A5371

A Single-Arm, Open-Label, Pilot Study of Semaglutide for Non-Alcoholic Fatty Liver Disease (NAFLD), a Metabolic Syndrome with Insulin Resistance, Increased Hepatic Lipids, and Increased Cardiovascular Disease Risk (The SLIM LIVER Study)

A Limited-Center Trial of the AIDS Clinical Trials Group (ACTG)

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ACTG
AIDS CLINICAL TRIALS GROUP

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A Single-Arm, Open-Label, Pilot Study of Semaglutide for Non-Alcoholic Fatty Liver Disease (NAFLD), a Metabolic Syndrome with Insulin Resistance, Increased Hepatic Lipids, and Increased Cardiovascular Disease Risk (The SLIM LIVER Study)

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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 U.S. 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.

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Print/Type

Signed: _____ Date: _____
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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5371@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5371@fstrf.org. A response should generally be received within 24 hours (Monday through 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.protA5371 e-mail group. Include the protocol number in the e-mail subject line.

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

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management Committee (CMC).

- Send an e-mail message to actg.cmcA5371@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to immunologic laboratory tests, contact the protocol immunologists, Alan Landay and Jennifer Kinslow.

- Send an e-mail message to alanday@rush.edu and jennifer_kinslow@rush.edu, with a cc to: actg.teamA5371@fstrf.org.

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. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact **Kathleen Donahue and Autumn Rolack** directly.
- For other questions, send an e-mail message to actg.teamA5371@fstrf.org (ATTENTION: **Kathleen Donahue and Autumn Rolack**).
- Include the protocol number, PID, and a detailed question.

Participant Registration
For participant registration questions or problems and study identification number (SID) lists:

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

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- 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.teamA5371@fstrf.org (ATTENTION: Christina Vernon).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@**dlhcorp**.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation at US sites, contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5371@fstrf.org (ATTENTION: Christina Vernon).

For questions related to protocol activation at non-US sites, contact the ACTG Site Coordination Group.
- Send an email message to actgsitecoordination@**dlhcorp**.com.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Justine Beck or Dapo Alli, Protocol Pharmacists, at 301-496-8213.

Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
The IND number **is** available on the protocol-specific web page (PSWP). For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax to 1-800-275-7619 or 301-897-1710.

Telephone Calls

Sites are responsible for documenting telephone calls made to A5371 team members.

- Send an e-mail message to actg.teamA5371@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

AASLD	American Association for the Study of Liver Diseases
ART	antiretroviral treatment
BMI	body mass index
CrCl	creatinine clearance
CRP	C-reactive protein
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase-4
FFA	free fatty acid
GLP	glucagon-like peptide
HAV IgM	**hepatitis A virus immunoglobulin M**
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
HS	high-sensitivity
IHTG	intra-hepatic triglyceride
iNKT	invariant natural killer T
IQA	immunology quality assurance
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MACS	Multicenter AIDS Cohort Study
MCP-1	monocyte chemoattractant protein-1
MEN2	multiple endocrine neoplasia type 2
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
MRS	magnetic resonance spectroscopy
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NRTI	nucleoside reverse transcriptase inhibitor
PE	**physical exam**
PLWH	people living with HIV
SAT	subcutaneous adipose tissue
SC	subcutaneous

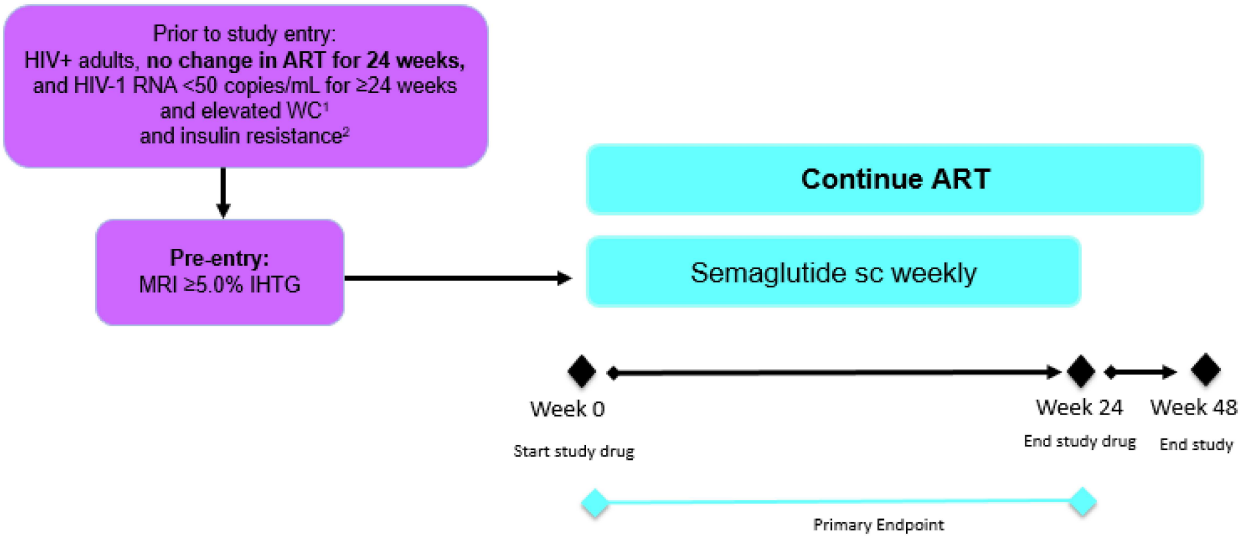
TG	triglyceride
TNF	tumor necrosis factor
TSH	**thyroid-stimulating hormone**
VAT	visceral adipose tissue
VLDL	very low-density lipoprotein
VQA	Virology Quality Assurance
WC	waist circumference

SCHEMA

A5371

A Single-Arm, Open-Label, Pilot Study of Semaglutide for Non-Alcoholic Fatty Liver Disease (NAFLD), a Metabolic Syndrome with Insulin Resistance, Increased Hepatic Lipids, and Increased Cardiovascular Disease Risk
(The SLIM LIVER Study)

DESIGN	A5371 is a phase II, single-arm, open-label, pilot study of the effects of semaglutide on intra-hepatic triglyceride (IHTG) content in **people** living with HIV **(PLWH)**, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis. IHTG will be quantified by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at two time points. Participants will also complete food diaries, adherence and strength assessments, and report on physical activity. Stool and blood samples will be collected at several visits. **Refer to the Protocol Synopsis for more details (Appendix I).**
DURATION	Approximately 48 weeks.
SAMPLE SIZE	50 participants.
POPULATION	Adults ≥18 years of age with HIV**,** not meeting criteria for diabetes but with central adiposity (i.e., minimum waist circumference **(WC)** of ≥95 cm for individuals assigned male sex at birth or ≥94 cm for individuals assigned female sex at birth), ≥5% IHTG content, plus at least one of the following indicators of insulin resistance or pre-diabetes: fasting plasma glucose 100-125 mg/dL, HbA1c between 5.7 and <6.5%, or HOMA-IR >3.0.
REGIMEN	Participants will all receive semaglutide subcutaneously once weekly for 24 weeks. Participants will receive a dose of 0.25 mg weekly starting at entry, followed by 0.5 mg weekly starting at week 2, and then 1.0 mg weekly from weeks 4 through 24. During weeks 25-48, all participants will be off study drug.



[1]≥95cm for individuals assigned male sex at birth/≥94cm for individuals assigned female sex at birth
[2]Fasting plasma glucose 100-125 mg/dL, HbA1c between 5.7 and <6.5%, or HOMA-IR>3.0

Schema Figure **1: Schema Diagram**

SCHEMA (Cont'd)

Screening: ≥18 y/o, PWH, WC≥95 cm for males or ≥94 cm for females, pre-diabetic by 1 of the following: fasting glucose 100-125, or HbA1c 5.7 to <6.5%, or HOMA –IR >3.0

↓

Main Entry criteria: MRI ≥5% IHTG, CD4 ≥200 cells/mm^3, CrCl ≥50 mL/min, AST and ALT both <3x ULN, Fasting TG ≤500 mg/dL, if on lipid lowering medications, stable regimen, not pregnant, willing to use contraception
Main Exclusion criteria: HAV infection, HBV infection, known delayed gastric emptying, HCV infection (not treated and cured), recent wt loss or gain of >5% body wt, current dx of DM.

↓

Study Design and Schedule of Activities
N=50

Study Week	Semaglutide Dose, weekly	Study event	Assessments
Entry 0	0.25 mg	Entry	Physical function, QoL, Diet, Stool sample, Injection training, PE, Safety labs: ALT, AST. Glucose. HbA1c, Lipids
1	0.25 mg		Phone/email symptom & adherence check
2	0.5 mg	Dose escalation	Phone/email symptom& adherence check
3	0.5 mg		Phone/email symptom & adherence check
4	1.0 mg	Final dose escalation	PE, Safety labs: ALT, AST. Glucose, HIV-1 PCR

Study Design and Schedule of Activities
N=50

Study Week	Semaglutide Dose, weekly	Study event	Labs and F/U
8	1.0 mg		Phone/email symptom& adherence check
12	1.0 mg		PE, Safety labs: ALT, AST. Glucose. HbA1c, Lipids, HIV-1 PCR
16	1.0 mg		Phone/email symptom& adherence check
20	1.0 mg		Phone/email symptom& adherence check
24	1.0 mg	Primary endpoint	Primary endpoint evaluations: MRI for IHTG, Lipids, HbA1c, Safety labs: ALT, AST. Glucose, HIV-1 PCR
48	(off drug)	Final visit	PE, Safety labs: ALT, AST. Glucose. HbA1c, Lipids

Schema Figure 2: Schema Flowchart

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Primary Hypothesis

Among antiretroviral therapy (ART)-treated, virologically suppressed adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes, 24 weeks of semaglutide will result in reductions in intra-hepatic triglyceride (IHTG) content, as quantified by magnetic resonance imaging-proton density fat fraction (MRI-PDFF).

1.1.2 Secondary Hypotheses

1.1.2.1 Semaglutide will be safe and well tolerated.

1.1.2.2 Semaglutide will improve cardiometabolic parameters central to the pathogenesis of atherosclerosis and increased cardiovascular risks.

1.2 Primary Objective

To evaluate whether semaglutide will reduce IHTG content, as quantified by MRI-PDFF, among ART-treated adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes.

1.3 Secondary Objectives

1.3.1 To evaluate the safety and tolerability of semaglutide in adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes.

1.3.2 To evaluate the effects of semaglutide on weight, minimum waist circumference (WC), and body mass index (BMI).

1.3.3 To evaluate the effects of semaglutide on insulin resistance or pre-diabetes, lipid profiles, and the prevalence of metabolic syndrome.

1.3.4 To evaluate relationships between observed changes in IHTG (refer to 1.2) and changes in metabolic parameters (refer to 1.3.2).

1.4 Exploratory Objectives

NOTE: Exploratory objectives will be explored dependent on results of primary and secondary outcomes.

1.4.1 To evaluate the durability of semaglutide on weight, minimum WC, and BMI after cessation of study therapy.

1.4.2 To evaluate the relationships between systemic measures of carbohydrate and lipid metabolism and a) IHTG and b) visceral adipose tissue (VAT) area in participants treated with semaglutide.

1.4.3 To evaluate the effects of semaglutide on MRI-quantified VAT and abdominal subcutaneous adipose tissue (SAT) area and density.

1.4.4 To evaluate the effects of semaglutide on circulating inflammatory biomarker and adipocytokine levels.

1.4.5 To evaluate the effects of semaglutide on muscle function, muscle area, and muscle fat.

1.4.6 To evaluate the effects of semaglutide adherence on primary and secondary outcomes.

1.4.7 To evaluate the effects of semaglutide on self-reported quality of life.

1.4.8 To evaluate the effects of semaglutide on the gut microbiome.

1.4.9 To evaluate relationships between changes in IHTG content and changes in VAT and SAT area and muscle fat quantity.

1.4.10 To evaluate the effects of semaglutide on circulating immune cell profiles.

2.0 INTRODUCTION

2.1 Background

Epidemiology

Thirty to 40% of adults with HIV also have Non-Alcoholic Fatty Liver Disease (NAFLD, defined as ≥5% hepatic steatosis without other demonstrable causes) [Guaraldi 2008, Crum-Cianflone 2009, Hadigan 2007, Morse 2015]. NAFLD is universally associated with steatosis, may progress to non-alcoholic steatohepatitis (NASH), and may be further complicated by cirrhosis, liver failure, and hepatocellular carcinoma [Schuppan 2013].

However, most of the excess morbidity and mortality associated with NAFLD is due to cardiovascular disease (CVD) [Targher 2005, Targher 2007, Targher 2010, Haring 2009, Adams 2005, Bhala 2011, Rafiq 2009, Ekstedt 2006, Musso 2011]. This is not surprising, since 80-90% of adults with NAFLD have generalized obesity, visceral adiposity, metabolic syndrome, or type 2 diabetes [Guaraldi 2008]. Further, IHTG accumulation is more closely linked to metabolic complications than VAT quantity in HIV and the general population [Alderete 2013, Fabbrini 2009, Korenblat 2008, Reeds 2017]. For example, in a study of over 358 adolescents, liver fat was more strongly associated with insulin sensitivity than visceral fat, with a greater prevalence in African Americans than Hispanics [Alderete 2013]. Additionally, NAFLD promotes a pro-inflammatory

environment [Gariani 2013] that could worsen the chronic immune activation and inflammation observed in people living with HIV (PLWH).

Adults with HIV and NAFLD have greater pre-atherosclerosis burden than matched adults without HIV [Sookoian 2008, Vodkin & Loomba 2015, Vodkin 2015]. Increased CVD risk with HIV infection is likely multifactorial, stemming from both traditional and HIV- and ART-specific risk factors. Importantly, NAFLD is a modifiable CVD risk factor. By reducing IHTG, insulin resistance, and its associated chronic pro-inflammatory environment, major contributors to CVD in persons with HIV should be lessened. Therefore, prevention and treatment of NAFLD is important to the health of individuals with HIV independent of prevention of progressive liver disease. Despite this, little is known about the natural history and/or pathophysiology of NAFLD in treated HIV infection, and persons with HIV have historically been excluded from trials of NAFLD/NASH therapies.

Pathogenesis

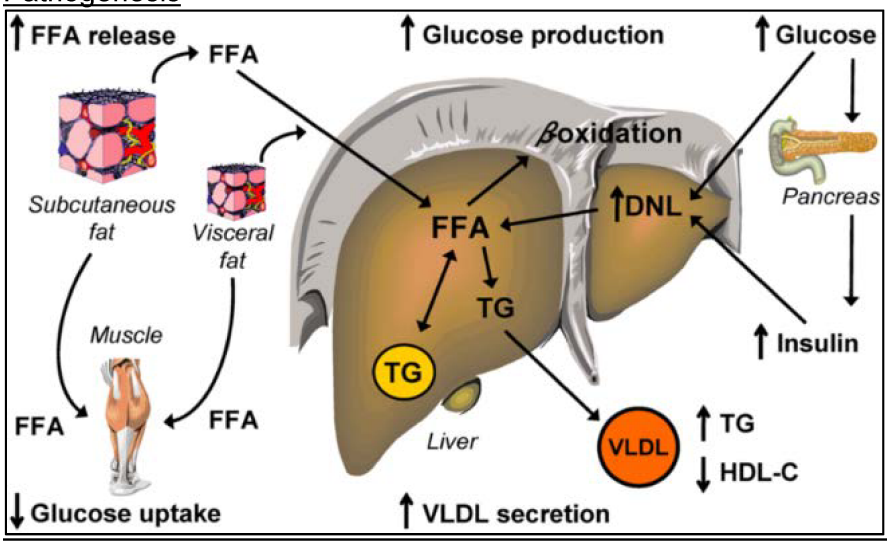


Figure 2.1-1: Metabolic origins of NAFLD.

The origins of NAFLD (Figure 2.1-1) are primarily metabolic and begin with lipolysis of VAT and SAT, which releases free fatty acids (FFAs) into the portal and systemic circulations. These FFAs concentrate in hepatocytes where they undergo three disposition pathways: 1) re-esterification to triglycerides (TG), which are then packaged and released back into the systemic circulation as very low-density lipoprotein (VLDL); 2) beta-oxidation to acetyl-CoA to enter the Krebs cycle; or 3) storage as IHTG. With IHTG accumulation, insulin signaling in the liver is impaired and hepatic glucose production is not effectively suppressed by insulin. Excess hepatic glucose undergoes *de novo* lipogenesis, furthering the cycle of aberrant IHTG storage and worsening hepatic steatosis.

IHTG are lipotoxic to hepatocytes [Cusi 2012, Neuschwander-Tetri 2010, Armstrong 2014, Birkenfeld 2014] and activate stress kinase and cell death signaling pathways,

leading to apoptosis and autophagy [Schuppan 2013, Gariani 2013]. These processes increase hepatic oxidative stress and inflammation, which further impair insulin signaling [Gariani 2013]. This is important since insulin resistance promotes atherosclerosis and impairs endothelial function, increasing the risk for CVD morbidity and mortality [Calori 2011].

The pathogenesis of NAFLD may be enhanced in and complicated by HIV infection. Although the exact mechanisms are not well understood, there may be several contributing factors not common in persons without HIV. First, HIV infection is characterized by persistent inflammation and immune activation [Vallet-Pichard 2012], which contributes to greater insulin resistance, furthering liver-associated metabolic dysregulation. Thus, the combination of traditional NAFLD pathogenesis and HIV-associated systemic and tissue level immuno-metabolic dysregulation could help explain apparent greater NAFLD severity in HIV infection [Vodkin 2015]. Second, in addition to traditional risk factors (older age, sedentary lifestyle), HIV-/ART-specific contributors to NAFLD and immuno-metabolic disturbances include dyslipidemia, microbial translocation from persistent gut barrier breach that does not reverse with ART, and mitochondrial dysfunction (Figure 2.1-2). As such, both traditional and HIV-/ART-specific NAFLD contributors should be considered when developing therapeutics.

