease in attenuation correlated with a decrease in grip strength. Furthermore, this measurement of muscle quality decreased with increasing age among the HIV-infected men, but did not decline significantly with age in the uninfected men (Figure 2). Particularly relevant to this study, HIV-infected men with the highest tertile of sTNFR-1 concentrations had the greatest fat infiltration (lowest CT attenuation), independent of CD4 cell count and HIV RNA [112]. The magnitude of this effect was equivalent to over 6 years of aging. Significant changes in both total body and leg lean mass were seen among SATURN-HIV participants with interferon-γ inducible protein (IP)-10 greater than the median level at baseline, but not among those with IP-10 levels below the median, suggesting that greater IP-10 changes with statin initiation may mediate improvements in LBM, particularly among participants with high inflammation [33]. These data suggest a strong association between skeletal muscle fat and heightened systemic inflammation, which may both contribute to the decline in physical function among persons aging with HIV. Moreover, fat attenuation is amenable to therapeutic intervention; intramuscular fat decreases with exercise, hormone replacement, or weight loss [113-118].

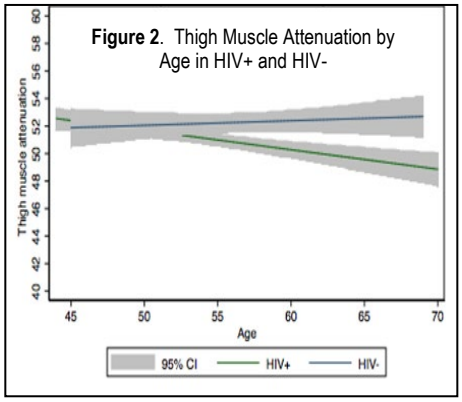


Figure 2. Thigh Muscle Attenuation by Age in HIV+ and HIV-

Statins Decrease Markers of Inflammation and Immune Activation in HIV-Infected Populations. In a randomized, double-blinded trial of rosuvastatin versus placebo among 147 HIV-infected adults with heightened inflammation or immune activation (SATURN-HIV), rosuvastatin was associated with significant reductions in sCD14, IP-10, and T-cell activation markers [26]. Initiation of rosuvastatin, atorvastatin, or pravastatin therapy among HIV-infected patients on protease-inhibitor therapy resulted in significant reductions in high sensitivity C-reactive protein (hsCRP) and TNF-α [119]. Significantly greater reduction in hsCRP and TNF-α was seen among HIV-infected persons initiating ART compared to without rosuvastatin [120].

The Role of Statin Therapy in Physical Function and Frailty of HIV-Uninfected Older Adults Is Controversial. Data among HIV-infected adults are even further limited, with most evidence from early in the AIDS era, among those with HIV-associated wasting or lipoatrophy. Early evidence of a potential beneficial effect of statins on body composition was demonstrated in a placebo-controlled study of pravastatin among HIV-infected men with hypercholesterolemia, the majority of whom also had lipoatrophy (also associated with heightened inflammation); a significant increase in total, limb, and subcutaneous fat was seen in subjects randomized to pravastatin versus placebo, suggesting a beneficial effect on lipoatrophy [121]. A subsequent large, HIV cohort study led by Dr. Brown found a greater increase in hip circumference among statin users compared with non-statin users and a greater increase in thigh circumference in statin users also taking thymidine analogues [122]. Although imaging was not available for this analysis, the anthropomorphic measures are suggestive of beneficial gains in muscle. In SATURN-HIV, participants randomized to rosuvastatin experienced gains in total LBM and leg lean mass compared with the placebo arm (absolute gain of 1.4 kg LBM in rosuvastatin arm versus 0.3 kg loss in placebo arm), without differences in total body fat or limb fat [8]. These findings suggest that the prior changes in anthropomorphic measures are due to increased LBM without gain in fat mass.

Summary of Preliminary Data. Our data from multiple cohort studies have shown the high prevalence of physical function impairments among HIV-infected persons, a more pronounced age-related decline in functional performance measurements among HIV-infected persons compared with HIV-uninfected controls beginning in middle-age, and a clear relationship between decreased physical function and clinical outcomes. We have also demonstrated strong and consistent associations between systemic inflammation and physical function measures in multiple studies, as well as more pronounced fatty infiltration of muscle among HIV-infected men versus HIV-uninfected men, suggesting that these would be potential pathways for interventions. Our data showing increased LBM gains among HIV-infected persons randomized to statin therapy also provide compelling rationale for the PREPARE study.

Study Extension. The final, month 48, follow-up visit of A5361s occurred during the COVID-19 pandemic for many participants. Because a large number of final evaluations could not be conducted, study follow-up has been extended to month 60. Data from these final evaluations are crucial to understanding the longer-term effects of statin therapy on physical function in REPRIEVE (A5332) participants.

We will also collect data on distinct changes in physical function that may have occurred between the month 36 and month 60 visits as a result of the COVID-19 pandemic, either directly through infection with the virus, or indirectly due to changes in physical activity, weight gain, social isolation, or stress.

