ACTG Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

A5391

Doravirine for Obese Persons on Integrase Inhibitors and Tenofovir Alafenamide (The Do IT Study)

A Multicenter Trial of Advancing Clinical Therapeutics Globally (ACTG)

NIAID CRMS # 38678

This file contains the current ACTG A5391 protocol, which includes the following document:

- Clarification Memo #1, dated 09 Feb 2023
- Protocol Version 2.0, dated 19 Aug 2022

Clarification Memo #1 for:

A5391

Doravirine for Obese Persons on Integrase Inhibitors and Tenofovir Alafenamide (The Do IT Study)

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

NIAID CRMS # 38678

ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems, Inc., a DLH Holdings Company
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CLARIFICATION MEMO

DATE: February 9, 2023

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

FROM: A5391 Protocol Team

SUBJECT: Clarification Memo #1 for Protocol A5391, Version 2.0

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

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

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

The reason for this CM is to correct an error in the list of prohibited medications, and to provide clarification on the use of topiramate by A5391 participants.

The following is a clarification (noted in strikethrough) to Protocol A5391, Version 2.0, 19 Aug 2022, titled, "Doravirine for Obese Persons on Integrase Inhibitors and Tenofovir Alafenamide (The Do IT Study)." This clarification will be included in the next version of the A5391 protocol if it is amended at a future date.

1. In section 4.2.8, Anticipated start or cessation of any of the following drugs during study period, second bullet, the use of topiramate is clarified with the following information:

   The use of the anticonvulsant/mood stabilizer topiramate is permitted by A5391 participants entering the study on a stable dose, as long as there is not an intent to change the dose or stop this medication during the 48-week study follow-up period.

2. In section 5.4.1, Prohibited Medications, the term “topiramide” has been removed from the list of Prohibited Medications as shown below:

   5.4.1 Prohibited Medications

   1. Rifampin/rifabutin
   2. Enzalutamide
   3. Anticonvulsants contraindicated in co-administration with any of the study drugs (carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, ~~topiramide~~)
   4. Mitotane
   5. St. John’s wort
   6. FDA-approved weight loss agents (e.g., bupropion-naltrexone, liraglutide, orlistat, lorcaserin, phentermine-topiramate)
   7. Non-prescription weight loss drugs (e.g., Hydroxycut; additional non-prescription agents at the discretion of the site investigator)
   8. Chronic oral steroid use (prednisone equivalent of ≥5 mg for >2 weeks)
   9. Bisphosphonates or other treatments for osteoporosis
   10. Any antiretrovirals not included in the study treatment

A5391

Doravirine for Obese Persons on Integrase Inhibitors and Tenofovir Alafenamide (The Do IT Study)

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
National Institute of Allergy and Infectious Diseases

Industry Support Provided by:
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FINAL Version 2.0
August 19, 2022

ACTG
AIDS CLINICAL TRIALS GROUP

A5391

Doravirine for **Obese Persons** on Integrase Inhibitors and Tenofovir Alafenamide
(The Do IT Study)

SIGNATURE PAGE

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5391@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5391@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.protA5391 e-mail group. Include the protocol number in the e-mail subject line.

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

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

- Send an e-mail message to actg.cmca5391@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 Immunologist.

- Send an e-mail message to actg.teamA5391@fstrf.org (ATTENTION: Alan Landay).

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 managers. 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 Scott Anderson and Rebecca Marshall directly.
- For other questions, send an e-mail message to actg.teamA5391@fstrf.org (ATTENTION: Scott Anderson and Rebecca Marshall).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/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.teamA5391@fstrf.org (ATTENTION: Mwenda Kudumu).

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 message 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.teamA5391@fstrf.org (ATTENTION: Mwenda Kudumu).

For questions related to protocol activation at non-US sites contact the ACTG Site Coordination Group.
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Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Oladapo Alli, Protocol Pharmacist, at 240-627-3593.

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

Expedited Adverse Event (EAE) Reporting/Questions
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Telephone Calls
Sites are responsible for documenting telephone calls made to A5391 team members.
- Send an e-mail message to actg.teamA5391@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

3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AZT	zidovudine
BIC	bictegravir
BMI	body mass index
CDC	Centers for Disease Control and Prevention (US)
CLIA	Clinical Laboratory Improvement Amendments
CrCl	creatinine clearance
CRPMC	NIAID Clinical Research Products Management Center
DAERS	DAIDS Adverse Events Reporting System
DBS	dried blood spot
DEXA	dual-energy X-ray absorptiometry
DMC	Data Management Center
DOR	doravirine
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
EAE	expedited adverse event
EC	Ethics Committee
eCRF	electronic case report form
EFV	efavirenz
EVG	elvitegravir
FDA	Food and Drug Administration (US)
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
GCLP	Good Clinical Laboratory Practice
GLP-1	glucagon-like peptide-1