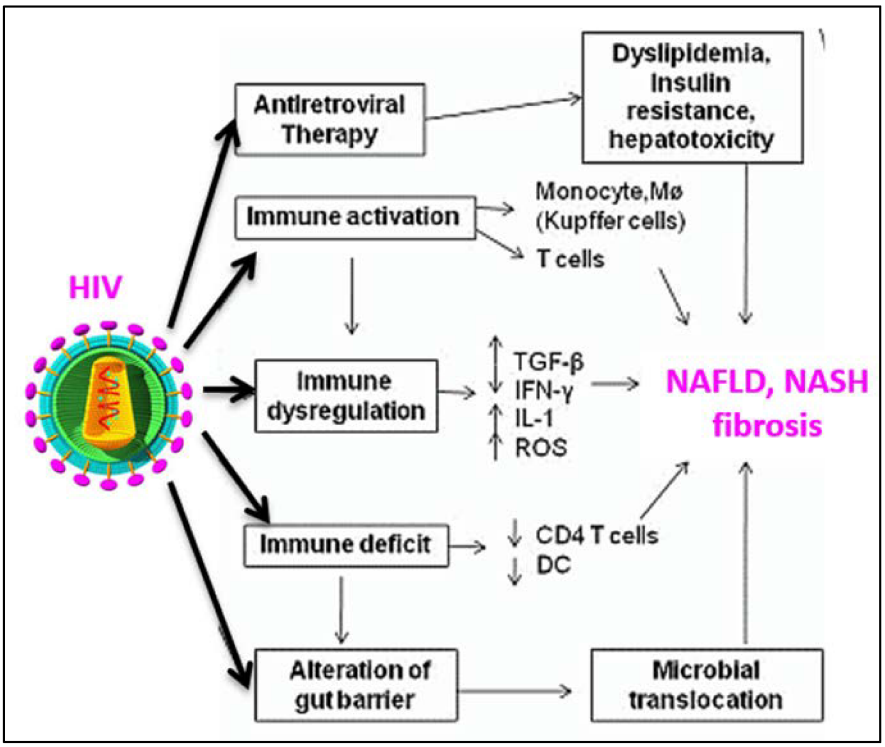


Figure 2.1-2: Factors contributing to NAFLD in treated HIV infection [adapted from Mastroianni 2014].

Complicating the NAFLD landscape in HIV is the recently identified weight gain associated with integrase strand transfer inhibitors (INSTIs). Newer INSTIs in particular

are associated with greater weight gain compared to non-INSTI based regimens both among patients initiating or switching therapy. Multiple studies have identified that a low CD4 count, high HIV-1 RNA, female sex, and black race seem to be consistent risk factors predicting a greater weight gain. The metabolic consequences of this weight gain are also not well understood, though the added weight gain is expected to further contribute to the incidence of NAFLD in HIV. As the mechanisms of this weight gain are not understood, there are currently no treatment recommendations to prevent or reverse the weight gain outside of lifestyle modification. Although A5371 will not be specifically focused on INSTI-associated weight gain, the study will provide preliminary data in persons with HIV (PWH) on the safety, tolerability, and efficacy of weight loss of a therapy with demonstrated weight loss efficacy in the general population.

Current Therapeutic Options

A critically important goal of NAFLD treatment is the reduction of IHTG storage to improve insulin signaling and attenuate cardiometabolic risk. IHTG reduction may also attenuate immunopathologic processes, including those leading to chronic liver damage. We propose a pilot, single-arm, pharmacologic approach to reduce IHTG treatment in adults with HIV on suppressive ART and with central adiposity, hepatic steatosis, and insulin resistance.

The American Association for the Study of Liver Diseases (AASLD) Guidelines for NAFLD treatment currently recommend 5-10% weight loss as first line therapy [Chalasani 2012, Harrison 2007, Musso 2010]. However, weight loss is often difficult to achieve and sustain with diet and exercise alone. Additionally, traditional diet and exercise regimens for weight loss may have insufficient efficacy in persons with HIV, although data are mixed [Lake 2017, O'Brien 2017]. Comorbid states like cardio-autonomic dysfunction [Cade 2008], frailty, peripheral neuropathy, and gait disturbances are common among aging persons with HIV [Berner 2017], and can affect exercise capacity, which may also be limited by obesity that accompanies NAFLD. Thus, alternative interventions are needed for this population.

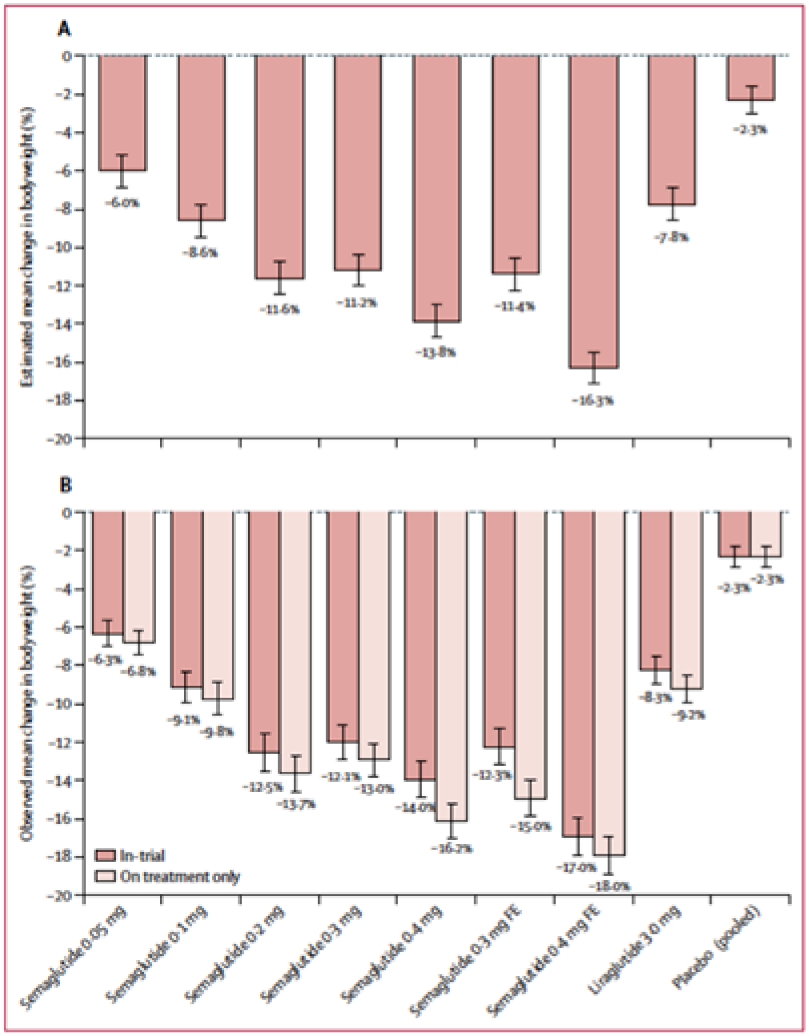
2.2 Rationale

Semaglutide

Semaglutide is a long-acting glucagon-like peptide (GLP)-1 receptor agonist that is FDA-approved at doses of up to 1 mg subcutaneous (sc) weekly for the treatment of diabetes, and is in phase III trials at doses between 1.0 and 2.4 mg weekly (mostly commonly max 2.4 mg weekly, titrated to participant tolerance) for weight loss and cardiovascular risk reduction in both diabetic adults and overweight and obese adults without diabetes [www.clinicaltrials.gov]. In registrational trials of semaglutide 1.0 mg weekly for the treatment of diabetes, significantly greater weight loss occurred with semaglutide than placebo or active comparator in all BMI groups (SUSTAIN 1-5), and CVD events were reduced over 2 years with semaglutide therapy (SUSTAIN 6) [Ahrén 2018].

In Phase II studies of semaglutide for weight loss in non-diabetic adults with BMI $\geq$30 kg/m^2, significant weight loss occurred proportional to the semaglutide dose (mean differences of -6% to -14% weight loss over 52 weeks for doses equivalent to 0.35-2.8

mg weekly, respectively) and weight loss was significantly greater than with liraglutide (a once daily GLP-1 agonist) or placebo (each in combination with diet and lifestyle recommendations) and did not plateau prior to 52 weeks (Figure 2.2-1) Categorically, 73%-84% of participants on semaglutide 0.1-0.2 mg daily/0.7-1.4 mg weekly lost at least 5% body weight, and 43%-64% lost at least 10% body weight over 52 weeks.



Error bars are SEMs. Estimated changes (primary endpoint) are ANCOVA-modelled with jump-to-reference multiple imputation of missing data. Observed changes are without imputation and use either all available data at week 52 (in-trial) or only data from those still on treatment. FE=fast (2-weekly) dose escalation.

Figure 2.2-1 Estimated mean changes (A) and observed mean changes (B) in bodyweight from baseline to week 52.

Safety of semaglutide for weight loss has been demonstrated, with few drug-drug interactions [Madsbad 2016] and low rates of mild-to-moderate, transient treatment emergent nausea as the primary event (approximately 15% of persons across the dosing spectrum of 0.35-2.8 mg weekly, with lower frequency of nausea at lower doses).

At 1.0 mg weekly in obese adults (n=30), semaglutide for *12 weeks* led to a 24% decrease in caloric intake, improved satiety, and a 5.0 kg mean body weight loss that was predominantly fat mass [Blundell 2017]. Other benefits in non-diabetic persons receiving semaglutide included reduced WC, blood pressure, glucose, HbA1c, and high-sensitivity-C-reactive protein (hs-CRP), improved lipid profiles and dose-dependent trends towards improvements in physical function scores [O'Neil 2018].

Additional GLP-1 agonist class data

GLP-1 agonism reduces intra-hepatic fat in diabetic adults without HIV [Cuthbertson 2012, Tang 2016, Feng 2017, Ishii 2019], as well as visceral fat content [Ishii 2019]. We postulate that semaglutide will reduce fat mass (and thus circulation of FFAs from lipolysis), improve insulin glucose homeostasis, and decrease circulating TG levels, which are together expected to reduce IHTG. Indeed, among 57 women with polycystic ovarian syndrome who were not required to have hepatic steatosis at entry, liraglutide 1.8 mg daily resulted in a 44% relative reduction in magnetic resonance spectroscopy (MRS)-quantified liver fat over *26 weeks* [Frossing 2017]. Similarly, in obese, non-diabetic Asian adults with NAFLD, liraglutide 3 mg resulted in a 7.2% absolute reduction in liver fat over *26 weeks* [Khoo 2017], and a 53% relative reduction/17% absolute reduction in obese, diabetic Japanese adults [Ishii 2019].

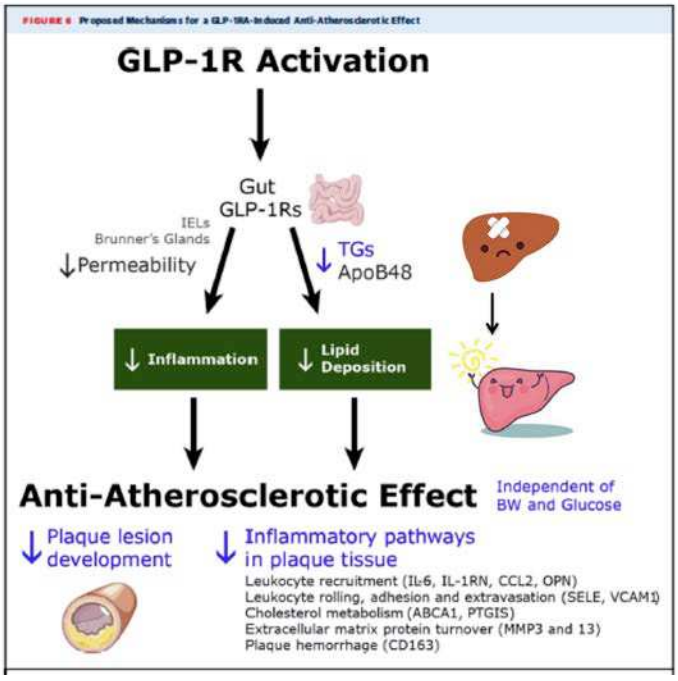


Figure 2.2-2: Proposed mechanisms for a GLP-1RA induced anti-atherosclerotic effect.

Regarding NASH, in a mouse model, semaglutide therapy reduced fibrosis and inflammation in addition to IHTG [Rakipovski 2018]. In the LEAN trial, liraglutide 1.8 mg daily prevented worsening of fibrosis [Armstrong 2016]. Finally, reduced circulating GLP-

1 levels and reduced hepatic GLP-1 and dipeptidyl peptidase-4 (DPP-4) receptor expression has been demonstrated in NAFLD patients [Miyazaki 2012], suggesting a role for GLP-1 in NAFLD.

GLP-1 agonism increases prandial insulin secretion, decreases prandial glucagon secretion, reduces TG levels and oxidized low-density lipoprotein (LDL) cholesterol uptake, suppresses appetite, improves hepatic and subcutaneous insulin sensitivity, and reduces lipotoxicity [Armstrong 2016, Tashiro 2014]. Together, loss of fat mass, reduced IHTG and improved metabolism may result in reduced systemic inflammation [Hannah 2016]. Semaglutide induces greater weight loss than liraglutide [O'Neil 2018], and weight loss does not plateau early in use, as with liraglutide [Astrup 2009, Pratley 2011]. As such, the benefits on IHTG are expected to be at least as great with semaglutide therapy, if not greater.

Other potential benefits of GLP-1 agonism include delay of diabetes onset in overweight and obese adults with pre-diabetes (hazard ratio 0.21, 95% confidence interval 0.13, 0.34) [le Roux 2017], *in vitro* and *in vivo* cardioprotective effects [Hu 2017, Rakipovski 2018, Marso 2016], and similar rates of serious adverse events as placebo [le Roux 2017]. Importantly, CVD risk reduction with GLP-1 agonism is not thought to be secondary to glucose-lowering [Kaul 2017], but other secondary effects, potentially including reduced visceral fat and NAFLD burden, which reduce systemic inflammation (Figure 2.2-2).

Indeed, GLP-1 agonism has been associated with reduced systemic inflammation, including reduced interleukins 1β and 6, tumor necrosis factor (TNF)-α, soluble CD163 [Hogan 2014], plasminogen activator inhibitor-1 [Forst 2012] and hs-CRP [Pi-Sunyer 2015], which may be of benefit to persons with HIV. Finally, HIV infection is also associated with greater non-calcified atherosclerotic plaque burden [Post 2014, Metkus 2015]. Non-calcified plaques are less stable than calcified plaques, and semaglutide may reduce atherosclerotic plaque inflammation and promote plaque stabilization [Balestrieri 2015].

Increased GLP-1 levels have been reported in men with HIV and impaired vs normal glucose tolerance [Andersen 2005], a finding hypothesized to be compensatory rather than causative of their impaired glucose tolerance. This compensatory hypothesis may be supported by the fact that gut barrier disruption and lipopolysaccharide leak in HIV should be associated with depletion of the neuro-endocrine cells that secrete GLP-1, and need for support by drugs such as GLP-1 agonists to maintain homeostasis [Culha 2016]. In mice, GLP-1 agonism has been shown to upregulate genes encoding mucins and other GI-protective proteins [Bang-Berthelsen 2016]; improve gut barrier function [Yusta 2015]; and, when given prior to lipopolysaccharide (LPS) exposure, reduce TNF-α, interferon-γ, and immune cell recruitment (as assessed by decreased circulating osteopontin levels) [Rakipovski 2018]. As such, semaglutide could have unique benefit in PLWH, who are known to have gut barrier disruption and microbial translocation, a known contributor to NAFLD.

In summary, semaglutide may improve HIV-/ART-specific contributors to NAFLD in addition to traditional NAFLD risk factors. The mechanism of action of the proposed intervention should lessen perturbations in insulin sensitivity and fatty acid metabolism, which are linked to increased IHTG content, the core problem of NAFLD. Furthermore semaglutide should lead to weight loss in a population with a growing obesity epidemic, and ultimately reducing other obesity-associated comorbidities. Semaglutide has not been studied for the prevention or treatment of NAFLD in HIV infection, but reduces fat mass and improves dysmetabolism, a critical driver of metabolic dysregulation in NAFLD and HIV infection.

Study Design

No standard of care for NAFLD exists in HIV infection or in the general population beyond routine diet and exercise recommendations, which are notoriously difficult to achieve and sustain and may have reduced efficacy in PLWH. The proposed intervention has the potential to reduce hepatic steatosis in PLWH. However, before recommending semaglutide as a therapeutic option, its safety and efficacy must be tested in this population. Therefore, we propose a phase II, single arm, pilot study of semaglutide sc weekly to reduce IHTG and attenuate immuno-metabolic dysregulation in adults with HIV and central adiposity, hepatic steatosis, and insulin resistance or pre-diabetes (a population at high risk of NAFLD and its consequences).

Notably, increased VAT-to-BMI ratios and HIV-/ART-induced alterations in lipid and glucose metabolism in PLWH predispose them to “lean NAFLD” in addition to the more traditional obese NAFLD paradigm. Increased minimum WC is 1) the best method for non-invasive assessment of VAT quantity, 2) a better screening tool for NAFLD than BMI in this population, and 3) similar to important BMI cutoffs for disease risk in populations without HIV.