3.0 SUBSTUDY DESIGN

A5361s is an optional substudy of REPRIEVE (A5332) and the Mechanistic Substudy of REPRIEVE (A5333s). Approximately 600 HIV-infected males and females who are enrolled in **REPRIEVE (A5332) with or without coenrollment into** A5333s will co-enroll in A5361s.

Participants will be followed for **up to 60** months from the date of enrollment into REPRIEVE (A5332) for the assessment of objective and self-reported measures of physical function. Based on their date of enrollment into REPRIEVE (A5332), participant follow-up on A5361s will be between **36** and **60** months.

Additional outcome measures and covariates to address the study objectives will be obtained from assessments performed as part of REPRIEVE (A5332) and A5333s (see section 10.0 for more detail).

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 **Ambulatory participants co-enrolled in both REPRIEVE (A5332) and the Mechanistic Substudy (A5333s).**

OR

Ambulatory participants that are newly enrolling into REPRIEVE (A5332) at A5333s ACTG sites.

4.2 Exclusion Criteria

4.2.1 Inability to ambulate independently (use of a cane or a walker is permitted) or rise from a chair without assistance.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, sites must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support

Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received.
Site-specific informed consent forms (ICFs) WILL NOT be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in their regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs WILL NOT be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. Sites should retain a copy of the Amendment Registration Notification in their regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Participant Enrollment System.

4.3.2 Protocol Activation

Prior to screening, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.3 Participant Registration

Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures. For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.4 Co-enrollment Guidelines

Co-enrollment is allowed per REPRIEVE (A5332) guidelines.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

No drugs will be provided by this study. Pitavastatin/placebo will be provided per REPRIEVE (A5332) section 5.0.

Participants may enroll and continue participation in A5361s regardless of their status on REPRIEVE (A5332) study treatment.

5.2 Prohibited Medications

Per REPRIEVE (A5332).

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of **Evaluations**

All study visits for A5361s assessments should be timed to coincide with regularly scheduled REPRIEVE (A5332) or A5333s visits. The A5361s post-entry visits are scheduled in months after REPRIEVE (A5332) entry.

Evaluation	Entry (± 14 days)[1]	Post-Entry Evaluations (months) (Preferably completed at the REPRIEVE (A5332) or A5333s visit, however ± 14 days of visit is acceptable)[2]					
	0	Month 12	Month 24	Month 36	Month 48	**Month 60 (see 6.2.1)**	Discontinuation
Modified Short Physical Performance Battery and Frailty Assessments	X	X	X	X	X	**X**	X
Rapid Eating and Activity Assessment for Patients Survey – Questions #26 and #27 only		X[3]	X[4]	X	X	**X**	X
Duke Activity Status Index[5]			X[4]				

[1] **Entry for participants newly enrolling into A5332 and A5333s or A5332 only, OR any subsequent follow-up visits for co-enrolled (A5332/A5333s) participants, up to month 24.**

[2] **Participants co-enrolled in A5332 and A5333s can enroll at any visit, up to month 24. The second visit will then be completed at the next A5332 or A5333s annual visit. Depending on the time of enrollment, participants will be followed from between 36 to approximately 60 months.**

[3] **In the event that the A5361s entry visit coincides with the month 12 visit for A5332 or A5333s, REAP questions #26 and #27 will be completed as part of a combined A5361s entry and month 12 visit.**

[4] **For newly enrolling** A5332 participants at **A5333s** ACTG sites, REAP questions #26 and #27 **at Months 12 and 24** and DASI at Month 24 will be captured as part of A5361s for participants not **co-enrolled** in A5333s.

[5] **At month 60, the DASI evaluation from the REPRIEVE (A5332) month 96 or study termination visit will be used.**

6.2 Timing of Evaluations

6.2.1 Entry and Post-Entry Evaluations

For participants newly enrolling into REPRIEVE (A5332) and A5333s: **Enrollment into** A5361s should preferably **occur on the same day as enrollment into A5332 or A5333s** (within 14 days of the visit is acceptable), and **prior to** initiation of randomized treatment in REPRIEVE (A5332).

For participants newly enrolling into REPRIEVE (A5332) only: Enrollment into A5361s should occur on the same day as enrollment into A5332 when possible (but must occur within 14 days of enrollment into A5332) and must occur prior to initiation of randomized treatment in REPRIEVE (A5332).

For participants already enrolled into **both** REPRIEVE (A5332) and A5333s: The A5361s entry visit can occur at any REPRIEVE (A5332) or A5333s visit (or ± 14 days of the visit), up to the month 24 visit. Subsequent visits will follow the remaining schedule in section 6.1.

For all participants: All post-entry visits should be scheduled to coincide with the q12 month regularly scheduled REPRIEVE (A5332) visits but within 14 days of visit is acceptable. Post-entry visits should be scheduled from the REPRIEVE (A5332) entry visit.