All participants will receive semaglutide for 24 weeks, a common initial assessment point for NAFLD evaluation by MRI-PDFF in clinical trials. A 24-week primary endpoint was chosen as 1) it will take participants 4 weeks to titrate to the therapeutic dose of semaglutide; 2) weight loss with semaglutide begins early and does not plateau early (as with liraglutide, refer to section 2.1), giving participants time to reach therapeutic weight loss (and IHTG reduction) goals on study; and 3) given the cost of the drug, assessing for preliminary efficacy after 24 weeks should allow determination of whether further study is warranted without undue commitment of resources and participant time. If semaglutide improves IHTG, this would be a significant clinical advancement and may aid mechanistic understanding of NAFLD pathogenesis in HIV infection. This study will also inform knowledge of the pathogenesis of NAFLD in treated HIV infection, and issues related to quality of life and therapeutic selection for PLWH and NAFLD. Finally, a secondary benefit of this study is the assessment of the safety and efficacy of semaglutide as a weight loss therapy in PLWH, which **is** greatly needed given the current obesity epidemic in the population.

Of note, since NAFLD therapy should occur concomitant with lifestyle optimization, general diet and exercise recommendations will be provided at study entry. Importantly, eligible participants will have central adiposity and some degree of insulin resistance, so

cardiovascular activity and dietary guidance are expected to have previously been part of routine clinical recommendations for enrolled participants who have been in routine care. However, we will offer these recommendations again to be consistent with clinical care guidelines. Examples of such standard diet and exercise materials and a link to the American Diabetes Association websites will be provided to all sites, which will include recommendations for 1) moderate-to-vigorous intensity cardiovascular activity according to the American Heart Association, American College of Cardiology, American Diabetes Association, and American College of Sports Medicine guidelines, and 2) information on healthy diet, including target calorie goals.

Study population

Children 13-17 years of age will not be included in this study as, compared to adults ≥18 years of age, 1) the pathogenesis of NAFLD may vary in that population, 2) the prevalence of NAFLD may be much lower, and 3) semaglutide is not approved for use in pediatric populations.

Primary outcome

MRI-PDFF is a non-invasive, image-based biomarker for NAFLD that is readily available and can accurately and precisely quantify IHTG content, which is the primary outcome. MRI-PDFF is strongly correlated with biopsy-proven hepatic steatosis, and changes in PDFF correlate with histologic response [Patel 2016, Middleton 2017, Hong 2018]. In a recent meta-analysis, the pooled sensitivity and specificity of MRI-PDFF for classifying grade versus 1-3 hepatic steatosis were 0.93 and 0.94, respectively [Qu 2019].

Other measures

Loss of muscle mass often accompanies weight loss, and may be associated with loss of muscle function (manifested by slowing in the time to rise from a chair, for example). Conversely, among obese persons, weight loss may be accompanied by small loss in muscle mass but improvements in muscle function and improved mobility. NAFLD has also been associated with impaired muscle function (grip strength) in men with HIV [Debroy 2019]. Gait speed is a commonly used measure of physical function, is strongly associated with disability and mortality [Studenski 2011, Perera 2016], and has been proposed as a key component of sarcopenia in a recent sarcopenia consensus definition in several populations including PLWH (manuscripts under review). 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. These tests require minimal equipment (a stopwatch and a chair without arms or wheels), can be completed within approximately 1 minute each, are responsive to interventions, and are assessments that ACTG sites already have experience conducting.

Changes in muscle and VAT and SAT will likely occur with semaglutide therapy, have important physiologic consequences, and will thus be evaluated in this study through measures of muscle function (chair rise), muscle area and fat infiltration (MRI), and VAT and SAT quantity and quality (MRI).

Stool samples will be collected for microbiome assessment as microbiome changes are linked with NAFLD development [Zhu 2015, Doulberis 2017], and 1) differences in the microbiome could account for potential differences in observed treatment response, and/or 2) it is unknown whether semaglutide therapy has microbiome effects in humans.

Finally, circulating immune cell profiles will be evaluated, with a focus on invariant natural killer T (iNKT) cells, which are required for maximal weight loss for GLP-1 therapy [Lynch 2016] and mucosal-associated invariant T cells (MAIT) cells, which are important for epithelial barrier function and are reduced in NAFLD [Hegde 2018]. These have not yet been studied in PLWH, but may have a role in dysmetabolism and NAFLD.

3.0 STUDY DESIGN

A5371 is a phase II, open-label, single arm, 48-week pilot study of the effects of 24 weeks of semaglutide on MRI-PDFF-quantified IHTG content in **PLWH** and central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis.

A total of 50 participants will be enrolled and followed on study for 24 weeks on treatment and an additional 24 weeks off study treatment to understand the durability of observed effects. All participants will receive semaglutide 1 mg sc weekly through week 24 (after 4 weeks of initial titration), followed by 24 weeks of observation off study drug.

Each participant will have two MRI-PDFF evaluations during the study. The first will occur at study pre-entry to determine eligibility; the second will occur at week 24 or Premature Study/Treatment Discontinuation (if the participant has received study drug for at least 12 weeks). Blood samples will be collected for measurement of immunologic, metabolic, and inflammatory biomarkers. Stool samples will be self-collected for microbiome assessment, and participants will perform repeat chair stands and gait speed measurement as measures of physical performance.

Because moderate weight loss and increased physical activity are considered first line therapy for NAFLD, participants will receive standardized recommendations for 1) moderate-to-vigorous intensity cardiovascular activity (refer to section 2.2) and 2) general information on **a** healthy diet, including target calorie goals at study entry.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.2 Two separate reports of HIV-1 RNA measurements <50 copies/mL, and no HIV-1 RNA measurement >500 copies/mL, during the 48 weeks prior to entry. One of the HIV-1 RNA values must be the screening visit value, and the other value obtained between 24 and 48 weeks prior to entry.

NOTE: All values must have been reported from a US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that is Virology Quality Assurance (VQA) certified.

4.1.3 No change in ART in the 24 weeks prior to entry.

NOTE A: Modifications of ART formulation (e.g., from standard formulation to fixed dose combination or single tablet regimen) will be permitted.

NOTE B: Within-class substitutions are not permitted.

4.1.4 No plan to change ART for the study duration.

4.1.5 Within 30 days prior to pre-entry, a minimum WC measurement of ≥95 cm for individuals assigned male sex at birth or ≥94 cm for individuals assigned female sex at birth.

NOTE: For transgender study participants, sites should use the parameter that matches sex assigned at birth.

4.1.6 At least one of the following drawn within 30 days prior to pre-entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs:

- Fasting plasma glucose 100-125 mg/dL (refer to section 6.3 for a definition of fasting).
- HbA1c between ≥5.7 and <6.5%

- HOMA-IR >3.0 (Refer to calculator: https://www.mdcalc.com/homa-ir-homeostatic-model-assessment-insulin-resistance)

4.1.7 Documentation of negative hepatitis A virus (HAV) immunoglobulin M (IgM) or HAV vaccination prior to study entry.

NOTE: If documentation is not available prior to screening, this should be obtained through routine clinical care within 30 days prior to entry.

4.1.**8** Hepatic fat content (i.e., IHTG) ≥5%, as determined by liver MRI-PDFF within 14 days prior to entry (and **between 1**-30 days after screening).

NOTE: Refer to section 6.2.1 for more details.

4.1.**9** CD4+ T-cell count ≥200 cells/mm^3 within 30 days prior to pre-entry (may be from standard of care) at any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that is Immunology Quality Assurance (IQA) certified.

4.1.**10** The following laboratory values obtained within 30 days prior to pre-entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs:

- Absolute neutrophil count (ANC) >750 cells/mm^3
- Hemoglobin >10 g/dL for individuals assigned male at birth and >9 g/dL for individuals assigned female at birth
- Creatinine clearance (CrCl) ≥50 mL/min, as calculated by the CKD-Epi equation.
  NOTE: Please refer to A5371 PSWP for the website link to calculate CrCl using the CKD-Epi calculator.

NOTE: Calculations will be done without using cystatin C. Please refer to the A5371 MOPS for further details.

- Aspartate aminotransferase (AST) (SGOT) ≤**3** x ULN **on at least two measurements, with at least one within 30 days prior to pre-entry. Participants must also have no evidence of AST >3 x ULN within the 3 months prior to entry, from routine clinical monitoring, if available. If no additional monitoring is available in the 3 months prior to entry, additional testing should be obtained within the screening interval (2-4 weeks apart) to ensure stability.**
- Alanine aminotransferase (ALT) (SGPT) ≤**3** x ULN **on at least two measurements, with at least one within 30 days prior to pre-entry. Participants must also have no evidence of ALT >3 x ULN within the 3 months prior to entry, from routine clinical monitoring, if available. If no additional monitoring is available in the 3 months prior to entry,**

additional testing should be obtained within the screening interval (2-4 weeks apart) to ensure stability.

- Fasting triglyceride level ≤500 mg/dL.

NOTE A: See section 6.3 for a definition of fasting.

NOTE B: If level is >500 mg/dL, level may be rechecked within the screening window.

4.1.**11** For individuals **taking** daily medications with anti-inflammatory properties, including but not limited to, statins and chronic corticosteroids (inhaled corticosteroids exempt), the doses must be stable as determined by the site investigator for ≥3 months prior to study entry, and the individual should have no active plans to change dosing during the study period.

4.1.1**2** For individuals taking daily lipid-lowering medications (such as statins, fibrates, niacin, fish oil), the doses must be stable as determined by the site investigator for ≥3 months prior to study entry, and the individual should have no active plans to change dosing during the study period.

NOTE: Lipid-lowering equivalents for niacin and fish oil are ≥1 g and ≥3 g daily, respectively.

4.1.1**3** Ability and willingness of participant to provide informed consent.

4.1.1**4** Willingness and ability to use auto-inject pen weekly for 24 weeks.

4.1.1**5** Willingness and ability to undergo MRI scans.

NOTE: Anxiolytics will not be provided through the study but may be provided at site expense.

4.1.1**6** For persons **able to become pregnant**, a negative serum or urine pregnancy test (urine test must have a sensitivity of <25 mIU/mL) both 1) at screening (within 30 days prior to pre-entry MRI) and 2) within 3 days before or at entry (prior to registration into study) by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/ CLIA-waived test, or at any network-approved non-US laboratory or clinic that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

NOTE: Individuals **able to become pregnant** are defined as individuals who have reached menarche and who have not been post-menopausal for at least 24 consecutive months (i.e., have had menses within the preceding 24 months), and have not undergone surgical sterilization such as hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy.

4.1.1**7** If participating in sexual activity that could lead to the participant becoming pregnant, the participant must agree to use contraception while on study drug (24 weeks) and for 2 months following the last dose of study drug. At least one of the following must be used:

- Intrauterine device (IUD)
- Hormone-based contraceptive
- Partner sterilization (i.e., vasectomy) and is the sole partner for the participant.

NOTE: **Participant** self-report of partner sterilization is acceptable.

4.1.1**8** For individuals taking Vitamin E (any dose), the dose must be stable as determined by the site investigator for more than 1 year prior to entry.

4.1.1**9** Adults age ≥18 years.

4.1.**20** Willingness to be contacted by telephone or e-mail by study staff throughout the study.

4.2 Exclusion Criteria

4.2.1 Known active hepatitis C virus (HCV) infection, defined as a detectable HCV RNA within 24 weeks prior to study entry.

NOTE A: Individuals with HCV RNA below the limit of quantitation for >24 weeks prior to study entry are eligible, i.e., individuals who have been treated for hepatitis C are eligible if they have completed therapy >24 weeks prior to study entry, and/or individuals who spontaneously cleared hepatitis C virus are eligible as long as they have had undetectable HCV RNA for >24 weeks. HCV RNA testing is not provided by the study.

NOTE B: If HCV antibody testing has not been performed in the 5 years prior to screening and the participant does not have history of cured HCV infection, HCV antibody testing should be repeated at screening. **If screening HCV antibody is positive or reactive, the individual is not eligible and should be referred for clinical evaluation through routine care.**

4.2.2 Active/chronic hepatitis B (HBV), defined as a positive hepatitis B surface antigen (HBsAg) at screening.

NOTE A: HBsAg testing is only required at screening if HBV laboratory results are not available within the last 5 years prior to screening and individual does not have documented immunity.

NOTE B: If HBsAg positive, individual is not eligible and should be referred for clinical evaluation through routine care.

4.2.3 Known active severe delayed gastric emptying, as determined by the site investigator.

4.2.4 Gain or loss of >5% body weight within 12 weeks prior to study entry.

NOTE: Self-report recall is acceptable.

4.2.5 Any plans to change diet or exercise regimen significantly, except for the adoption of study provided suggestions for diet and exercise, within the study period.

NOTE: "Significantly" refers to intent to join a weight-loss program such as Weight Watchers, or start a specific diet (such as ketogenic or very low carbohydrate).

4.2.6 Known acute or chronic liver disease with cirrhosis or portal hypertension.

4.2.7 History of liver transplant.

4.2.8 Breastfeeding or plans to become pregnant.

4.2.9 Current diagnosis of diabetes mellitus or current use of diabetes medications, or a laboratory measurement of hemoglobin A1c ≥6.5% at screening.

NOTE: Stable use of metformin (i.e., for ≥12 weeks) for indication other than diabetes (e.g., polycystic ovarian syndrome or pre-diabetes/impaired fasting glucose) may be permitted with approval of the Clinical Management Committee (CMC).

4.2.10 Known retinopathy (excluding remote history of cotton wool spots).

4.2.11 Personal or family (first-degree relative) history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2).

4.2.12 Untreated, poorly controlled, or previously undiagnosed thyroid disease defined as the presence of abnormal thyroid-stimulating hormone (TSH) at screening with no clear explanation.

4.2.13 Unexplained hypercalcemia corrected for albumin that is >10.5 mg/dL at screening. Please refer to the A5371 MOPS for the calculation.

4.2.14 Use of any immunomodulatory (including prednisone equivalent of ≥10 mg), HIV vaccine, investigational therapy, or TNF-α therapy within 3 months prior to study entry.

4.2.15 Use of human growth hormone, tesamorelin, supraphysiologic testosterone to achieve therapeutic blood levels, or any use of other anabolic steroids within 3 months prior to study entry or plans to start these while on study.

NOTE: Chronic, stable hormone replacement therapy ≥3 months prior to entry in men with diagnosed hypogonadism or transgender person on masculinizing hormonal therapy is permitted.

4.2.16 Use of estrogens or progesterones at supraphysiologic doses within 3 months prior to study entry.

NOTE: Stable doses used for contraception, post-menopausal hormone replacement or feminizing hormone therapy for transgender persons ≥3 months prior to entry is permitted.

4.2.17 Known allergy/sensitivity or any hypersensitivity to components of study drug or its formulation.

4.2.18 Current serious illness requiring systemic treatment and/or hospitalization.

NOTE: The individual can be rescreened when they complete therapy or are clinically stable as determined by the site investigator.

4.2.19 Use of GLP-1 agonists within 24 weeks prior to study entry.

4.2.20 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.21 Excessive consumption of alcohol of ≥3 months within 90 days prior to screening, defined as:

- Consuming ≥5 alcoholic drinks for men or consuming ≥4 alcoholic drinks for women during a single occasion (i.e., at the same time or within a couple of hours of each other), or
- ≥3 drinks on 4 or more days of the week on average for men or ≥2 drinks on 4 or more days of the week on average for women.

NOTE: For transgender study participants, sites should use the parameter that matches sex assigned at birth.

4.2.22 Known chronic pancreatitis or more than one episode of pancreatitis ever in the past.

4.2.23 Inability to keep study product at 36°F to 46°F (2°C to 8°C) prior to first use, or to maintain the study product at a controlled room temperature between 59°F and 86°F (15°C to 30°C) following first use.

4.2.24 Intent to use any medication likely to cause significant changes in weight during the study period.

NOTE: **Refer to section 5.4.2 for** a list of medications in this category.

4.2.25 Use of stavudine within 12 months prior to study entry.

4.2.26 Prior bariatric surgery (e.g., lap band, gastric sleeve, or Roux-en-Y bypass surgery) or major gastric surgery or plans to undergo weight reduction surgery while on study.

4.2.27 Individuals with any metal, implantable devices (e.g., pacemakers, prosthetics), or shrapnel, per standard MRI exclusion criteria.

4.2.28 Any condition that the site investigator believes would make the individual unsuitable for participation.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE) **responsible for oversight of the study**. 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 of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's 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 required documents have been received. Site-specific ICF(s) *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. A copy of the Amendment Registration Notification should be retained in the site's 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 or legal representative will be asked to read and sign the approved protocol consent form.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC **Subject** Enrollment System.

4.3.2 Protocol Activation

Prior to enrollment, 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

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

4.4 Co-enrollment Guidelines

- US sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5371 protocol chairs.
- Non-US sites are encouraged to co-enroll participants in A5243, “Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.” Co-enrollment in A5243 does not require permission from the A5371 protocol chairs.
- **Participants from the A5332 REPRIEVE study may co-enroll in A5371.**
- Participants from the A5322 HAILO study may co-enroll in A5371.
- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the CMC via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as study-provided semaglutide (Ozempic).

5.1 Regimens, Administration, and Duration

5.1.1 Regimen

Beginning at entry, participants will receive open-label semaglutide subcutaneously once weekly, dosed as per section 5.1.2.

NOTE: Participants must remain on their non-study-provided ART throughout the study.

5.1.2 Administration and Duration

Semaglutide will be administered subcutaneously weekly into the abdomen, thigh or upper arm, and will be initiated at study entry at a dose of 0.25 mg once weekly, increased at week 2 to 0.5 mg once weekly, and finally increased to 1.0 mg once weekly at week 4 for continuation through week 24. The dose may be reduced **or dose escalation held** for **in**tolerability, if necessary, in discussion with the CMC (refer to section 8.1.1).

The drug should be administered on the same day each week at any time of the day without regard to meals. Refer to the A5371 MOPS for more details.

Participants must insert a new needle prior to each injection and safely discard the needle after each injection. Sites will instruct participants how to appropriately dispose of the needles. Participants will rotate injection sites weekly if injecting in the same body area. To ensure that participants are using the appropriate technique, they will receive training in titrating the injection pen and will be observed injecting semaglutide at study entry, with retraining and observation conducted as needed.

Study treatment will be 24 weeks in duration. Durability of medication effects will be assessed at 24 weeks after study treatment discontinuation (study week 48).

5.2 Study Product Formulation and Preparation

5.2.1 Semaglutide

Semaglutide is a clear, colorless solution that will be supplied as pre-filled, multidose, disposable, single-participant-use pens that deliver doses of 0.25 mg, 0.5 mg, or 1.0 mg. Each pen contains a total of 1.5 mL of semaglutide solution at a concentration of 1.34 mg/mL.

Prior to initial use, semaglutide should be stored between 2°C and 8°C (36ºF to 46ºF). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze semaglutide and do not use semaglutide if it has been frozen. After initial use, the semaglutide pen can be stored for 56 days at controlled room temperature (15°C to 30°C; 59°F to 86°F) or in a refrigerator (2°C to 8°C; 36°F to 46°F). Semaglutide should be protected from excessive heat and sunlight. Do not freeze. When not in use, the semaglutide pen should be stored without an injection needle attached and with the cap on.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Semaglutide (Ozempic®) manufactured by Novo Nordisk®, sharps container(s), and alcohol swabs will be purchased for the study and available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the semaglutide, sharps container(s), and alcohol swabs for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

All participants will be required to continue their ongoing ART regimen for the duration of the study. Changes in ART are discouraged during the study, but may be allowed if clinical need arises as determined by sites. If possible, sites should

consult the A5371 CMC via email (actg.cmca5371@fstrf.org) prior to any ART changes. ART will not be provided by the study.

5.4.2 Prohibited Medications

Medications prohibited while on study treatment are: (1) stavudine; (2) GLP-1 agonists; (3) estrogens or progesterones at supraphysiologic doses, with the exception of doses used for contraception, post-menopausal hormone replacement or feminizing hormone therapy (for transgender persons) that have been stable for ≥3 months prior to study entry; (4) use of any immunomodulatory therapy HIV vaccine, investigational therapy, or TNF-α therapy; (5) use of human growth hormone, tesamorelin, supraphysiologic testosterone to achieve therapeutic blood levels (with the exception of stable doses for ≥3 months prior to entry in men with diagnosed hypogonadism or transgender persons on masculinizing hormonal therapy), or use of other anabolic steroids; **and** (6) diabetes medications other than metformin use for non-diabetes indications (see 4.2.8). Medications likely to cause significant changes in weight **are prohibited**: **glucocorticoids (e.g., prednisone, at doses ≥10mg), typical and atypical antipsychotics (e.g., olanzapine, haloperidol), dronabinol, megestrol acetate, and mirtazapine if prescribed for weight management (usually with diagnosis of AIDS wasting; other indications not related to weight okay if stable dosing), GLP-1 agonists, bupropion-naltrexone, orlistat, lorcaserin, phentermine-topiramate, and commercial over-the-counter weight loss supplements such as Hydroxycut.**

5.4.3 Precautionary Medications

None.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations

Evaluation	Screening	Pre-Entry	Entry	On-treatment weeks									**Study Completion**
				1	2	3	4	8	12	16	20	Week 24 or Premature Treatment/Study D/C (see section 6.2.4)	48
Visit windows	*Within 30 days prior to pre-entry*	*≥1 day after screening and within 14 days prior to entry*		*±3 days*			*-3 and +7 days*	*±7 days*	*±14 days*				
Documentation of HIV	X												
Collection of demographic information	X												
Medical history	X		X										
Medication history	X		X										
Clinical assessment	X		X				X		X			X	X
Hematology	X		X				X		X			X	X
Liver function tests	X		X				X		X			X	X
Chemistry	X		X				X		X			X	X
Hemoglobin A1c	X		X						X			X	X
Insulin	X												
HOMA-IR	X												
Lipid panel and LDL measurement	X		X						X			X	X
TSH	X												
Pregnancy test	X		X				As indicated		As indicated			X	
CD4+/CD8+	X											X	

Evaluation	Screening	Pre-Entry	Entry	On-treatment weeks									Study Completion
				1	2	3	4	8	12	16	20	Week 24 or Premature Treatment/Study D/C (see section 6.2.4)	48
Visit windows	*Within 30 days prior to pre-entry*	*≥1 day after screening and within 14 days prior to entry*		*±3 days*			*-3 and +7 days*	*±7 days*	*±14 days*				
HCV antibody, HBsAg, **HAV IgG and/or HAV IgM** tests	X												
HIV-1 RNA	X						**X**		**X**			X	
Stored plasma/PBMC/serum			X						**X (plasma and serum only)**			X	X (plasma and serum only)
Stool kit (D=distribute, C= collect)		X^D	X^C						X^D			X^C	
MRI-PDFF		X										X	
3-day food diary (D=distribute, C= collect)		X^D	X^C						X^D			X^C	
Hypoglycemia questionnaire			**X**				**X**		**X**			**X**	
Quality of life **questionnaire**			X									X	
Physical activity and diet **questionnaire**			X									X	X
ART adherence **self-report**			X									X	
Study treatment adherence **assessment**							X		X			X	
Acceptability and tolerability **self-report**							X		X			X	
Physical function assessments			X									X	X
Study product dispensation			X				X		X				

Evaluation	Screening	Pre-Entry	Entry	On-treatment weeks									Study Completion
				1	2	3	4	8	12	16	20	Week 24 or Premature Treatment/Study D/C (see section 6.2.4)	48
Visit windows	*Within 30 days prior to pre-entry*	*≥1 day after screening and within 14 days prior to entry*		*±3 days*			*-3 and +7 days*	*±7 days*	*±14 days*				
Injection training/ retraining/observation			X				As needed		As needed				
Study drug cartridge count							X		X			X	
Exercise and diet education			X										
Hypoglycemia and hydration education			**X**										
Telephone or email contact				X	X	X		X		X	X		

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Screening and pre-entry evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 30 days prior to pre-entry unless otherwise indicated.

Participants must arrive fasting (refer to section 6.3 for a definition of fasting) for the screening visit. If the participant is not fasting, the visit will be rescheduled.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured on participants who do not enroll in a Screening Failure form and entered into the ACTG database.

Pre-Entry
Pre-entry evaluations must be completed after screening and within 14 days prior to entry evaluations unless otherwise specified. Screening blood work should be completed and reviewed, and all other entry criteria must be met, *prior* to performance of MRI-PDFF. MRI-PDFF should only proceed once screening evaluations are completed.

6.2.2 Entry Evaluations

Entry evaluations will occur only after the site has received confirmation from the MRI reading center that the pre-entry MRI-PDFF scan is of acceptable quality and that the participant has ≥5% IHTG (and is otherwise eligible). Participants must arrive fasting for the entry visit. If the study participant is not fasting, the entry visit should be rescheduled (see section 6.3 for a definition of fasting) within 7 days.

6.2.3 Post-Entry Evaluations

Participants must arrive fasting (see section 6.3 for a definition of fasting) for the weeks 12, 24, and 48 visits or a premature discontinuation visit. If the study participant is not fasting, the participant should return to the clinic **for fasting evaluations** within the visit window per **Table 6.1-1, Schedule of Evaluations (SOE)**.

If a participant experiences an acute inflammatory condition within 14 days prior to a scheduled visit, any scheduled blood collection should be postponed for 7 days. Examples of inflammatory conditions that would justify delaying blood

collection include an infection requiring hospitalization, a systemic viral illness such as an influenza-like illness, a severe drug hypersensitivity reaction, myocardial infarction, fever on the day of visit defined as T° >38.5°C, and major trauma. Sites are encouraged to contact the A5371 CMC via email (actg.cmcA5371@fstrf.org) with any questions regarding whether a specific situation would require a delay in blood collection.

Because of diurnal variations in values that may be measured on stored samples, all blood collections should be collected prior to 11AM local time. If this is not possible, then each participant's samples should be collected at approximately the same time of day (morning or afternoon) throughout the study.

Evaluations at week 4 must occur -3/+7 days of the visit. Evaluations at weeks 12, 24, and 48 must occur ±14 days of the visit.

Telephone or e-mail contact during weeks 1 through 3 must occur ±3 days. Week 8 contact must occur ±7 days. For weeks 16 and 20, contact must occur ±14 days.

Study Treatment Completion Evaluations
The week 24 evaluations will be the participant's final visit on treatment. The participant should be on study drug at the time of all week 24 evaluations (visit to occur within 7 days of the last study drug dose). If there are scheduling issues, additional study drug can be provided, if needed, to ensure continued administration. If a participant does not bring in their stool sample at week 24, the participant can bring the stool sample to the study clinic within 14 days.

Study Completion Evaluations
Participants will have the week 48 evaluations per the SOE.

6.2.4 Discontinuation Evaluations

Evaluations for Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the entry visit.

Premature Treatment Discontinuation Evaluations
Participants who discontinue study treatment early and have received at least 12 weeks of study treatment will have the week 24/premature discontinuation evaluations performed at the time study treatment has stopped. In contrast, participants who prematurely discontinue study treatment before receiving 12 weeks will not complete a discontinuation visit but should be followed to resolution of any applicable adverse event **before being taken off-study**, per section 8.0.

Participants who discontinue treatment because of an adverse event should be followed on study, off study treatment until resolution of the adverse event, per section 8.0. These participants will only be required to have clinical assessments

performed as determined by the severity of the AE, as recommended by the CMC and local principal investigators, until the resolution of the adverse event.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue from the study and have received at least 12 weeks of study treatment will have the premature discontinuation evaluations performed as indicated in the SOE as soon as possible.

No premature study discontinuation evaluations need to be completed for participants who received less than 12 weeks of study treatment.

6.3 Instructions for Evaluations

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for Laboratories Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials, which is available at: https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

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/daids-sourcedocpolicy.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) and AE reporting of adverse events requirements.

Fasting Instructions
Fasting is required at screening, entry, and weeks 12, 24, and 48 or a premature discontinuation visit. Fasting is defined as nothing to eat or drink, except for prescription medications or water, for at least 8 hours before the evaluations. If participants are in a non-fasting state, they should return to the clinic for fasting evaluations within the visit window identified in the SOE.

6.3.1 Documentation of HIV

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Collection of Demographic Information

Per the SOE, demographic information will be recorded **on the screening checklist**.

6.3.3 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures as an adult (≥18 years) (verbal history accepted)
- Coronary heart disease or other cardiovascular disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Hepatitis C, with documentation of undetectable HCV RNA for ≥24 weeks
- Hepatitis B
- **History of hepatitis A infection or HAV immunization immunoglobulin G (IgG)**
- Pancreatitis
- Renal impairment
- Cholecystitis

Any allergies to any medications or their formulations must also be documented.

6.3.4 Medication History

A medication history must be taken, including start and stop dates. Table 6.3.4-1 below lists the medications that must be included in the history.

The medication history evaluation will be assessed at the screening and entry visits and recorded on the eCRFs at the entry visit.

Table 6.3.4-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Complete ART history, as available
Immune-based therapy, including corticosteroids	Within 2 years prior to entry
Blinded study treatment	Within 1 year prior to study entry
HIV-1-related vaccines	Complete history
HAV vaccine	**Within 30 days prior to study entry**
Prescription drugs for treatment of opportunistic infections	Within 30 days prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	Within 30 days prior to study entry
Prescription drugs (other)	Within 30 days prior to study entry
Alternative therapies	Within 30 days prior to study entry
Dietary supplements	Within 30 days prior to study entry

Medication Category	Complete History or Timeframe
Diet or weight loss therapy, either prescribed or over the counter	Within 12 months prior to study entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Within 12 months prior to study entry except as noted below
Growth hormones	Within 12 months prior to study entry

*Includes: hormone-releasing IUDs (e.g., current Mirena use); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy (including aldactone/spironolactone).

6.3.5 Clinical Assessments

Complete Physical Examination
A physical examination will be performed at screening and is to include an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac examination; abdominal examination; and examination of the lower extremities for edema. The physical examination will also include signs and symptoms, diagnoses, and vital signs (height, weight, minimum WC [refer to the A5371 MOPS for minimum waist definition and measurement instruction], temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Examination
A targeted physical examination is to be conducted **per the SOE**, beginning at entry. The examination at each in-person visit will include **vision assessment if participant has vision complaints (blurred vision, sudden loss of vision, black spots, flashing lights, and difficulty reading or seeing small details) and** vital signs (weight, temperature, pulse, respiration rate, and blood pressure); additional examination components will be driven by any previously identified or new adverse event/targeted condition (as described in below bullets), that the participant has experienced since the last visit.

Minimum WC measurement will occur at entry and then again at weeks 12, 24, and 48 (or Premature Study or Treatment Discontinuation for participants receiving at least 12 weeks of study drug).

Post entry, see section 8.3 for collection requirements for pregnancy.

At screening and entry, refer to section 6.3.3 medical history for reporting requirements. Post-entry, refer to section 7.2 for AE collection requirements. Starting at entry and during the study, the following targeted events must be recorded regardless of grade:

- AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
- Bone fractures as an adult (verbal history accepted)
- Coronary heart disease or other cardiovascular disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes mellitus
- Tuberculosis
- Hepatitis C virus infection
- Hepatitis B virus infection
- **Hepatitis A virus infection**
- Hypertension
- **Hypotension**
- **Hypoglycemia**
- **Vision changes**
- Renal impairment
- Liver disease
- Pancreatitis
- Cholecystitis
- Bleeding or coagulation disorders
- Any inflammatory condition, including, but not limited to;
  - Systemic illness or genital infections requiring antimicrobial therapy
  - Immune reconstitution inflammatory syndrome
  - Lupus
  - Rheumatoid arthritis
  - Inflammatory bowel disease

Concomitant Medications

Post-entry, the following new and discontinued concomitant medications must be recorded:

- Any new medication
- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.4 for examples)
- Growth hormone or growth hormone-releasing analogs
- Any drugs with anti-inflammatory properties
- Any weight loss drugs
- Any drugs expected to increase weight

Study Treatment Modifications

At each visit beginning at entry, record all study drug modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, any inadvertent or deliberate delays of 3 or more days past due date **(10 days since last dose)** of any injection since the last visit. Record any permanent discontinuation of treatment.

ART Modifications
Beginning at entry, record all ART modifications, including any temporary interruptions, and document the reason for the modifications and interruptions. "Temporary ART interruption" is defined as inadvertent or deliberate interruption of any ART component for at least 3 consecutive days but fewer than 14 days at any time during the study; "ART discontinuation" is defined as inadvertent or deliberate interruption of any ART component for at least 14 days prior to week 48. Sites should inform the A5371 CMC via email (actg.cmca5371@fstrf.org) of any ART interruptions or discontinuations to obtain participant management instructions.

6.3.6 Laboratory Evaluations

At screening and entry, all laboratory values must be recorded. For post-entry assessments, all hemoglobin, hemoglobin A1c, WBC with differential, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, glucose, platelets, and lipid profile values should be recorded regardless of grade. For all other labs, record all Grade ≥2 values and any laboratory toxicity leading to a change in study treatment. Refer to section 7.2 for AE reporting requirements for abnormal laboratory findings. **Refer to section 6.2.3 for rescheduling fasting evaluations.**

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), WBC differential, absolute neutrophil count (ANC), platelets.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, indirect bilirubin, total protein, albumin. **Refer to section 4.1.10 regarding additional testing that may be needed within the screening interval (2-4 weeks apart).**

Chemistry
Glucose, CrCl, electrolytes (e.g., sodium, potassium, chloride, phosphate, bicarbonate), calcium, blood urea nitrogen (BUN).

Hemoglobin A1c
Performed per the SOE.

Insulin
Insulin (performed in real time at screening only, afterwards insulin will be measured at the end of the study from batched stored samples collected at weeks 0, 24, and 48).

HOMA-IR
HOMA-IR is calculated by site at screening only. Refer to calculator at https://www.mdcalc.com/homa-ir-homeostatic-model-assessment-insulin-

resistance. Post-screening, HOMA-IR is calculated by the Statistical Data Analysis Center (SDAC).

Lipid Panel and LDL Measurement
Triglycerides, **high-density lipoprotein (**HDL**)** cholesterol, calculated or direct LDL cholesterol, total cholesterol.

TSH
A TSH will be ordered to screen for overt thyroid disease. If the TSH is abnormal and the individual has not undergone testing for causes, the individual will need to undergo evaluation through routine clinical care prior to enrollment (refer to exclusion criterion 4.2.**12**).

Pregnancy Test
A pregnancy test will be performed per the SOE. At week 24, the pregnancy test will be performed prior to the MRI. For individuals **able to become pregnant**: Serum or urine β-HCG. (Urine test must have a sensitivity of <25 mIU/mL). Record pregnancy and pregnancy outcome per section 8.3.

6.3.7 Immunologic Studies

CD4+/CD8+
Absolute CD4+ and CD8+ T cell count and percentages must be obtained within 30 days prior to pre-entry (may be standard of care) at a laboratory that possesses a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

All CD4+ and CD8+ T cell count and percentage values should be recorded; refer to section 7.2 for AE reporting requirements for abnormal laboratory findings.

HCV Antibody, HBsAg, **HAV IgG and/or HAV IgM** Tests
HCV antibody, HBsAg, **HAV IgG, and/or HAV IgM** tests may be performed, if needed by the site's local laboratory per the SOE. Refer to sections **4.1.7,** 4.2.1 and 4.2.2.

6.3.8 Virologic Studies

HIV-1 RNA
Screening HIV-1 RNA must be performed within 30 days prior to pre-entry at a laboratory that possesses a CLIA certification or equivalent (US sites) or VQA certification (non-US sites). Eligibility will be determined based on the screening value. The two values for eCRF documentation (values in inclusion criterion 4.1.2) must include the screening value and one measurement obtained 24-48 weeks prior to entry. Documentation of all other HIV-1 RNA values performed in the 48 weeks prior to entry will not be required on the eCRFs.