Enrollment completed in 2018 under PREPARE (A5361s) Version 1.0. In Version 2.0, an additional visit is added to occur at month 60. If the participant is past their Month 60 visit in the REPRIEVE (A5332) study, the PREPARE (A5361s) Month 60 evaluations can be performed at the next REPRIEVE (A5332) in-person visit. Refer to the A5361s Manual of Procedures (MOPS) for special instructions for participants who are already off-study.

ALTERNATE COMPLETION OF POST-ENTRY EVALUATIONS

- **If a participant can safely be seen for an in-person REPRIEVE (A5332) study visit, the A5361s visit that is due at the same time should also be completed.**

  If local guidelines or restrictions prevent the site from completing any of the assessments (or components of the mSPPB or frailty assessments) required at a visit, the reason for the missing assessment should be documented in the source documents and on the corresponding CRF. Complete evaluations as possible, even if full mSPPB and frailty assessments cannot be performed.

- **If a participant has an in-person REPRIEVE (A5332) study visit but A5361s assessments could not be completed due to local guidelines or restrictions, the assessments should be completed at the next REPRIEVE (A5332) in-person visit if the restrictions have been canceled by then.**

- **If an in-person REPRIEVE (A5332) study visit that coincides with an A5361s visit is delayed or missed, the A5361s visit should be completed whenever the participant is next seen for an in-person REPRIEVE (A5332) visit.**

6.2.2 Discontinuation Evaluations

Premature Discontinuation from REPRIEVE Study Treatment
No additional A5361s assessments are required at the time of premature discontinuation from REPRIEVE (A5332) study treatment.

Participants who prematurely discontinue from REPRIEVE (A5332) study treatment will continue to be followed as indicated in section 6.1.

Premature Discontinuation from REPRIEVE (A5332) Study
Participants who prematurely discontinue from REPRIEVE (A5332) will be discontinued from A5361s and have an A5361s discontinuation visit performed as indicated in section 6.1.

Premature Discontinuation from Study A5361s
Participants who discontinue from A5361s will have an A5361s discontinuation visit performed as indicated in section 6.1.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: **https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf**.

If a participant is able to ambulate independently at entry but later is unable to complete the assessments, the participant should remain on study, and the reason for the lack of assessment should be recorded.

The protocol team and/or study monitoring entity (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

6.3.1 modified Short Performance Battery (mSPPB)

6.3.1.1 Repeat Chair Stand

Repeat chair stand is a functional test of lower extremity performance that is highly affected by changes in muscle strength and has been proposed as a proxy measure of lower-extremity strength for the clinical setting. Participants rise from a standard height chair that does not have wheels or arms 10 times. Split times are captured after completion of both five rises and 10 rises (see MOPS for further details).

6.3.1.2 Grip Strength

Grip strength is an easily performed, inexpensive, reproducible assessment that is strongly associated with bone mineral density (BMD), fall risk, and fracture, and it is well correlated with more direct measures of lower-extremity strength. Three measurements with the dominant hand will be taken using a Jamar Dynamometer. (See MOPS for further details.)

6.3.1.3 Standing Balance Test

Participants are asked to stand in three different positions with progressive narrowing of the base of support, namely the side-by-side stand, the semi-tandem stand (i.e., heel of one foot touching the great toe of the other foot), the full tandem stand (i.e., heel-toe position), and the single-leg stand (i.e., opposite foot in hip-flexed, knee flexed position with toes 2 inches or more from the floor). The duration for which the participant can hold the stance without taking a step or grabbing for support is recorded. (See MOPS for further details.)

6.3.1.4 Gait Speed

Walking is a complex task requiring balance, mobility, strength, and coordination. In many functional performance batteries, including the mSPPB, timed walking is an integral component. It is an excellent predictor of lower extremity function and is well correlated with falls and fractures resulting from falls; it also is a strong predictor of disability and mortality. Two measurements of usual gait speed on a 4-meter course will be obtained. (See MOPS for further details.)

6.3.2 Frailty Self-Reported Components

These three questions inquire about an unintentional change in weight, whether the participant’s health leads to limitations in vigorous activities, and whether the participant feels that “everything that I do is an effort.”

6.3.3 REAP Questions #26 and #27

These questions will be administered at 12, 36, 48**, and 60** months, and **at** discontinuation as a measure of self-reported physical activity; these assessments are obtained at entry in REPRIEVE (A5332) and at month 24 in A5333s. In the event that **the A5361s entry visit coincides with the month 12 visit for** A5332 **or A5333s**, REAP questions #26 and #27 will be completed as part of **a combined** A5361s **entry and A5332/**A5333s **month 12 visit**.

For REPRIEVE (A5332) participants not enrolled in A5333s, REAP questions #26 and #27 at month 24 will also be completed as part of A5361s.

The questions are as follows: In an average week, how often do you: (usually/often, sometimes, rarely/never, does not apply):

- #26 Do less than 30 total minutes of physical activity 3 days a week or more? (Examples: walking briskly, gardening, golf, jogging, swimming, biking, dancing, etc.)
- #27 Watch more than 2 hours of television or videos a day?