For US sites, post-entry evaluations will be performed at the protocol-designated laboratory and values will be **keyed**. In addition, results will be reported back to sites. For non-US sites, record HIV-1 RNA values on the eCRF.

6.3.9 Stored Plasma/PBMC/Serum

Blood will be collected as indicated on the SOE for metabolic, adherence, and circulating inflammatory biomarker profiles. Insulin will be measured at the end of the study from batched stored samples collected at weeks 0, 24, and 48. At week**s 12 and** 48, **p**lasma and serum **only** will be collected and stored**; PBMC will not be collected**. **For immunogenicity studies, plasma and serum will be collected and stored at entry, and weeks 12 and 24.** Testing will be performed at a central laboratory. Collection, processing, and shipping instructions are provided in the current A5371 LPC that is posted on the PSWP.

If a participant arrives for a visit in a non-fasting state, the **fasting evaluations** should be re-scheduled within the visit window noted in the SOE.

Samples will be stored according to the LPC and are expected to be used for sCD14, hs-IL-6, sCD163, hs-CRP, IP-10, adiponectin, and MCP-1 measurement, although final determination will occur at study end.

Phenotyping of Immune Cell Subsets and Activation Markers
PBMCs will be stored according to the A5371 laboratory processing chart (LPC) and are expected to be used for the following advanced flow assays:

- Activated (HLA-DR+/CD38+) CD4+ and CD8+ T lymphocytes
- Monocyte (CD14/CD16/CCR2/CX3CR1/CD36/CD11c) subsets
- Invariant natural killer (6B11/CD69) and mucosal associated invariant (Vα7.2/CD161) T lymphocytes

NOTE: Advanced flow analysis requires a CD4+/CD8+ and WBC with differential from a sample obtained at the same time.

6.3.10 Stool Kit

Stool collection kits will be distributed to each participant per the SOE. Stool samples will be self-collected within 2 days before the study visits noted in the SOE. Instructions for collection **(stool-collection instructions that can be given to the participant)**, storage, and transport of samples are included in the A5371 MOPS.

6.3.11 MRI-PDFF

MRI-PDFF can be performed on a modern (1.5T or 3.0T field strength) MR scanner equipped with a phased array surface coil for signal reception and the ability to acquire data using one of the following pulse sequence:

- IDEAL-IQ (GE)/M-Dixon (Philips) or q-Dixon (Siemens) or
- Multi-echo (6 or more) spoiled gradient echo technique

The sites will be required to send test data sets to ensure that the acquisition meets imaging requirements before participation begins.

MRI-PDFF will be performed at the time points indicated in the SOE for IHTG, VAT, and SAT density and area, and areas of psoas and other trunk musculature. The pre-entry scans will be read centrally for IHTG within five business days of receipt, and the site will be notified whether the participant has ≥5% IHTG, to determine whether the individual is eligible to participate in the study. No clinical report will be provided to the site. Sites will do a local clinical read and refer as needed if an incidental finding is identified. Instructions for shipping/transfer of the MRI-PDFF images will be site-specific and communicated individually with each site.

MRI-PDFF scanning will also be performed at the premature study/treatment discontinuation visit if the participant has received ≥12 weeks of study drug.

6.3.12 Food Diary and Questionnaires

The food diary and questionnaires are posted on the DMC Portal in the Forms Management Utility.

3-Day Food Diary
Participants will be distributed a food diary per the SOE. All participants will complete a food diary for the 3 days preceding stool collection. The completed food diary will be collected at the stool collection visit noted in the SOE. These diaries will be analyzed centrally for macronutrients and estimated caloric content. **See A5371 MOPS for additional instructions for sharing 3-Day Food Diary results.**

Hypoglycemia Questionnaire
A hypoglycemia questionnaire will be administered as indicated in the SOE.

Quality of Life **Questionnaire**
Standardized quality of life questionnaire will be administered as indicated in the SOE.

Physical Activity and Diet **Questionnaire**
Information about physical activity and diet will be collected from all participants as indicated in the SOE.

ART Adherence **Self-Report**
At the time points indicated in the SOE, participants will be asked to report on ART adherence.

Study Treatment Adherence **Assessment**
A self-reported study treatment adherence assessment will be performed for each participant as indicated in the SOE.

Acceptability and Tolerability **Self-Report**
At the time points indicated in the SOE, participants will be asked to report on study drug acceptability and tolerability.

6.3.13 Physical Function Assessments

At the time points indicated in the SOE, participants will be asked to rise from a standard height chair that does not have wheels or arms 10 times from a seated position. Time to complete 5 and 10 rises from the chair will be captured. Gait speed will be assessed by the average of two measurements walking at usual pace (see the A5371 MOPS for further details).

6.3.14 Study Product Dispensation

At the time points indicated in the SOE, study product will be dispensed.

6.3.15 Injection Training, Retraining, and Observation

At the time points indicated in the SOE, to ensure that participants are using the appropriate technique, participants will receive training in titrating the injection pen and will be observed injecting semaglutide, with retraining and observation conducted as needed (see the A5371 MOPS for further details).

6.3.16 Study Drug Cartridge Count

Participants will be instructed to bring the cartridges to the in-person study visits. At the time points indicated in the SOE, cartridge counts will be performed for each participant.

6.3.17 Exercise and Diet Education

At the time point indicated in the SOE, participants will receive diet and exercise recommendations. Education materials are posted on the PSWP.

6.3.18 Hypoglycemia and Hydration Education

At entry, participants will receive hypoglycemia and hydration education. Education materials are posted on the A5371 PSWP.

6.3.19 Telephone or Email Contact

At the time points indicated in the SOE, participants will be contacted by telephone and/or via e-mail and asked about study drug adherence and any

changes in signs/symptoms**, including symptoms of hypotension, dizziness, hypoglycemia, and vision changes (such as blurred vision, sudden loss of vision, black spots, flashing lights, and difficulty reading or seeing small details). Record signs/symptoms on the clinical events log unless they meet AE reporting requirements.** At week 20, participants will be reminded about stool collection and to complete the food diary. Contact is recorded on the eCRF. Refer to the A5371 MOPS for guidance.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) 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 **(study entry)** condition.

7.2 Adverse Event Collection Reporting Requirements for this protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met:
- All Grade ≥3 AEs
- Grade ≥2 laboratory values
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement

Post-entry the following must be recorded on the eCRFs within 48 hours, and the CMC must be notified within 48 hours by e-mail (actg.cmca5371@fstrf.org) if the following occur:
- **Grade ≥3 AEs attributable to study product;**
- **"Liver" events leading to treatment being held or permanent treatment discontinuation, as defined in section 8.2.1.**
- **Any occurrence of symptoms of hypoglycemia with fasting glucose measurement <60mg/dL (see section 8.2.2)**

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System DAERS system as indicated.
All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:
- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions, and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are: semaglutide.

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is per the EAE manual.

- After the protocol-defined EAE reporting period, unless otherwise noted, only suspected, *unexpected* serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol monitoring team will monitor the conduct of the study via regular summaries of accrual, baseline characteristics, data completeness, and study status; study status summaries will include details on premature study and/or treatment discontinuations, which will enable the team to monitor the discontinuation rates.

The DAIDS clinical representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable. Additionally, the DAIDS clinical representative and the protocol monitoring team will review AE summaries, cumulative and new AEs (since last report), prepared quarterly by the SDAC.

The study will undergo interim review at least annually by an independent ACTG-appointed Study Monitoring Committee (SMC). The SMC will review summaries of accrual, baseline characteristics, conduct of the study (including premature treatment and study discontinuations), and AEs. The first interim review will occur no more than 1 year after the first participant enters the study. An interim review may also be convened if a concern (e.g., higher than anticipated treatment discontinuation rate) is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team. See section 10.5 for statistical and other considerations related to interim monitoring.

Study enrollment will be held and the SMC will convene an emergency meeting to review all study AEs, in collaboration with the DAIDS clinical representative, if any of the following is observed: (1) three participants with the same Grade 3 events attributable to study product, (2) two participants with Grade 4 events attributable to study product, (3) two participants with hepatoxicity events leading to treatment being held or permanent treatment discontinuation (see section 8.2.1.1), or (4) death. After reviewing the types of AEs and relatedness to the study product, the SMC will make recommendations as to whether to stop the study, alter monitoring/drug dosing, or other changes as required to the protocol and participant management.

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

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

8.1.1 Following consultation with and approval by the A5371 CMC (actg.cmca5371@fstrf.org), study treatment dose may be reduced **or dose escalation held** for intolerability, with initial dose reduction to 0.5 mg, and further dose reduction to 0.25 mg/week permitted. Participants who cannot tolerate at least 0.25 mg/week will be discontinued from the study.

NOTE: Most treatment-emergent nausea is mild-to-moderate and resolves with continued use (see section 8.2.4).

8.1.2 For decline in CrCl to <40 mL/min or 50% decline from entry value, see section 8.2.3 for management and additional monitoring instructions.

Grade 1 or 2
There will be no dose interruptions, modification, or discontinuations for any Grade 1 or 2 toxicity except as specified below.

For participants experiencing Grade 1 or 2 AEs who have received at least 12 weeks of study drug and choose to discontinue study treatment, the premature treatment discontinuation evaluations should be completed (per section 6.2.4) and the site should contact the A5371 CMC (actg.cmcA5371@fstrf.org).

NOTE: If participants discontinue study treatment due to experiencing Grade 1 or 2 AEs, this should be noted as the reason for discontinuation.

Grade ≥3
Study treatment may be held for all drug-related toxicities Grade ≥3 (with the exception of liver enzyme elevation, as described below in section 8.2.1) until the toxicity returns to Grade ≤2 or to the level at the time of study entry.

Study treatment may be restarted when the toxicity grade returns to Grade ≤2 or to the level at the time of study entry, but the CMC should be notified prior to re-challenge. Upon re-challenge, if Grade ≥3 toxicities recur, then study treatment should be permanently discontinued (with the exception of liver enzyme elevation, as described below in section 8.2.1).

All Grade ≥3 hypersensitivity reactions will result in permanent discontinuation of study treatment.

NOTE: Participants who permanently discontinue study treatment due to toxicity reasons should be followed until symptoms resolve to Grade ≤2. See sections 6.1 and 6.2 for evaluations for participants not completing treatment.

8.2 Other Conditions

8.2.1 Hepatotoxicity – LFTs

8.2.1.1 **If participants with abnormal entry liver indices develop elevations of AST or ALT >2x entry values or total bilirubin >1.5x entry values during the study, repeat testing should be performed within 48-72 hours. If there are persistent elevations (AST or ALT >2x baseline or total bilirubin >1.5x entry values) upon repeat testing, then close observation (testing and physical examination 2-3 times per week) should be implemented.**

Study treatment should be held for the following reasons:

- **If either entry measurements is <2 x ULN, temporarily hold study treatment if the respective value of ALT or AST increases to >5x entry values.**
- **If either entry measurement is 2 x ULN or greater, temporarily hold study treatment if either ALT or AST increases to 3x entry values.**
- **If ALT or AST increases to >2x entry values and the increase is accompanied by a concomitant increase in total bilirubin to >2x entry values.**
- **Signs and symptoms of acute liver toxicity including fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).**

NOTE: If study treatment is held, the CMC must be notified within 48 hours by e-mail (actg.cmca5371@fstrf.org).

Close observation includes:

- **Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the participant is asymptomatic.**
- **Obtaining a more detailed history of symptoms and prior or concurrent diseases.**
- **Excluding acute viral hepatitis A, B, C, D, and E; autoimmune hepatitis; or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.**
- **Obtaining a history of exposure to environmental chemical agents.**
- **Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).**
- **Consideration for obtaining gastroenterology or hepatology consultations.**

- **Locally performed laboratory testing with results promptly communicated to the site investigator for participants living in a remote area.**

8.2.1.2 Study treatment **can be resumed when symptoms have resolved** and AST/ALT return to ≤2x the entry value. If an elevation in AST or ALT of ≥3x the entry value recurs following reintroduction of study treatment and the cause is possibly or definitely related to study drug, semaglutide should be permanently discontinued. The site should notify the **CMC within 48 hours by e-mail (actg.cmca5371@fstrf.org)** if this occurs.

8.2.2 Hypoglycemia

Hypoglycemia appears to be a risk primarily when **people with diabetes** are treated with semaglutide in combination with insulin or other antidiabetic medications, including insulin secretagogues (i.e., not with semaglutide alone). As **people with diabetes** are excluded from this study, the risk of hypoglycemia is expected to be very low.

All participants must receive education on monitoring and management of hypoglycemia at study entry. If participants report symptoms of hypoglycemia on routine assessments and/or the hypoglycemia questionnaires during telephone/e-mail contact or study visits, they will first be provided instructions to ensure adequate fluid and food intake. If the symptoms persist over the subsequent 24 hours, participants should be instructed to come to the clinic in fasting state for assessment of blood pressure, electrolytes, fasting glucose, and a clinical assessment. If fasting blood glucose is <60 mg/dL, the CMC should be notified via e-mail (actg.cmca5371@fstrf.org) within 48 hours. If the participant rapidly responds to treatment with no recurrence of symptoms, they will have weekly glucose assessments in clinic while the dose is titrating up. If symptoms persist, study treatment will be discontinued.

If symptoms of documented, clinically significant, severe hypoglycemia occur and are believed to be possibly or definitely related to study treatment, the CMC should be notified, study treatment should be temporarily held, and the participant should be closely observed. Re-challenge may occur at the discretion of the CMC, in consultation with the site investigator.

Because symptoms of hypoglycemia are non-specific and often due to other causes, it is very important to attempt to document measured blood glucose at the time of occurrence of symptoms. If participant has symptoms of hypoglycemia (e.g., sweating, palpitations, and tremulousness), hold semaglutide and measure glucose as soon as feasible (does not require fasting). Take care that there is not a prolonged period between symptom onset, sample collection,

and glucose measurement. Sites may choose to provide a home glucose-monitoring device for this purpose, at their own discretion and as a supplement to glucose measurements performed in the clinic, but these will not be provided by the study. If a participant experiences hypoglycemic symptoms, they should be instructed to consume 15-20 grams glucose or simple carbohydrates. Examples include:

- 4 ounces (0.5 cup) of juice or regular soda **(e.g., Coke [Coca-Cola®])**
- 8 ounces of non-fat or 1% milk
- 1 tablespoon sugar, honey, or corn syrup
- 2 tablespoons of raisins
- 15-20 grams sugar from hard candy, jellybeans, and gumdrops.

8.2.2.1 Fasting Blood glucose 55-64 mg/dL (Grade 1)

Continue study treatment and monitor for symptoms of hypoglycemia.

8.2.2.2 Fasting Blood glucose 40-54 mg/dL (Grade 2)

- Temporarily hold study treatment and evaluate for other potential causes of hypoglycemia.
- Repeat fasting blood glucose within 1 week. If repeat is ≥55 mg/dL, study treatment can be resumed.
- If symptoms of hypoglycemia recur and blood glucose is again 40-55 mg/dL, discontinue study treatment permanently.

8.2.2.3 Fasting Blood glucose <40 mg/dL (Grade 3 or 4)

- Temporarily hold study treatment and evaluate for other potential causes of hypoglycemia.
- Repeat fasting blood glucose within 1 week. If repeat is ≥55 mg/dL, and no other potential causes of hypoglycemia are identified, re-challenge can be attempted, after discussion with the CMC, if the low blood glucose is believed to be secondary to alternative causes.
- If the low blood glucose is believed to be due to study treatment, discontinue study treatment permanently.

8.2.3 Calculated CrCl

Consideration of potential causes of reduced renal function should be made, if any participant experiences a calculated CrCl <40 mL/min or 50% decline from study entry. The calculated CrCl should be repeated within 7 days and recorded on the eCRF. As semaglutide does not require renal dosing, and is not expected to cause renal dysfunction, specific clinical circumstances should be discussed with the A5371 CMC (actg.cmca5371@fstrf.org) prior to modification of study treatment.

8.2.4 Nausea/Vomiting

Development of Grade ≥**2** nausea or vomiting should lead to evaluation for causes other than study treatment, e.g., new medication, pancreatitis, viral illness, etc. If nausea and vomiting are suspected secondary to study treatment, study treatment can be held until symptoms are Grade <2 or to baseline**. Symptoms will be re-assessed every 2-4 days. For participants with Grade ≥2 symptoms of nausea or vomiting, a weekly clinical assessment will include measurement of blood pressure and pulse, and ascertainment of fasting glucose, complete metabolic panel, and magnesium.** If Grade ≥3 nausea or vomiting return following re-challenge and are suspected to be due to study treatment, study treatment should be permanently discontinued and premature treatment discontinuation evaluations should be performed at the time of study treatment discontinuation, where applicable. Use of antiemetic agents is encouraged for Grade ≤2 nausea and vomiting but are not provided by the study. In clinical trials thus far, discontinuation for nausea and vomiting has been infrequent, with most nausea being manageable and resolving within a few weeks. If persistent nausea occurs during dose titration, the dose titration schedule may be altered, in discussion with the CMC.

8.2.5 Diarrhea

Development of Grade ≥3 diarrhea should lead to evaluation for causes other than study treatment. If diarrhea is suspected to be secondary to study treatment, study drug can be held until diarrhea is Grade ≤2 or to baseline (study entry). If diarrhea Grade ≥3 returns following re-challenge and is suspected to be due to study treatment, study treatment should be permanently discontinued and premature treatment discontinuation evaluations should be performed at the time of study treatment discontinuation. Participants who develop Grade ≤2 diarrhea are encouraged to use antidiarrheal agents (e.g., Imodium or Lomotil), although these will not be provided by the study.