6.3.4 DASI

In the event that enrollment is expanded to eligible A5332 participants at US ACTG sites, functional capacity (Duke Activity Status Index [DASI]) questionnaire will be completed at month 24 for participants not enrolled in A5333s.

For the month 60 evaluation, the DASI evaluation from the REPRIEVE (A5332) month 96 or study termination visit will be used.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Reporting Requirements in the Clinical Database

A5361s has no adverse event reporting requirements.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

A5361s reporting of EAEs to DAIDS is not required because A5361s is an observational/non-interventional study (i.e., there are minimal interventional risks from the study for participants).

7.4 Study Monitoring

The Protocol Core Team will monitor the conduct and continued feasibility of the study via quarterly summaries of enrollment, study retention, co-enrollment, and endpoint evaluability. On an annual basis the Study team will prepare a Protocol Team Review Summary Letter for distribution to site investigators in accordance with the ACTG SOP for Study Data and Safety Monitoring.

The study status of PREPARE is monitored by the REPRIEVE DSMB as part of the REPRIEVE trial study monitoring plan.

Detailed plans for data monitoring will be outlined in a Study Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

Management of HIV antiretroviral therapies and complications of disease should be performed according to the REPRIEVE (A5332) protocol or routine clinical care, where applicable.

9.0 CRITERIA FOR DISCONTINUATION

- Request by the participant to withdraw.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- Premature discontinuation from REPRIEVE (A5332).
- At the discretion of the study monitor, site investigator, IRB, Office of Human Research Protections (OHRP), National Institute on Aging (NIA), NIAID, NHLBI, or other government agencies as part of their duties to ensure that research participants are protected.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5361s will determine the effects of pitavastatin on physical function and evaluate mechanistic pathways through which pitavastatin affects physical function.

The study will enroll participants from REPRIEVE (A5332) and its mechanistic substudy (A5333s) and follow them for **up to 60** months after entry to REPRIEVE (A5332). Treatment groups (placebo versus pitavastatin) will be defined according to randomization in REPRIEVE (A5332). The primary analyses for all treatment group comparisons will be intent to treat, while supportive secondary analyses as well as analyses examining mechanistic pathways will be as-treated.

While measures of physical function (including both objective and long-term measures of self-assessment) will be assessed as part of A5361s, many of the outcome measures of interest will be available through data collected in REPRIEVE (A5332) and A5333s, as outlined in the Table **10.1-1**. If the target recruitment numbers cannot be achieved through A5333s enrollment, the study will open to all participants in REPRIEVE (A5332) enrolled at US ACTG sites. For these participants, only the outcomes measured as part of A5361s or REPRIEVE (A5332) will be available for analysis.

Table **10.1-1**: Data Sources for A5361s Outcome Measures

Outcome Measure	REPRIEVE (A5332) Entry	Year 1	Year 2	Year 3	Year 4	**Year 5**
Physical function battery	A5361s[1]	A5361s[2]	A5361s	A5361s	A5361s	**A5361s**
Frailty components	A5361s[1]	A5361s[2]	A5361s	A5361s	A5361s	**A5361s**
Duke Activity Status Index (DASI)	A5332[3]		A5333s[4]			**A5332[6]**
Self-reported physical activity and sedentary time (REAP)[5]	A5332[3]	A5361s[2]	A5333s[4]	A5361s	A5361s	**A5361s**
Myalgia symptom assessment	A5332[3]	A5332[3]	A5332	A5332	A5332	**A5332**
Samples for inflammatory markers	A5332[3]	A5332[3]				
Fasting lipids and insulin sensitivity	A5332/ A5333s[3]		A5332/ A5333s			**A5332**
CT scan for fatty infiltration of the skeletal trunk muscles	A5333s[3]		A5333s			

[1] Will be available only to participants who enroll concurrently into REPRIEVE (A5332) and A5361s.
[2] Will be available only to participants who enroll into A5361s concurrently or within 12 months of REPRIEVE (A5332) entry.
[3] For participants who enroll into A5361s after REPRIEVE (A5332) entry, the data and samples collected in REPRIEVE and A5333s prior to A5361s entry will be used.
[4] In the event that enrollment is expanded to all A5332 participants, will be captured as part of A5361s for participants not enrolled in A5333s.
[5] Questions 26 and 27 only.
[6] The DASI evaluation from the REPRIEVE (A5332) month 96 or study termination visit will be used.

10.2 Outcome Measures

10.2.1 Primary Outcome Measures

10.2.1.1 Chair rise rate measured annually over **60** months

This primary outcome for the primary physical function objective is a simple transformation of the measured outcome of time to perform 10 chair stands. It is chosen to provide a continuous outcome for participants regardless of their ability to perform 10 chair stands.

It is a well-established measure of lower extremity strength and our previous studies in HIV-infected populations have shown that, among components of the SPPB, this measure is the most likely to show deficits [8,100]. In addition, in middle-age adults from the general population, chair rise rate is a strong independent predictor of mortality [**123**].

10.2.1.2 Inflammatory Index Score (IIS) quantified at 12 months

The IL-6 and TNF-α pathways are both hypothesized to lead to sarcopenia, muscle weakness, and decreased physical function. The IIS was found to be a better predictor than IL-6 or measures of TNF-α activity alone in a geriatric population [100] and is predictive of mortality in an HIV cohort [5]. This validated instrument will be used to address the effect of pitavastatin on systemic inflammation composed of serum IL-6 and sTNFR-1. The score is calculated with the following formula:

$$1/3 \log [\text{IL-6}] + 2/3 \log [\text{sTNFR-1}]$$

10.2.1.3 Paraspinal muscle density measured in Hounsfield units (HU) at REPRIEVE (A5332) entry and month 24.

10.2.2 Secondary Outcome Measures

10.2.2.1 Secondary physical function outcome measures assessed annually for **60** months.

Raw scores for each of the additional components of the SPPB (grip strength, gait speed, ability to hold the one leg stand for 30 seconds) as well as the composite SPPB score (composite scoring of chair stand, balance, and gait) measured annually to month **60**.

Physical function deficits defined as a composite SPPB score ≤10 assessed annually to month **60** [124,**125**].

Frailty (classified as non-frail, pre-frail, and frail) as well as the frequency of its components (exhaustion, weight loss, low activity, slow walk, grip strength) and the number of frailty components present [**126**].

Self-reported physical activity via two questions measured on a three-point ordinal scale on the REAP assessment.

10.2.2.2 Secondary outcome measures for the mechanistic objective quantified at REPRIEVE (A5332) entry and 12 months

Serum concentrations of each individual biomarker of the IIS (IL-6, sTNFR-1) as well as other biomarkers implicated in the pathogenesis of physical function impairment (these may include markers such as sTNFR-2, IP-10, IGF-1, TGF- β1) or those that may mediate the effects of statin treatment on systemic inflammation (CMV IgG).

The specific list of biomarkers of interest may be modified closer to the time of analysis based on the identification of additional biomarkers or pathways involved in this process.

10.2.2.3 Secondary outcome measures for the mechanistic objectives related to fatty infiltration of the skeletal trunk muscles assessed at REPRIEVE (A5332) entry and 24 months:

Shoulder and upper back muscle density measured in HU.

Paraspinal and trunk muscle volume (area).

10.3 Randomization/Registration

Participants will be enrolled into A5361s via the ACTG enrollment system. See section 4.0 for specific information on the timing of A5361s and REPRIEVE (A5332) enrollment.

10.4 Sample Size and Accrual

600 participants will be enrolled over a period of 2 years. Participants will be followed until the time of their **5**-year assessment on REPRIEVE (A5332) (up to **60** months depending on the time of enrollment).

10.4.1 Sample Size Justification for Outcome Measures of Physical Function

Assuming a modest exchangeable correlation between repeated measurements over time (rho=0.6), this sample size will provide 85% power to detect a 0.29 rise/minute/year difference between the pitavastatin and placebo treatment groups and 80% power to detect a more modest difference of 0.27 rise/minute/year difference. These power calculations are based on sample-size

formulae for testing a between group difference in slopes in a repeated measures design as provided by Diggle, Liang, and Zeger [**123**].

Preliminary data from HIV-uninfected adults in the Baltimore Longitudinal Study of Aging (BLSA) suggest an annual age-associated decline of 0.01 m/s in gait speed after age 60 [127]. Among HIV-infected men in the Multicenter AIDS Cohort Study (MACS) cohort, gait speed decline among HIV-uninfected men aged 40 and older was also 0.01 m/s per year [**95**]. In contrast, gait speed among the HIV-infected men from the MACS was 0.025 m/s per year (2.5 times faster decline in HIV-infected compared to HIV-uninfected). A similar annual age-associated decline of 0.29 rises/minute in chair rise time begins at about age 40 [Schrack, et al., unpublished data, 2015]. Based on these differences with gait speed trajectory and similar trajectories in grip strength, we anticipate a two-fold higher rate of decline in chair rise among HIV-infected participants in PREPARE compared to the BLSA, and thus estimate that the annual age-associated decline in chair rise rate in this HIV-infected population will be about 0.58 rises/minute. The target effect size of 0.29 rise/minute/year difference between the pitavastatin and placebo treatment groups thus reflects a normalization of this age-associated decline.

If the primary results of REPRIEVE (A5332) show a benefit of pitavastatin and statins are prescribed among middle-aged HIV-positive adults for primary prevention of cardiovascular disease, long-term statin therapy of 20–30 years would be expected to prevent a decline of 6–9 chair rises/minute into older age. This preservation of function is of major clinical relevance. In the Colorado Cohort, a difference of 5.7 rises/minute was found between non-fallers and single fallers, and 1.8 rises/minute between single fallers and repeat fallers [Erlandson, unpublished data, 2014]. Further, in a large longitudinal cohort of adults followed between ages 53 and 66 in England, a difference between each quintile of the repeat chair stand pace was between 3–5 rises/minute. A worsening from the second slowest to the slowest quintile in this cohort was associated with a nearly two-fold increase in mortality (from HR of 1.44 to 2.13) over 13 years of follow-up [128].