8.2.6 Pancreatitis

8.2.6.1 Pancreatitis is defined as the presence of nausea, vomiting, and abdominal pain associated with any elevation in serum lipase.

8.2.6.2 If a diagnosis of symptomatic Grade ≥2 pancreatitis is made and is believed to be secondary to study treatment, study treatment will be permanently discontinued and premature treatment discontinuation evaluations should be performed, where applicable. If the diagnosis is believed to be secondary to other causes, those should be managed per local standard of care, with study treatment held until pancreatitis is Grade <2.

For symptomatic Grade <2 pancreatitis, conservative management with temporary hold of study treatment can be attempted. If symptomatic

pancreatitis recurs following re-challenge and is believed to be secondary to study treatment, study treatment should be discontinued.

For asymptomatic lipase elevations, administration of study treatment may continue.

8.2.7 Fatigue and Headache Symptoms

If participant has new onset or Grade ≥2 fatigue or headache symptoms for >14 days, work-up for causes other than study product should be initiated. Also:

- Consult the A5371 CMC via email (actg.cmcA5371@fstrf.org) before discontinuation of study treatment.
- Consider temporarily holding study treatment.

8.2.8 Allergic Reactions

If a participant develops a skin reaction, rash, angioedema, or other symptoms felt to represent an allergic reaction potentially related to study treatment, temporarily hold the study treatment and instruct participant to return to the CRS or emergency health center immediately for care. If the reaction is determined to be related to study treatment, permanently discontinue the study treatment and perform premature treatment evaluations, where applicable.

8.2.9 Study Drug Injection Site Reactions

If a participant develops a Grade 1 or 2 injection site reaction, it should be managed at the discretion of the site investigator. If the injection site reaction is Grade 3 or 4, the site should contact the A5371 CMC via email (actg.cmcA5371@fstrf.org).

8.3 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone 1-800-258-4263 or fax: 800-800-1052. For studies conducted at sites outside the United States, report to The Antiretroviral Pregnancy Registry—Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.

Pregnancy Outcomes and Reporting

Pregnant individuals must discontinue study treatment and study evaluations, but will be encouraged to remain in contact with the study team to provide pregnancy outcome data. Individuals who become pregnant should complete the premature study discontinuation assessments (except MRI) within 14 days of the site becoming aware of the pregnancy/stopping study medication (whichever is earlier), but the off-study eCRF will be completed at the end of the pregnancy. Birth outcomes will be recorded on an eCRF at the end of pregnancy.

If an individual discontinues from the study before the end of the pregnancy, the site staff should request permission to contact the participant regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity **if no improvement per instructions** (see section 8.1 Toxicity **and section 8.2 Other Conditions**).
- Requirement for prohibited concomitant medications (see section 5.4).
- Request by participant to terminate treatment (refer to section 6.2.4).
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

9.2 Premature Study Discontinuation

- Failure by the participant to attend ≥2 consecutive study visits.
- Participant repeatedly noncompliant (i.e., missed ≥6 injections as prescribed). The study team should be consulted on specific circumstances before a participant is discontinued for noncompliance.
- **Participant's inability** to tolerate at least 0.25 mg/week of study treatment.
- **Participant's inability** complete study procedures, including the MRIs, as required.
- **Participant changes diet or exercise regimen significantly (refer to section 4.2.5).**
- **Participant's inability to keep study product at 36°F to 46°F (2°C to 8°C) prior to first use, or to maintain the study product at a controlled room temperature between 59°F and 86°F (15°C to 30°C) following first use (refer to section 4.2.23).**
- Request by participant to terminate **study** (refer to section 6.2.4).
- Request by the participant to withdraw.
- Pregnancy or breastfeeding.
- At the discretion of the IRB/EC, **ACTG,** FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, or investigator.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5371 is a phase II, single-arm, open-label, clinical trial designed to study the effects of semaglutide on MRI-PDFF-quantified IHTG in persons with HIV on suppressive ART. Eligible participants will receive semaglutide; all participants will be followed on-

treatment for 24 weeks and on-study for 48 weeks. The total sample size is 50 participants.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov. Outcomes of interest for secondary and exploratory objectives intended for subsequent publications are listed under "Other Outcome Measures."

10.2.1 Primary Outcome Measure

Change (absolute) in IHTG (%) (from pre-entry to week 24).

10.2.2 Secondary Outcome Measures

10.2.2.1 Change (percent) in IHTG (%) (from pre-entry to week 24).

10.2.2.2 Change (absolute) in BMI, body weight, and minimum WC from week 0 to weeks 12 and 24.

10.2.2.3 Level of IHTG (%) at pre-entry and week 24.

10.2.2.4 Occurrence of premature discontinuation of study treatment, including reasons for discontinuation.

10.2.2.5 Occurrence of Grade ≥3 adverse event that are related to study treatment.

10.2.2.6 Changes in insulin resistance (HOMA-IR) and glucose from week 0 to weeks 12 and 24.

10.2.2.7 Change (absolute) in lipid profiles (triglycerides, HDL cholesterol, LDL cholesterol, total cholesterol) from week 0 to weeks 12 and 24.

10.2.2.8 Presence of metabolic syndrome at weeks 0, 12, and 24. Metabolic syndrome is defined as having ≥3 of the following: increased minimum WC, high triglyceride level, reduced HDL cholesterol, increased blood pressure, and elevated fasting blood glucose, based on current guidelines.

10.2.3 Other Outcome Measures

10.2.3.1 Cartridge counts of adherence at weeks 4, 12, and 24.

10.2.3.2 Changes in physical function (gait speed defined as <1 m/sec or ≥1 m/sec, chair rise rate defined as time in seconds to rise 5 times and 10 times) from week 0 to weeks 24 and 48.

10.2.3.3 Change (absolute) in muscle fat area and density as measured by MRI from pre-entry to week 24.

10.2.3.4 Quality of life measures at weeks 0 and 24.

10.2.3.5 Change (absolute) in adipose tissue (VAT and SAT) area and density as measured by MRI from pre-entry to week 24.

10.2.3.6 Change in inflammatory and metabolic biomarkers from week 0 to week 24.

10.2.3.7 Gastrointestinal microbial taxonomy, abundance, diversity and function from fecal samples at weeks 0 and 24 and change from week 0 to 24 (pending additional funding).

10.2.3.8 Proportions of immune cells at weeks 0 and 24 and change from week 0 to 24.

10.2.3.9 Change (absolute) in body weight, BMI, minimum WC, lipid profiles, glucose, HOMA-IR, and select inflammatory and metabolic biomarker from week 24 to week 48.

10.2.3.10 Physical activity and dietary changes between weeks 24 and 48.

10.3 Randomization and Stratification

There is no randomization or stratification in this study. Eligible participants will be registered at study entry and will receive study treatment.

Participant enrollment targets are at least 40% persons currently identifying as cisgender or transgender women and 50% non-white. **Each site will be guaranteed three slots, one of which must be filled with a woman (cisgender or transgender), and two of which must be filled with non-white participants (of course, the woman could be non-white and fulfill both requirements).** If after 60% of enrollment is completed **and enrollment of women is <40%**, **additional restrictions to enhance enrollment of women may occur to ensure ≥40% enrollment of women. The remaining participant slots will be available by competitive enrollment.** If after 50% of enrollment is completed the enrollment of non-Hispanic Caucasians is >70%, restrictions will be placed on their enrollment. Sites will be encouraged to enroll transgender participants.

10.4 Sample Size and Accrual

The planned total sample size is 50 participants. Allowing for 25% loss to follow-up, the anticipated evaluable sample size is 37 participants. It is anticipated that participants will accrue to the study at a rate of 6-7 participants per month; at this rate, the study should fully accrue in approximately 7-8 months.

This study's primary objective is to evaluate whether 24 weeks of semaglutide will improve IHTG in ART-treated, adults with HIV, hepatic steatosis, central obesity, and insulin resistance or pre-diabetes. The primary comparison will examine the absolute change in IHTG from pre-entry to week 24.

The sample size is based on a two-sided, one-sample t-test with 5% significance level and 90% statistical power, and assumes, based on published literature, that semaglutide will reduced (improve) IHTG. A range of effect sizes and corresponding standard deviations (SDs) were considered to determine the sample size for this study. There is limited literature on the SD of the change in MRI-PDFF-quantified IHTG; one study of a different intervention showed an estimate of 4.6% for the intervention arm and 9.9% for the placebo arm. Considering this range of reported SDs, possible scenarios considering different SDs and mean differences are shown below (see Table 10.4-1).

Assuming a 9% SD, with 37 participants, there is 90% statistical power to identify a significant change in IHTG, under the assumption that the true change is 5% over 24 weeks. Inflating the sample size to account for 25% loss to follow-up and premature treatment discontinuation, yields a total sample size of 50 participants. With a short intervention, regular telephone/email contract, and once weekly dosing, we anticipate <25% loss to follow-up.

Table 10.4-1: Sample Sizes under Different Scenarios Assuming: One-sample T-test with Two-sided 5% Alpha (significance level) and ≥90% Power

N Inflated by 25% for LTFU			
Total N Enrolled	N Evaluable	Mean Change from Pre-entry to Week 24 (%)	Standard Deviation of Change in IHTG (%)
8	6	-9	5
12	9	-9	7
18	13	-9	9
11	8	-7	5
18	13	-7	7
27	20	-7	9
18	13	-5	5
31	23	-5	7
50	37	-5	9
43	32	-3	5
80	60	-3	7
130	97	-3	9

Table 10.4-2: Statistical Power under Different Scenarios Assuming: N=37 Evaluable per Arm

One-sample T-test with Two-sided 5% Alpha N Enrolled Included by 25% for LTFU		
Power	Mean Change from Pre-entry to Week 24 (%)	Standard Deviation of Change in IHTG (%)
94%	-3	5
72%	-3	7
51%	-3	9
100%	-5	5
99%	-5	7
91%	-5	9
77%	-5	11
100%	-7	5
100%	-7	7
100%	-7	9
96%	-7	11

10.5 Data and Safety Monitoring

At SMC reviews, data will be considered as detailed in section 7.4. There are no pre-specified stopping guidelines.

10.6 Analyses

10.6.1 Primary Analysis

The primary analysis will be limited to participants who remain on treatment through week 24.

Absolute change from pre-entry to week 24 in IHTG (%) will be summarized with the mean and a 95% confidence interval (CI) for the mean change, and will be assessed, with a two-sided t-test with 5% alpha. In addition, a supplemental analysis will consider all participants with an on-treatment IHTG assessment, regardless if they prematurely discontinued treatment.

10.6.2 Secondary Analyses

The percent change in IHTG (%) from pre-entry to week 24 will be summarized in a similar manner as the primary analysis. The mean percent change and corresponding 95% CI for the mean change will be summarized, and assessed with a two-sided t-test with 5% alpha. Additional supplemental analyses of percent change in IHTG will be considered to account for participants who

prematurely discontinue treatment. Level of IHTG will be summarized with descriptive summary statistics.

Safety will be evaluated by estimating the proportion of participants who experience any Grade ≥3 AE, or, for AST/ALT, elevation ≥3x higher than entry or ≥500 U/L (whichever value is lower), that are related to study treatment. In addition, tabular summaries of all protocol-defined AEs will be included to evaluate the nature and rate of AEs. Participant-level listings of premature treatment discontinuations, with reasons for discontinuations, will be provided. No formal statistical tests will be provided for safety or tolerability analyses.

Levels of insulin resistance, lipid profiles, BMI, body weight, minimum WC, and the presence of metabolic syndrome will be summarized with descriptive summary statistics by study week. Absolute changes in BMI, insulin resistance, lipid profiles, weight, and minimum WC will also be summarized at each time point with means and 95% confidence intervals. The comparison of change in the presence of metabolic syndrome will use GEE for binary data to provide an estimate of decreased risk within arm, corresponding p-values and 95% CIs will be also provided. To evaluate the relationships between changes in IHTG and changes in metabolic parameters (insulin resistance, lipid profiles, number of metabolic syndrome components), correlation analysis will be used.

Durability of treatment efficacy will be measured by summarizing the change in body weight, BMI, minimal WC, lipid profiles, glucose, HOMA-IR, and select circulating inflammatory and metabolic biomarkers between weeks 24 and 48.

11.0 PHARMACOLOGY PLAN

Not applicable.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens 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 concerning 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

12.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, participants' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

12.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the ACTG, IRB/EC, the site monitors, the FDA, the NIAID, the OHRP, other local, US, and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (**Appendix II**) 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. 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, 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, FDA, NIAID, OHRP, other local, US, 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, FDA, NIAID, 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 trial will be governed by ACTG policies.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

16.0 REFERENCES

Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129:113-21.

Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. Diabetes Obes Metab 2018;20:2210-19.

Alderete TL, Toledo-Corral CM, Desai P, et al. Liver fat has a stronger association with risk factors for type 2 diabetes in African-American compared with Hispanic adolescents. J Clin Endocrinol Metab 2013;98:3748-54. doi: 10.1310/jc.2013-1138. Epub 2013 Jul 19.

Andersen O, Haugaard SB, Holst JJ, et al. Enhanced glucagon-like peptide-1 (GLP-1) response to oral glucose in glucose-intolerant HIV-infected patients on antiretroviral therapy. HIV Med 2005;6:91-8.

Armstrong MJ, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. Hepatology 2014;59:1174-97.

Armstrong MJ, Hull D, Guo K, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64:399-408.

Astrup A, Rossner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374:1606-16.

Balestrieri ML, Rizzo MR, Barbieri M, et al. Sirtuin 6 expression and inflammatory activity in diabetic atherosclerotic plaques: effects of incretin treatment. Diabetes 2015;64:1395-406.

Bang-Berthelsen CH, Holm TL, Pyke C, et al. GLP-1 induces barrier protective expression in Brunner's glands and regulates colonic inflammation. Inflamm Bowel Dis 2016;22:2078-97. doi: 10.1097/MIB.0000000000000847.

Berner K, Morris L, Baumeister J, Louw Q. Objective impairments of gait and balance in adults living with HIV-1 infection: a systematic review and meta-analysis of observational studies. BMC Musculoskelet Disord 2017;18:325. doi: 10.1186/s12891-017-1682-2.

Bhala N, Angulo P, van der Poorten D, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology 2011;54:1208-16.

Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology 2014;59:713-23.

Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19:1242-51. doi: 10.1111/dom.12932.

Cade WT, Reeds DN, Lassa-Claxton S, et al. Post-exercise heart rate recovery in HIV-positive individuals on highly active antiretroviral therapy. Early indicator of cardiovascular disease? HIV Med 2008;9:96-100. Epub 2007 Dec 18.

Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. Diabetes Care 2011;34:210-5.

Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Am J Gastroenterol 2012;107:811-26.

Crum-Cianflone N, Dilay A, Collins G, et al. Nonalcoholic fatty liver disease among HIV-infected persons. J Acquir Immune Defic Syndr 2009;50:464-73.

Culha MG, Inkaya AC, Yildirim E, et al. Glucagon like peptide-1 receptor agonists may ameliorate the metabolic adverse effect associated with antiretroviral therapy. Med Hypotheses 2016;94:151-153.

Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology 2012;142:711-25 e6.

Cuthbertson DJ, Irwin A, Gardner CJ, et al. Improved glycaemia correlates with liver fat reduction in obese, type 2 diabetes, patients given glucagon-like peptide-1 (GLP-1) receptor agonists. PLoS One 2012;7:e50117.

Debroy P, Lake JE, Malagoli A, Guaraldi G. Relationship between grip strength and nonalcoholic fatty liver disease in men living with HIV referred to a metabolic clinic. J Frailty Aging 2019;8:150-3.

Doulberis M, Kotronis G, Gialamprinou D, et al. Non-alcoholic fatty liver disease: An update with special focus on the role of gut microbiota. Metabolism 2017;71:182-97. doi: 10.1016/j.metabol.2017.03.013. Epub 2017 Mar 31.

Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006;44:865-73.

Fabbrini E, Magkos F, Mohammed BS, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proc Natl Acad Sci U S A 2009;106:15430-5.

Feng W, Gao C, Bi Y, et al. A randomized trial comparing gliclazide, liraglutide, and metformin effects on diabetes with nonalcoholic fatty liver disease. J Diabetes 2017;9:800-9.

Forst T, Michelson G, Ratter F, et al. Addition of liraglutide in patients with Type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function. Diabet Med 2012;29:1115-8. doi: 10.1111/j.1464-5491.2012.03589.x.

Frøssing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. Diabetes Obes Metab 2018;20:215-18. doi: 10.1111/dom.13053. Epub 2017 Aug 11.

Gariani K, Philippe J, Jornayvaz FR. Non-alcoholic fatty liver disease and insulin resistance: from bench to bedside. Diabetes Metab 2013;39:16-26.

Guaraldi G, Squillace N, Stentarelli C, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis 2008;47:250-7.

Hadigan C, Liebau J, Andersen R, et al. Magnetic resonance spectroscopy of hepatic lipid content and associated risk factors in HIV infection. J Acquir Immune Defic Syndr 2007;46:312-7.

Hannah WN Jr, Harrison SA. Effect of weight loss, diet, exercise, and bariatric surgery on nonalcoholic fatty liver disease. Clin Liver Dis 2016;20:339-50.

Haring R, Wallaschofski H, Nauck M, et al. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. Hepatology 2009;50:1403-11.

Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. Gut 2007;56:1760-9.

Hegde P, Weiss E, Paradis V, et al. Mucosal-associated invariant T cells are a profibrogenic immune cell population in the liver. Nature Commun 2018;9:2146.

Hogan AE, Gaoatswe G, Lynch L, et al. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia 201**4**;57:781-4.

Hong CW, Mamidipalli A, Hooker JC, et al. MRI proton density fat fraction is robust across the biologically plausible range of triglyceride spectra in adults with nonalcoholic steatohepatitis. J Magn Reson Imaging 2018;47:995-1002. doi: 10.1002/jmri.25845.