10.4.2 Sample Size Justification for Mechanistic Outcome Measures

With a sample size of 300 participants in each treatment group and conservatively assuming 10% of participants will be inevaluable for either REPRIEVE (A5332) entry or follow-up outcomes; we have 90% power to detect a 0.28 SD difference between the pitavastatin and placebo treatment groups for the systemic markers of inflammation and immune activation. For IIS, the magnitude of this change has been shown to be associated with a 10% increase in 10-year mortality risk [129].

For fat attenuation, with an estimated 20% drop-out or non-evaluable scans and standard deviation of 6 [130], we will have 95% power to detect a difference in paraspinal muscle density of 1.8 HU between the two groups. A difference of 1–3

HU is considered clinically significant and is the effect observed in exercise interventions [114,116-118] .

10.5 Data and Safety Monitoring

A5361s is a prospective, observational study of participants enrolled into REPRIEVE (A5332) **with or without co-enrollment into** A5333s in which no treatment or intervention is provided. The statisticians will prepare quarterly administrative reports. These reports will include participant REPRIEVE (A5332) and A5361s entry information and will also note protocol execution issues such as participant accrual, participant retention, co-enrollment, and endpoint evaluability.

Details of the aforementioned reports will be described in a Study **Progress, Data, and Safety** Monitoring Plan prepared by SDAC prior to enrollment of the first participant.

10.5.1 Interim Monitoring Guidelines

In accordance with the ACTG SOP for Study Data and Safety Monitoring, the Protocol Team will review study enrollment, conduct and feasibility. Benchmarks for data are as follows:

- Enrollment of 600 study participants will be completed over a period of 2 years from enrollment of the first study participant.
- 90% of expected data are available across time points.

10.6 Analyses

The following sections provide a brief overview of the general analytic approaches for the A5361s primary analysis. A detailed plan that fully delineates all planned statistical analyses, and includes secondary and exploratory objectives, will be in a separate Statistical Analysis Plan (SAP).

10.6.1 Effects of Pitavastatin on Physical Function

Descriptive statistics (median, Q1, Q3, P10, P90, min, max) and graphical presentations of each component of the SPPB, its composite score as well as the prevalence of physical function deficits (SPPB ≤10) will be examined at REPRIEVE (A5332) entry and over time. A5361s entry evaluations performed after the start of REPRIEVE (A5332) study treatment will be excluded from these summaries.

Analyses of chair rise rate will use linear mixed effects models with time modeled on a continuous scale, where REPRIEVE (A5332) entry is time 0.

The primary parameter of interest will be the difference in the rate of change (slope) between placebo and pitavastatin over time (i.e., the interaction between treatment and time). The primary analysis will include available measured outcomes (including those obtained at REPRIEVE [A5332] entry) in the outcome

vector and will omit the treatment group main effect (intercept) from the model. This approach allows for variable evaluation time and inclusion of data for all participants regardless of their time of entry into A5361s. It takes advantage of the fact that randomized group allocation in REPRIEVE (A5332) means that there is no underlying difference in physical function between treatment groups at REPRIEVE (A5332) entry and will be the most powerful [131]. Further, the analysis will be robust in the event of uneven participant drop-out related to the rate of decline in physical impairment. In the event of non-linear change in outcome over time, we will first assess alternative transformations of the outcomes or time axis. If such transformations are not feasible, modeling will be performed using an arbitrary time effect (i.e., time modeled as a factor on four levels). In this case, the treatment effect of interest for the primary treatment group comparison will be the average difference across post-baseline time points; an interaction of treatment and time will also be assessed and secondary comparisons by year will also presented. It is noted that the power of the study to detect a comparable effect size is reduced under this alternative modelling framework.

These primary analyses will be extended to evaluate subgroup effects of treatment, namely different treatment effects by race (white vs non-white), sex, baseline CD4 cell count (<350 cell/mm vs. ≥350 cells/mm), ART duration (categorized as <10 or ≥10 years), physical function deficits at REPRIEVE (A5332) entry (SPPB **≤**10 vs. **>**10), and systemic inflammation (by tertile of IIS) at REPRIEVE (A5332) entry. Sensitivity analyses excluding participants who enrolled into A5361s after REPRIEVE (A5332) entry will also be performed.

Given the expected discretized distribution of the remaining SPPB outcomes (including the overall composite score), longitudinal analyses for these measures as well as the self-reported physical function outcomes from the REAP assessment will use the methods of Wei and Johnson to provide an overall assessment of treatment group differences between the groups over time.

The prevalence of the frailty phenotypes and their components over time and by treatment group will be described. Treatment group differences in the prevalence of the frailty phenotype (non-frail, pre-frail, frail) will be assessed via marginal modeling with a cumulative logit using generalized estimating equations.

10.6.2 Evaluation of the mechanistic pathways through which pitavastatin affects physical function

Distributions of the secondary biomarker outcomes as well as outcomes of fatty muscle infiltration will be described and plotted over time. Pointwise treatment group comparisons will use linear regression adjusted for baseline to provide estimation of the difference in the baseline-adjusted level of the outcomes at each time point. Outcome transformations will be applied as appropriate. Treatment group comparisons of markers of inflammation and immune activation will be limited to those not described in A5333s. Analyses of fatty infiltration of

muscle will also assess the association of these changes with changes in lipid components and HOMA-IR.

The relationship between markers of inflammation/immune activation, fatty infiltration, and physical function will be assessed via longitudinal modeling of the chair rise rate and expanding each of the appropriate models used to assess treatment group difference including pre- and post-treatment biomarker and fatty infiltration outcomes. The analyses will also examine associations with the following measured covariates/risk factors:

- Demographic and behavioral variables (age, race, sex, menopausal status, BMI, smoking, alcohol use, physical activity by REAP)
- Co-morbid conditions (HBV/HCV, hypertension, diabetes mellitus, chronic kidney disease)
- Use of angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker (ACE-I/ARB) therapy
- HIV-related variables (CD4 cell count [nadir and current]), HIV RNA, antiretroviral exposure (cumulative and current exposure to ART)
- Muscle symptoms (via the myalgia symptom assessment collected through REPRIEVE [A5332])
- Concomitant medications, specifically, ACE-I/ARB therapy and use of hormonal therapy

Given the assumed temporal associations under study, analyses, including on-treatment measures of biomarkers and fatty muscle infiltration, will only include dependent outcomes assessed from month 24 onward. These analyses will be conducted with and without adjustment for treatment assignment to allow assessment of the degree to which the effects of treatment might be mediated through treatment-associated changes. While further, more formal causal mediation analyses are planned, given the expected statistical developments in the relevant statistical methodology over the next 5 years, these analysis plans will be developed closer to the time of analysis.

11.0 PHARMACOLOGY PLAN

Not applicable.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form screens (eCRFs) will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

12.2 Role of Data Management

12.2.1 Instructions for entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [132]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solutions. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, or legal guardian and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, NIA, NIAID, NHLBI, OHRP, **and** other **US, local, and international regulatory entities** as part of their duties.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, NIA, NIAID, NHLBI, OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this study will be governed by ACTG and REPRIEVE policies.

15.0 BIOHAZARD CONTAINMENT

Not Applicable

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APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

For Protocol A5361s: Pitavastatin to REduce Physical Function Impairment and FRailty in HIV (PREPARE)

SHORT TITLE FOR THE STUDY: PREPARE Substudy of REPRIEVE (A5332)
Final Version **2.0**, Dated **06 July 2021**

SUMMARY

PURPOSE:
The purpose of this study is to investigate the effect of pitavastatin in slowing frailty (weakness) or disability in people who are aging with HIV. Pitavastatin belongs to a group of drugs called statins. Studies have shown that statins may have other benefits, one of which may be helping slow the development of frailty or disability that occur with aging.

NUMBER OF PARTICIPANTS:
About 600 people who also participate in the REPRIEVE Study (A5332) and REPRIEVE Mechanistic Substudy (A5333s) or the REPRIEVE Study (A5332) only.

STUDY TREATMENT:
There is no treatment provided in this study.

LENGTH OF STUDY:
Initially, you were going to be in this study for up to 48 months, depending on when you joined. Due to the COVID-19 pandemic, this study has been extended to up to 60 months, which will result in an additional visit about one year after your last on this study.

REQUIRED ACTIVITIES:
You will have physical function tests to measure your muscle strength and function:
- **Repeated chair rises**
- **Hand grip strength test**
- **Standing balance test**
- **4-Meter (12 foot) walk**

RISKS:
It is possible that you may trip, slip, or fall while doing the physical function tests.

BENEFITS:
No direct benefits should be expected from participating in this study.

OTHER CHOICES:
You have the option of not participating in this substudy and still participating in the REPRIEVE Study (A5332) and REPRIEVE Mechanistic Substudy (A5333s).

INTRODUCTION

You are being asked to take part in this research study because you are infected with human immunodeficiency virus (HIV), the virus that causes AIDS, and are currently enrolled in the REPRIEVE (A5332) **with or without co-enrollment into** A5333s studies at an ACTG site. The PREPARE A5361s substudy is sponsored by the National Institutes of Health (NIH). The doctor in charge of this substudy at this site is (insert name of Principal Investigator). Before you decide if you want to be a part of this substudy, we want you to know about the substudy.

This is a consent form. It gives you information about this substudy. The study staff will talk with you about this information. You are free to ask questions about this substudy at any time. If you agree to take part in this substudy, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS SUBSTUDY BEING DONE?