Hu SY, Zhang Y, Zhu PJ, Zhou H, Chen YD. Liraglutide directly protects cardiomyocytes against reperfusion injury possibly via modulation of intracellular calcium homeostasis. J Geriatr Cardiol 2017;14:57-66.

Ishii S, Nagai Y, Sada Y, et al. Liraglutide reduces visceral and intrahepatic fat without significant loss of muscle mass in obese patients with type 2 diabetes: a prospective case series. J Clin Med Res 2019;11:219-24. doi: 10.14740/jocmr3647.

Kaul S. Mitigating cardiovascular risk in type 2 diabetes with antidiabetes drugs: a review of principal cardiovascular outcome results of EMPA-REG OUTCOME, LEADER, and SUSTAIN-6 trials. Diabetes Care 2017;40:821-31.

Khoo J, Hsiang J, Taneja R, et al. Comparative effects of liraglutide 3 mg vs structured lifestyle modification on body weight, liver fat and liver function in obese patients with non-alcoholic fatty liver disease: a pilot randomized trial. Diabetes Obes Metab 2017;19:1814-17.

Korenblat KM, Fabbrini E, Mohammed BS, Klein S. Liver, muscle, and adipose tissue insulin action is directly related to intrahepatic triglyceride content in obese subjects. Gastroenterology 2008;134:1369-75.

Lake JE, Stanley TL, Apovian CM, et al. Practical review of recognition and management of obesity and lipohypertrophy in human immunodeficiency virus infection. Clin Infect Dis 2017; 1422-1429.

le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399-1409.

Lynch L, Hogan AE, Duguette D, et al. iNKT cells induce FGF21 for thermogenesis and are required for maximal weight loss in GLP1 therapy. Cell Metab 2016;24:510-19.

Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. Diabetes Obes Metab 2016;18:317-32.

Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44. Epub 2016 Sep 15.

Mastroianni CM, Lichtner M, Mascia C, et al. Molecular mechanisms of liver fibrosis in HIV/HCV coinfection. Int J Mol Sci 2014;15:9184-208. doi: 10.3390/ijms15069184.

Metkus TS, Brown T, Budoff M, et al. HIV infection is associated with an increased prevalence of coronary noncalcified plaque among participants with a coronary artery calcium score of zero: Multicenter AIDS Cohort Study (MACS). HIV Med 2015;16:635-9.

Middleton MS, Lawitz EJ, Jayakumar S, et al. Hepatic proton density fat fraction correlates with histologic measures of steatosis and is responsive to changes in those measures in a multi-center nonalcoholic steatohepatitis clinical trial. 2nd International Workshop on NASH Biomarkers, Washington DC, May 5-7, 2017.

Miyazaki M, Kato M, Tanaka K, et al. Increased hepatic expression of dipeptidyl peptidase-4 in non-alcoholic fatty liver disease and its association with insulin resistance and glucose metabolism. Mol Med Rep 2012;5:729-33.

Morse CG, McLaughlin M, Matthews L, et al. Nonalcoholic steatohepatitis and hepatic fibrosis in HIV-1-monoinfected adults with elevated aminotransferase levels on antiretroviral therapy. Clin Infect Dis 2015;60:1569-78.

Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology 2010;52:79-104.

Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011;43:617-49.

Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nontriglyceride fatty acid metabolites. Hepatology 2010;52:774-88.

O'Brien KK, Tynan AM, Nixon SA, Glazier RH. Effectiveness of progressive resistive exercise (PRE) in the context of HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis 2017;17:268.

O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet 2018;392:637-49. doi: 10.1016/S0140-6736(18)31773-2. Epub 2018 Aug 16.

Patel J, Bettencourt R, Cui J, et al. Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Therap Adv Gastroenterol 2016;9:692-701. doi: 10.1177/1756283X16656735.

Perera S, Patel KV, Rosano C, et al. Gait speed predicts incident disability: a pooled analysis. J Gerontol A Biol Sci Med Sci 2016;71:63-71.

Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11-22.

Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Ann Intern Med 2014;160:458-67.

Pratley R, Nauck M, Bailey T, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. Int J Clin Pract 2011;65:397-407.

Qu Y, Li M, Hamilton G, Zhang YN, Song B. Diagnostic accuracy of hepatic proton density fat fraction measured by magnetic resonance imaging for the evaluation of liver steatosis with histology as reference standard: a meta-analysis. Eur Radiol 2019;29:5180-9.

Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7:234-8.

Rakipovski G, Rolin B, Nøhr J, et al. The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE$^{-/-}$ and LDLr$^{-/-}$ mice by a mechanism that includes inflammatory pathways. JACC Basic Transl Sci 2018;3:844-57.

Reeds DN, Chambers KT, Patterson BW, Finck BN. Intrahepatic triglyceride is more strongly associated with insulin-resistant glucose metabolism than visceral adiposity in HIV, and is improved with tauroursodeoxycholic acid treatment. [Abstract 023]. In: 19th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV; October 23-25, 2017; Milan, Italy.

Schuppan D, Schattenberg JM. Non-alcoholic steatohepatitis: pathogenesis and novel therapeutic approaches. J Gastroenterol Hepatol 2013;28(Suppl 1):68-76.

Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol 2008;49:600-7.

Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50-8.

Tang W, Xu Q, Hong T, et al. Comparative efficacy of anti-diabetic agents on nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized and non-randomized studies. Diabetes Metab Res Rev 2016;32:200-16.

Targher G, Bertolini L, Poli F, et al. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 2005;54:3541-6.

Targher G, Bertolini L, Rodella S, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care 2007;30:2119-21.

Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363:1341-50.

Tashiro Y, Sato K, Watanabe T, et al. A glucagon-like peptide-1 analog liraglutide suppresses macrophage foam cell formation and atherosclerosis. Peptides 2014;54:19-26. doi: 10.1016/j.peptides.2013.12.015. Epub 2014 Jan 10.

Vallet-Pichard A, Mallet V, Pol S. Nonalcoholic fatty liver disease and HIV infection. Seminars in liver disease 2012;32:158-66.

Vodkin I, Loomba R. Editorial: NAFLD in HIV infection--call for action. Authors' reply. Aliment Pharmacol Ther 2015;41:591.

Vodkin I, Valasek MA, Bettencourt R, et al. Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case-control study. Aliment Pharmacol Ther 2015;41:368-78.

Yusta B, Baggio LL, Koelher J, et al. GLP-1R agonists modulate enteric immune responses through the intestinal intraepithelial lymphocyte GLP-1R. Diabetes 2015;64:2537-49.

Zhu L, Baker RD, Baker SS. Gut microbiome and nonalcoholic fatty liver diseases. Pediatr Res 2015;77:245-51. doi: 10.1038/pr.2014.157. Epub 2014 Oct 13.

APPENDIX I: PROTOCOL SYNOPSIS

A5371

A Single-Arm, Open-Label, Pilot Study of Semaglutide for Non-Alcoholic Fatty Liver Disease (NAFLD), a Metabolic Syndrome with Insulin Resistance, Increased Hepatic Lipids, and Increased Cardiovascular Disease Risk (The SLIM LIVER Study)

DESIGN

A5371 is a phase II, single-arm, open-label pilot study of the effects of semaglutide on intra-hepatic triglyceride (IHTG) content in people living with HIV, central adiposity, insulin resistance or pre-diabetes, and hepatic steatosis. Participants will complete seven study visits (screening, pre-entry, entry, and weeks 4, 12, 24, and 48) and be contacted by telephone or e-mail six times (between study visits). IHTG will be quantified by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at two time points. Stool and blood samples (for hematology, liver function tests, chemistry, lipid panel and LDL measurement, CD4, and HIV-RNA) will be collected at several visits. Participants will also complete food diaries, a hypoglycemia questionnaire, adherence and strength assessments, and report on physical activity, diet, quality of life, and acceptability of study drug.

OBJECTIVES

Primary Objective

To evaluate whether semaglutide will reduce IHTG content, as quantified by MRI-PDFF, among ART-treated adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes.

Secondary Objectives

1. **To evaluate the safety and tolerability of semaglutide in adults with HIV, hepatic steatosis, central adiposity, and insulin resistance or pre-diabetes.**
2. **To evaluate the effects of semaglutide on weight, minimum waist circumference (WC), and body mass index (BMI).**
3. **To evaluate the effects of semaglutide on insulin resistance or pre-diabetes, lipid profiles, and the prevalence of metabolic syndrome.**
4. **To evaluate relationships between observed changes in IHTG and changes in metabolic parameters.**

OUTCOME MEASURES

Primary Outcome Measure

Change (absolute) in IHTG (%)
[Time Frame: Measured from pre-entry to Week 24]

Secondary Outcome Measures

Change (percent) in IHTG (%)
[Time Frame: Measured from pre-entry to Week 24]

Change (absolute) in body mass index (BMI)
[Time Frame: Measured from Week 0 to Weeks 12 and 24]

1. **Change (absolute) in body weight**
   [Time Frame: Measured from Week 0 to Weeks 12 and 24]

2. **Change (absolute) in minimum waist circumference (WC)**
   [Time Frame: Measured from Week 0 to Weeks 12 and 24]

3. **Level of IHTG (%)**
   [Time Frame: Measured at pre-entry and Week 24]

4. **Occurrence of premature discontinuation of study treatment, including reasons for discontinuation.**
   [Time Frame: Measured through Week 24]

5. **Occurrence of Grade ≥3 adverse event that are related to study treatment**

6. **Change (absolute) in insulin resistance (HOMA-IR)**
   [Time Frame: Measured from Week 0 to Weeks 12 and 24]

7. **Change (absolute) in glucose**
   [Time Frame: Measured from Week 0 to Weeks 12 and 24]

8. **Change (absolute) in lipid profiles (triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol)**
   [Time Frame: Measured from Week 0 to Weeks 12 and 24]

9. **Presence of metabolic syndrome**

10. **Metabolic syndrome is defined as having ≥3 of the following: increased minimum WC, high triglyceride level, reduced HDL cholesterol, increased blood pressure, and elevated fasting blood glucose, based on current guidelines.**
    [Time Frame: Measured at Weeks 0, 12, and 24]

DURATION **Approximately 48 weeks.**

SAMPLE SIZE **50 participants.**

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

1. **Adults ≥18 years of age with HIV.**

2. **Two separate reports of HIV-1 RNA measurements <50 copies/mL, and no HIV-1 RNA measurement >500 copies/mL, during the 48 weeks prior to entry.**

3. **No change in ART in 24 weeks prior to entry or plans to change during study.**

4. **Not meeting criteria for diabetes but with central adiposity (i.e., minimum waist circumference of ≥95 cm for individuals assigned male sex at birth or ≥94 cm for individuals assigned female sex at birth), ≥5% IHTG content, plus at least one of the following indicators of insulin resistance or pre-diabetes: fasting plasma glucose 100-125 mg/dL, HbA1c between 5.7% and <6.5%, or HOMA-IR >3.0.**

5. **Documented evidence of immunity to hepatitis A virus (HAV) or documented history of HAV vaccination within 30 days prior to entry.**

6. **CD4+ T-cell count ≥200 cells/mm^3 within 30 days prior to pre-entry.**

7. **The following laboratory values obtained within 30 days prior to pre-entry:**
   a. **Absolute neutrophil count (ANC) >750 cells/mm^3.**
   b. **Hemoglobin >10 g/dL for individuals assigned male sex at birth and >9 g/dL for individuals assigned female sex at birth.**
   c. **Creatinine clearance (CrCl) ≥50 mL/min, as calculated by the CKD-Epi equation.**
   d. **Aspartate aminotransferase (AST) (SGOT) ≤3 x ULN on at least two measures.**
   e. **Alanine aminotransferase (ALT) (SGPT) ≤3 x ULN on at least two measures.**
   f. **Fasting triglyceride level ≤500 mg/dL.**

8. **For individuals prescribed daily medications with anti-inflammatory properties, the doses must be stable.**

9. **For individuals taking daily lipid-lowering medications, the doses must be stable.**

10. **Agree to use contraception if able to become pregnant.**

11. **For individuals taking vitamin E (any dose), the dose must be stable.**

Exclusion Criteria

1. **Pregnant, breastfeeding, or plans to become pregnant.**

2. **Known active hepatitis C virus (HCV) infection.**

3. **Active/chronic hepatitis B virus (HBV).**

4. **Known retinopathy (excluding remote history of cotton wool spots).**

5. **Known active severe delayed gastric emptying.**

6. **Gain or loss of >5% body weight within 12 weeks prior to study entry.**

7. **Any plans to change diet or exercise regimen significantly, except for the adoption of study-provided suggestions for diet and exercise, within the study period.**

8. **Known acute or chronic liver disease with cirrhosis or portal hypertension.**

9. **History of liver transplant.**

10. **Current diagnosis of diabetes mellitus or current use of diabetes medications, or a laboratory measurement of hemoglobin A1c ≥6.5% at screening.**

11. **Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2).**

12. **History of unexplained hypercalcemia corrected for albumin that is >10.5 mg/dL.**

13. **Use of any immunomodulatory (including prednisone equivalent of ≥10 mg), HIV vaccine, investigational therapy, or TNF-α therapy within 3 months prior to study entry.**

14. **Use of human growth hormone, tesamorelin, supraphysiologic testosterone to achieve therapeutic blood levels, or any use of other anabolic steroids within 3 months prior to study entry or plans to start these while on study.**

15. **Use of estrogens or progesterones at supraphysiologic doses within 3 months prior to study entry.**

16. **Known allergy/sensitivity or any hypersensitivity to components of study drug or its formulation.**

17. **Current serious illness requiring systemic treatment and/or hospitalization.**

18. **Use of GLP-1 agonists within 24 weeks prior to study entry.**

19. **Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.**

20. **Excessive consumption of alcohol of ≥3 months within 90 days prior to screening.**

21. **Known chronic pancreatitis or more than one episode of pancreatitis ever in the past.**

22. **Intent to use any medication likely to cause significant changes in weight during the study period.**

23. **Use of stavudine within 12 months prior to study entry.**

24. **Prior bariatric surgery (e.g., lap band, gastric sleeve, or Roux-en-Y bypass surgery) or major gastric surgery or plans to undergo weight reduction surgery while on study.**

25. **Individuals with any metal, implantable devices (e.g., pacemakers, prosthetics), or shrapnel, per standard MRI exclusion criteria.**

REGIMEN **Participants will receive semaglutide subcutaneously once weekly for 24 weeks. Participants will receive a dose of 0.25 mg weekly starting at entry, followed by 0.5 mg weekly starting at week 2, and**

then 1.0 mg weekly from weeks 4 through 24. During weeks 25-48, all participants will be off study drug.

SITES **This is a limited-center study being conducted at both US and non-US ACTG clinical research sites (CRSs) with the ability to perform MRI-PDFF.**

APPENDIX II: SAMPLE INFORMED CONSENT
DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For Protocol: A5371
A Single-Arm, Open-Label Pilot Study of Semaglutide for Non-Alcoholic Fatty Liver Disease (NAFLD), a Metabolic Syndrome with Insulin Resistance, Increased Hepatic Lipids, and Increased Cardiovascular Disease Risk
(The SLIM LIVER Study)
FINAL Version 2.0, dated **06/22/20**

SHORT TITLE FOR THE STUDY: The SLIM LIVER Study

SUMMARY

PURPOSE

This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate the safety and tolerability of a drug called semaglutide and to see whether it can reduce fat in the liver (also called intra-hepatic triglycerides, IHTG).

STUDY TREATMENT

Semaglutide, a liquid that is given once a week using a pre-filled self-injection (or "auto-inject") pen, will be provided to you through this study. Semaglutide (brand name Ozempic) is a drug that is used to treat people who have diabetes; it also causes weight loss and may provide some protection against cardiovascular disease and diabetes. In people living with HIV, the use of semaglutide to reduce weight and the level of IHTG are experimental. You will continue taking your anti-HIV medications that are prescribed by your doctor while you are in this study. The anti-HIV medications will not be provided to you in this study.

NUMBER OF PARTICIPANTS

About 50 participants will take part in this study.

LENGTH OF STUDY

The study treatment will last for 24 weeks (about 6 months). Participants will be followed for an extra 24 weeks after stopping medication. The total time on study will be 48 weeks (about 12 months).

REQUIRED ACTIVITIES

Blood and stool collections

- At all visits, some blood will be collected from a vein in your arm.
- At two visits, you will be asked to provide a stool sample.

Special Procedures

- You will use an auto-inject pen weekly for 24 weeks **to deliver study product to yourself.**
- At a two visits, a **magnetic resonance imaging** (MRI) scan will be performed.
- At three visits, you will be asked to perform some tests of physical function.
- **The study staff** will contact **you** by telephone or e-mail **several times during** the study.

RISKS

The following are possible **while taking study treatment:**
Nausea, vomiting, diarrhea, abdominal pain, constipation, thyroid tumor, inflammation of the pancreas, low blood sugar, **low blood pressure,** kidney problems, **eye problems, liver damage,** allergic reaction, risks related to injections, discomfort when collecting stool, and risks related to MRI scans.

BENEFITS

There may be a direct benefit to you, but no guarantee can be made. It is also possible that you **will not** receive **any** benefit from being in this study.

OTHER CHOICES

Instead of being in this study, you have the option of continuing with your current treatment or starting a new treatment under the care of your regular doctor or other health care provider.

INTRODUCTION

You are being asked to take part in this research study because you are at risk for having non-alcoholic fatty liver disease (also known as NAFLD [excess fat in the liver]), you are not diabetic, and because you have been taking anti-HIV medications that have controlled your HIV for at least 1 year. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

Up to 40% of people living with HIV (PLWH) have NAFLD. In people with controlled HIV, most illnesses and deaths that are associated with NAFLD are due to cardiovascular disease (any disease of the heart or blood vessels that, for example, can lead to a stroke or heart attack). This is not surprising, because most people with NAFLD also have what are called metabolic complications (such as high cholesterol, obesity, increased belly fat, or type 2 diabetes) that can lead to cardiovascular disease. People with higher levels of intra-hepatic triglycerides (IHTG, a type of fat stored in the liver) often have metabolic complications. A drug that can lower the level of IHTG in PLWH might treat NAFLD and reduce the risk of cardiovascular disease.