Aging with HIV may be related to an earlier development of frailty (weakness) or disability, including difficulties in tests of strength or walking speed. Few treatments have been shown to prevent or slow these impairments in people with or without HIV. Some studies have suggested that the class of drugs called statins (for example, pitavastatin) might be helpful in slowing frailty or disability. This might happen by decreasing fat within the muscle or by decreasing inflammation markers (substances in the blood that determine how your body reacts to infection or irritation) in the blood. Other studies have shown that statins increase the risk of muscle aches and pains. This substudy is being done to determine the impact of the drug pitavastatin on muscle.

WHAT DO I HAVE TO DO IF I AM IN THIS SUBSTUDY?

If you would like to take part in this substudy, you will be asked to sign this consent form.

At the study entry visit and at yearly visits coinciding with your REPRIEVE (A5332) study visits, we will measure your muscle strength and muscle function through several tests. These tests include repeated chair rises, hand grip strength test, standing balance test, and a 4-meter (12 foot) walk and should take no more than 20 minutes to complete. You will also be asked some questions about your physical activity at the month 12, **24,** 36**,** 48**, and 60** visits. You will be asked in an average week, how often do you: (usually/often, sometimes, rarely/never, does not apply):
Do less than 30 total minutes of physical activity 3 days a week or more?
Watch more than 2 hours of television or videos a day?

Your answers to questions about your ability to perform everyday tasks that you will be asked at your last REPRIEVE (A5332) study visit will be used as part of your month 60 evaluation in this substudy.

If you are also enrolled in A5333s, we will measure the muscle size and amount of muscle fat from the CT scan that was done as a part of your involvement in REPRIEVE (A5332) and A5333s. We will also measure changes in various substances in your blood related to inflammation and immune function (how your body reacts to infection) using blood that was collected as part of your involvement in REPRIEVE (A5332) and/or the Mechanistic Substudy of REPRIEVE (A5333s). Please note that no additional CT scans will be completed and no extra blood samples will be collected as part of this substudy.

You can receive the results of your physical function assessments at the time of your visit if you are interested. The results of the laboratory analyses and CT scans will not be reported to you.

COVID-19 Pandemic Considerations

During the COVID-19 pandemic, the following adjustments may be made to your study visits:

- **If you have an in-person REPRIEVE (A5332) study visit, you will also have the visit for this substudy that is due at the same time.**
- **If you have an in-person REPRIEVE (A5332) study visit but there are some tests for this sub-study that could not be completed because of local restrictions, the tests will be completed at your next in-person REPRIEVE (A5332) study visit if the restrictions have been lifted by then.**
- **If your in-person REPRIEVE (A5332) study visit is delayed or missed, and you had a visit for this substudy due at the same time, you will have the visit for this substudy when you are next seen in the study clinic for an in-person REPRIEVE (A5332) visit.**

Premature Discontinuation Evaluation

If you stop participating in the REPRIEVE (A5332) study early you will also have to stop participating in this study. You will be asked to return to the clinic to have premature study discontinuation evaluations completed. These evaluations will take about 30 minutes and include the same assessment of your physical function as you would have at other study visits.

HOW MANY PEOPLE WILL TAKE PART IN THIS SUBSTUDY?

About 600 people will take part in this study.

HOW LONG WILL I BE IN THIS SUBSTUDY?

You will be in this substudy for up to **60** months, depending on when you join.

WHY WOULD THE DOCTOR TAKE ME OFF THIS SUBSTUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- The substudy is stopped or cancelled.
- You are not able to attend the study visits as required by the REPRIEVE (A5332) study.

- You withdraw from the REPRIEVE (A5332) study.
- Your primary care provider requests to take you off the study because the study is no longer in your best interest.

WHAT ARE THE RISKS OF THE SUBSTUDY?

The physical function tests are designed to be like your usual activities. These tests are associated with a small risk of tripping, slipping, or falling.

ARE THERE RISKS RELATED TO PREGNANCY?

This is an observational substudy in which no study treatment is provided, so there are no risks related to pregnancy in this study.

ARE THERE BENEFITS TO TAKING PART IN THIS SUBSTUDY?

If you take part in this substudy, there may not be a direct benefit to you. The results of your physical function assessments will be shared with you at the time of these assessments. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS SUBSTUDY?

You can choose not to be in this substudy and still participate in the REPRIEVE (A5332) study.

Please talk to your doctor about this and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protections, or other **US, local, and international regulatory entities** as part of their duties, (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), NIH, study staff, and study monitors. Having a Certificate of Confidentiality does not prevent you from releasing information about you and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child

abuse and/or neglect or a risk of harm to your or others, we will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME?

Taking part in this substudy may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

You will receive $25 for each substudy visit that you complete (up to a total of $**150**).

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this substudy, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this substudy is completely voluntary. You may choose not to take part in this substudy or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the substudy, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this substudy or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:

- Name or title of person on the IRB or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this substudy, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Representative (print) (As appropriate)	Legal Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date