The purpose of this study is to evaluate the safety and tolerability of a drug called semaglutide and to see whether it can reduce IHTG. IHTG will be measured by magnetic resonance imaging (MRI; an MRI machine contains a powerful magnet that uses simple radio waves to take pictures of organs). Semaglutide (brand name Ozempic®) is a drug that is used to treat people who have diabetes; it also causes weight loss and may provide some protection against cardiovascular disease and diabetes. In PLWH, the use of semaglutide to reduce weight and the level of IHTG are experimental. The study will enroll about 50 people. You will be on the study for 48 weeks (about 12 months).

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

If you are interested in joining this study, you will have a screening visit. You will arrive fasting for this visit. At this visit, the study staff will:

- perform a physical exam
- ask you questions about how you are feeling and the medications that you are taking
- measure your weight, height, waist size, blood pressure, and temperature
- draw blood for some routine laboratory tests
- test for hepatitis **A, B, or** C virus, if needed

All of these activities and tests will be used to see if you are eligible to enter the study.

If you appear to be eligible for the study, you will have an MRI of your liver as part of a pre-entry visit.

<u>Information Collected at Screening</u>
There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, assigned sex at birth, current gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, HIV viral load) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns and/or common reasons why people do not join a study.

If you enroll into the study
At study entry, you will receive exercise, diet, **hypoglycemia (low levels of blood sugar), and hydration** education and be asked about any problems you are having with taking your anti-HIV medication**s**. **If you have any vision issues, you will have a vision assessment.** You will also receive semaglutide, a liquid that is given once a week using a pre-filled self-injection (or "auto-inject") pen. Semaglutide and the auto-inject pens will be provided by the study at no cost to you. The injection is into the skin using a very small needle, similar to insulin injections, and not a deep injection like most vaccines. You will be given information and some training on the use of the auto-inject pen. At one study visit, the clinic staff will watch you use the auto-inject pen. If needed, retraining and observation will occur. You may ask for and receive additional instructions any time you feel you need it.

You must be able to:
- Keep the auto-inject pens **that are given to you** between 36°F and 46°F (2°C and 8°C) prior to first use.
- Maintain the auto-inject pens at a room temperature between 59°F and 86°F (15°C to 30°C) or in a refrigerator (2°C to 8°C; 36°F to 46°F) following first use.
- **Protect the auto-inject pens from extreme cold. If an auto-inject pen has been frozen, do not use it.**
- Protect auto-inject pens from excessive heat and sunlight.

After the study entry visit, you will be seen in the clinic about 4 times. The study staff will tell you how long each visit could be. You may need to come to the clinic for additional visits if you develop side effects. As part of the study, if you agree, the clinic staff will contact you by phone or by e-mail several times between clinic visits to check on how you are doing.

You will have a brief physical exam at all visits. **If you have any vision issues, the brief physical exam will include a vision assessment.**

The samples of your blood and stool that are collected as part of this study may be used for additional research tests including liver function, thyroid disease, cholesterol and blood sugar tests (tests for diabetes), your HIV viral load (a measure of the amount of HIV in your blood), and your CD4 and CD8 T cell count (a measure of the strength of your immune system, the system that helps your body fight infections). Details of the study visits and procedures are explained in **ATTACHMENT A**.

You will have another MRI of your liver at the end of study treatment (week 24).

You will continue to take your anti-HIV medications **throughout the study**. You will receive semaglutide.

You will be provided the results of blood tests when they are available. At most visits, blood samples will be collected from you and stored for later research tests. You will not receive the results of these tests because they will be done in the future. No more than about 5 tablespoons of blood will be collected from you at any single visit.

You will be asked to arrive fasting at four study visits at entry and weeks 12, 24, and 48. This means that you will not eat or drink anything other than water and your prescribed medications for at least 8 hours before the visit. The study staff will remind you when you need to fast. If you are not fasting for any of these visits, the visits will be rescheduled, and you will need to return to the clinic on a different day.

At two visits, you will be given a food diary to complete over 3 days. The study staff will give you instructions for completing and returning this diary.

At some visits, you will have one or more questionnaires to complete. The questionnaires ask about your physical activity, what you eat and drink, your quality of life, and how you feel about taking the study treatment.

At three visits, you will be asked to perform physical function tests (chair stands, or standing up from a seated position multiple times and a timed walk test). These are tests of muscle strength.

At two visits, you will be asked to provide a stool sample. You will collect this sample yourself **between study visits**, **using** instructions and a kit provided to you by the clinic staff. Stool samples will be tested to evaluate the health of your gut microbiome (a collection of the microorganisms in your body); changes in your microbiome are linked to NAFLD. Researchers may be able to evaluate whether either of the study treatments affect the gut microbiome. Results from these tests will not be shared with you because they will be used for research only.

If you must stop study treatment before you complete the 24 weeks (close to 6 months) and you have received at least 12 weeks of study treatment, you will need to have one final visit before you leave the study.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood and stool will be stored and used for study-required metabolic and immunologic testing.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you. If you are enrolling in this study at a site outside the US you must know that samples collected from you may be shipped and stored outside of the country from which they are collected.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

ATTACHMENT B describes how your stored samples might be used in other studies. Please read that document and then decide if you want to give your consent to the use of any of your samples in other studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 50 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for 48 weeks (about 12 months).

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- The study is stopped or cancelled
- You are not able to attend the study visits as required by the study
- You are not able to complete the study procedures, including the MRIs, as required
- You are not able to continue taking study treatment
- You become pregnant or you are breastfeeding
- **You change diet or exercise regimen significantly**
- **You are unable to keep study product at 36°F to 46°F (2°C to 8°C) prior to first use, or to maintain the study product at a controlled room temperature between 59°F and 86°F (15°C to 30°C) following first use**

The study doctor may also need to take you off your study treatment without your permission if:

- Continuing the study treatment may be harmful to you.
- **If you are experiencing symptoms with the study treatment, the study doctor may reduce the study treatment dose, hold the study treatment dose where it is, or stop the study treatment. The study treatment may be started again if the symptoms go away.**
- You need a treatment that you may not take while on the study
- You are not able to take the study treatment as required by the study

If you must stop taking study treatment before the study is over but you have taken the study treatment for at least 12 weeks, the study doctor will ask you to return for one final visit. If you have not taken the study treatment for at least 12 weeks, you will not return for a final visit.

If you developed a side effect that is still ongoing **when you decide to leave the study**, the study staff and study doctor will explain to you if you need an additional visit and the side effect that has to be checked, the evaluations that will be done, and answer any questions you may have.

What if I have to permanently stop taking the study-provided semaglutide after I start taking it?

During the study:
If you must permanently stop taking the study-provided semaglutide before your study participation is over, the study staff will discuss other options that may be available to you, including no additional medication.

After the study:
After you have completed your study participation, the study will not provide you with the semaglutide you received on the study. In the opinion of your physician, if continuing to take this or a similar product would be of benefit to you, the study staff will discuss how you may be able to obtain it.

WHAT ARE THE RISKS OF THE STUDY?

Semaglutide may have side effects, some of which are listed below. Please note that these lists include only the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study treatment side effects please ask the medical staff at your site.

Semaglutide
The following side effects have been associated with the use of semaglutide:

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Constipation
- Fatigue
- Headache
- Thyroid tumor, including cancer, which was seen when the drug was tested in rodents, but we do not know if this happens in people. Symptoms of this may include:
  - Lump or swelling in the neck
  - Hoarseness
  - Trouble swallowing or
  - Shortness of breath
- Inflammation of the pancreas. Symptoms of this may include:
  - Abdominal pain with or without vomiting.
- Low blood sugar; signs and symptoms of low blood sugar may include:
  - Headache
  - Drowsiness
  - Weakness
  - Dizziness
  - Confusion
  - Irritability
  - Hunger

  - Fast heart beat
  - Sweating
  - Feeling jittery
- **Low blood pressure**
- Kidney problems (if you become dehydrated)
- **Eye problems**
  - **Among people that took semaglutide, a small number of people with both type 2 diabetes and a high risk for heart problems had eye disease develop or it worsened. If you have had eye problems, it is possible that you may be at increased risk for complications while taking semaglutide.**
- Hepatotoxicity (liver damage)
- Allergic reaction. Symptoms of this may include:
  - Itching
  - Rash
  - Difficulty breathing
  - Swelling

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with study treatment. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study team before enrolling in any other clinical trials while on this study.

Risks of Injection
The following side effects have been associated with the use of semaglutide:
- Rash, redness, itching at injection site

Risks of MRI Scan
Some things may interfere with MRI and some can be potentially dangerous. You should inform the study team if you have any of the following:
- Heart problems
- Pacemaker
- Metal implanted under your skin, such as an insulin pump
- Hearing aid or cochlear implant
- Surgical clips or staples
- Any metal prosthesis. A prosthesis is an artificial body part, like an artificial leg.
- Shrapnel
- Tattooed eyeliner
- Metal dental items
- Braces
- Pregnancy

Metal in or on the body
The MRI scanner functions like a magnet and any metals in your body can be pulled off by the machine. If you have metal implants (under the skin) such as a pacemaker or metal pins or rods, you may be at risk when you are close to the machine. To minimize this risk, we will ask

you a series of questions about metal exposure over the course of your lifetime from work experiences and medical procedures.

Claustrophobia (fear of small spaces)
When you have the MRI, you will lie on a small bed and the bed will be inserted inside a large tube. The opening of the tube is narrow, and some people may experience claustrophobia (anxiety or nervousness while inside small spaces) when in the scanner. If you think that you may experience excessive anxiety or nervousness while inside the scanner, you should not participate in this study. If you decide to participate in the study and begin to experience claustrophobia while inside the scanner, the procedure will be stopped at your request. If you are unable to complete the MRI, you will not be able to participate in this study.

Other
There is a possibility that a serious abnormality, not as a result of your study participation but an incidental finding, may be discovered in the MRI picture of your liver. If this is the case, you will be notified by the site. You will be referred to your primary care physician for clinical follow up. Clinical follow-up will not be provided or paid for by the study.

Risks of Stool Collection
You may have mild discomfort when collecting the stool samples, particularly if you have sores or hemorrhoids. In some cases, a very small amount of bleeding may occur. If you are already having pain in the rectal area, be sure to let the study team know.

ARE THERE RISKS RELATED TO PREGNANCY?

The MRI scans may harm an unborn baby.

It is not known if the study treatment, semaglutide, harms unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant while taking semaglutide in the study. If you want to become pregnant, you should wait 2 months after your last dose of semaglutide before you try to become pregnant.

If you can become pregnant and are sexually active, you must use one reliable form of birth control that you can discuss with the study staff. One of the following methods MUST be used while taking semaglutide and for 2 months following **your** last dose of semaglutide:

- Intrauterine device (IUD)
- Hormone-based contraceptive

If your partner has had a vasectomy and you do not have any other partners, you do not need to use one of the forms of birth control listed above.

If you **are having sex that could lead to pregnancy**, you must have a pregnancy test before you enter this study and at a few other visits. These tests must show that you are not pregnant. If you think you may be pregnant at any other time during the study, tell your study staff right away. The study staff will talk to you about your choices.

If you become pregnant while on study, you will have to stop study treatment and discontinue the study. You will complete premature study discontinuation evaluations except for an MRI scan. The study staff would like to stay in contact with you to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in individuals taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you **will not** receive **any** benefit from being in this study. Information learned from this study may help others who have HIV and NAFLD.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Regular and consistent diet and exercise are the first treatment that doctors usually prescribe for NAFLD, and would be the care recommended to you outside of the study. Study-provided drugs, laboratory tests to monitor how well these drugs are working, and quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?

<u>For Sites in the US</u>
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, this research is covered by a Certificate of Confidentiality from the U.S. 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.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, 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), National Institutes of Health (NIH), study staff, study monitors, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself 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 yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For Sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. In addition to the efforts of the study staff to help keep your personal information private, this research is covered by a Certificate of Confidentiality from the US Federal Government. The Certificate of Confidentiality may not provide protections for the participant's data in your country. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself 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 yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study-related visits, physical examinations, laboratory tests, study medications or other procedures. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study *(delete references to insurance company or health care system if not applicable at site)*. In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

(Sites should insert a statement about any participant compensation for MRIs and study visits.)

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of your being in this study, you will be given immediate treatment for injuries and be referred for further treatment, if necessary.

[Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry CTI, this must be indicated in the informed consent.]

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*
- *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 study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. 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 study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study 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 subject, contact:

- Name or title of person on the Institutional Review Board or Ethics Committee (IRB or EC) 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 study, please sign your name below.

Participant's Name (print)	Participant'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

ATTACHMENT A: A5371 STUDY VISITS AND PROCEDURES

Section A: Study Visits

Attachment A Table 1: Expected Study Visit Schedule

Procedure	Screening	Pre-entry	Study entry (Day 0)	On-study	Week 24 or if stopping treatment early*	Week 48
Physical exam	✓		✓	At all visits	✓	✓
Blood collected	✓		✓	At all visits	✓	✓
Pregnancy test	✓		✓	Possibly	✓	
MRI performed		✓			✓	
Stool kit and 3-day food diary provided		✓		At one visit		
Stool kit and 3-day food diary collected			✓		✓	
Questionnaires			✓	At **all** visits	✓	✓
Adherence checked			✓		✓	
Exercise and diet education			✓			
Low blood sugar and hydration education			✓			
Physical function tests			✓		✓	✓
Study drug provided			✓	At two visits		
Injection training, retraining, and observed injection			✓	As needed		
Telephone or email contact				Between some clinic visits		

*If you have taken at least 12 weeks of study treatment, you will have these evaluations performed.

Section B: Explanation of Visit Schedule

Screening: This visit will take place within 30 days before the pre-entry visit.

Pre-entry: This visit will take place within 2 weeks before you enter the study.

Study Entry/Day 0: This is the day that you will start your study treatment. This visit will take place within 2 weeks after you have the first **magnetic resonance imaging** (MRI) **scan** of the study.

On-study: You will continue to take your anti-HIV medications, which are not provided by the study. After study entry, you will have a**bout 3** study visits while you are taking study treatment **(semaglutide).** Your last visit **while you are** taking **semaglutide** will be at week 24. If you stop semaglutide early but have taken at least 12 weeks of **it**, you will have a visit that is similar to the week 24 visit.

Week 48 will be your final study visit.

Section C: Explanation of Procedures

Physical exam: You will have a complete physical exam at screening and then only a brief physical exam at all other visits. **You will be asked about feeling light-headed and if you have experienced any problems with your eyes or vision. If you have experienced any problems with your eyes or vision including blurred vision, sudden loss of vision, black spots, flashing lights, and difficulty reading or seeing small details, you will have a vision assessment.**

Blood collected: Blood will be collected from a vein in your arm at all visits for research tests, which may include liver function, thyroid disease, cholesterol and blood sugar tests (tests for diabetes), your HIV viral load (a measure of the amount of HIV in your blood), and your CD4 and CD8 T cell count (a measure of the strength of your immune system, the system that helps your body fight infections). You may be tested to see if you have **or previously had** hepatitis **A, B, or** C **infections**.

Pregnancy test: If you are able to become pregnant, you will have a pregnancy test, using either a blood sample or a urine sample. A pregnancy test will be done at screening, entry, and week 24, and any time you think you may be pregnant.

Exercise and diet education: You will receive diet and exercise recommendations at the beginning of the study.

Low blood sugar and hydration education: At the beginning of the study, you will receive education about very low levels of blood sugar and how to stay hydrated when feeling nauseated.

MRI performed: An MRI machine contains a powerful magnet that uses simple radio waves to take pictures of organs. An MRI will be performed two times during the study. The clinic staff will give you any information you might need to prepare for this procedure. There is no pain associated with this procedure. You will be positioned on your back on a small bed and made to feel as comfortable as possible. You will be inserted inside a large tube. Once the scan starts, you will need to lie still for about 30 minutes. You will be able to ask the technician to end the scan at any time if you feel uncomfortable.

Stool kit: You will be asked to provide a stool sample **twice during the study** using a test kit and instructions that the clinic staff gives you. The stool sample will be self-collected at home within 2 days before **a** study visit.

3-day food diary: The study includes a 3-day food diary that you will be asked to complete twice during the study.

Questionnaires: At **all** visits, you will have one or more questionnaires to complete. The study includes questionnaires about your physical activity, what you eat and drink, your quality of life, and how you feel about taking the study treatment.

Adherence checks: At some visits, you may be asked about any problems you are having with taking your anti-HIV medication**s**, your study treatment, or both.

Physical function tests: You will be asked to stand up multiple times from a seated position, and be timed on how long it takes you to walk a short distance.

Injection training, retraining, and observation: You will receive training on how to use the auto-inject pen. You will also be observed using the auto-inject pen when you start study treatment. If needed, you will be retrained and possibly observed **again** during the study. **You may ask for help with the auto-inject pen at any time.**

Telephone or email contact: Between entry and week 24, you will be contacted by **study staff by** telephone or email up to six times.

ATTACHMENT B: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples." The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored.
[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review the researcher's plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples.

OR
____ (initials) I understand but I do not agree to this storage and possible use of my samples.

<u>Research with Human Genetic Testing</u>
Your extra samples will not be used for human genetic testing.

The ACTG has two different studies that collect samples for genetic testing.

If you live in the US, this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

If you live outside of the US, this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like to participate in one of these studies if it is being done where you live. If you would like to participate, you will sign a separate consent form.