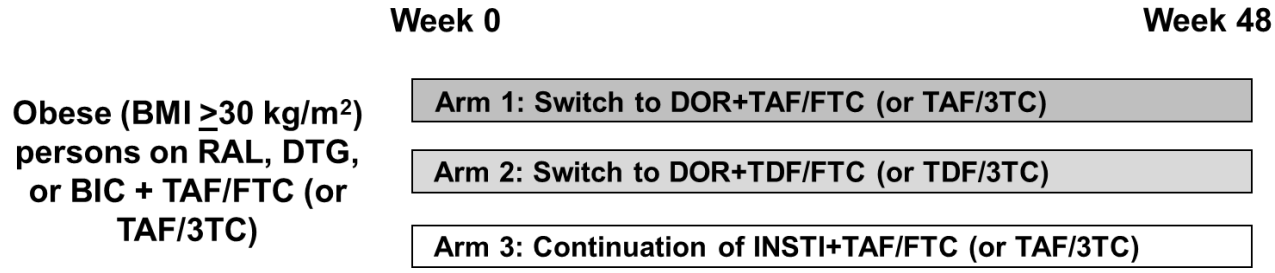
HDL	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
IND	investigational new drug
INSTI	integrase strand transfer inhibitor
IQA	Immunology Quality Assurance
IRB	Institutional Review Board
IUD	intrauterine device
LDL	low-density lipoprotein cholesterol
LPC	laboratory processing chart
mg	milligram
MOPS	Manual of Procedures
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside(tide) reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PSWP	Protocol-Specific Web Page
PWH	people with HIV
RAL	raltegravir
RSC	Regulatory Support Center
SAE	serious adverse event
SOE	Schedule of Evaluations
SOP	Standard Operating Procedure
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV-DP	tenofovir-diphosphatemtricitabine
VQA	Virology Quality Assurance
WHO	World Health Organization

SCHEMA

A5391

Doravirine for Persons with Excessive Weight Gain on Integrase Inhibitors and Tenofovir Alafenamide (The Do IT Study)

DESIGN	A phase IV, 48-week, 3-arm, open-label, randomized study to assess whether an antiretroviral therapy (ART) switch from bictegravir (BIC), dolutegravir (DTG), or raltegravir (RAL) with tenofovir alafenamide/emtricitabine (TAF/FTC) or TAF/lamivudine (TAF/3TC) to either a regimen containing doravirine (DOR) with TAF/FTC (or TAF/3TC depending on location), or DOR with tenofovir disproxil fumarate (TDF)/FTC (or TDF/3TC depending on location) results in reduced weight gain, or weight loss, as compared to continuation of current BIC-, DTG-, or RAL-containing ART.
DURATION	48 weeks
SAMPLE SIZE	222 participants (74 per arm)
POPULATION	Persons living with human immunodeficiency virus (HIV) aged ≥18 years **with a BMI ≥30 kg/m^2 on** an integrase strand transfer inhibitor (INSTI) + TAF/FTC (or TAF/3TC) **regimen for at least 48 weeks prior to entry with maintenance of** virologic suppression (HIV-1 RNA <50 copies/mL or below the lower limit of HIV-1 RNA detection available at the site)**.**
STRATIFICATION	Enrollment will be stratified by sex assigned at birth and race (African American/Black vs. non-African American/Black).
REGIMEN	Participants on BIC, DTG, or RAL-containing ART with TAF/FTC (or TAF/3TC) for at least 48 weeks prior to entry, will be randomized 1:1:1 to switch to DOR + TAF/FTC (or TAF/3TC) (Arm 1), or DOR + TDF/FTC (or TDF/3TC) (Arm 2), or to continue on their current INSTI +TAF/FTC (or TAF/3TC) (Arm 3). Total duration of study treatment in all arms will be 48 weeks. DOR will be provided to Arms 1 and 2 participants through the study. Nucleoside reverse transcriptase inhibitors (NRTIs) and INSTIs will not be provided by the study.



Schema Figure 1: Schema Diagram

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

Compared to continued bictegravir (BIC), dolutegravir (DTG), or raltegravir (RAL) + tenofovir alafenamide/emtricitabine (TAF/FTC) or TAF/lamivudine (TAF/3TC) therapy (Arm 3), a switch to doravirine (DOR) + TAF/FTC (or TAF/3TC) (Arm 1) will result in less weight gain or an overall weight loss at 48 weeks among **obese** persons **(i.e., a BMI ≥30 kg/m^2)**. A switch from TAF/FTC (or TAF/3TC) to tenofovir disproxil fumarate (C)/FTC (or TDF/3TC) (Arm 2) will result in further reduction in weight gain or overall weight loss compared to Arm 1.

1.2 Primary Objective

To assess if an antiretroviral therapy (ART) switch to DOR (either switch to DOR and remain on TAF/FTC [or TAF/3TC, Arm 1] or switch to DOR and TDF/FTC [or TDF/3TC, Arm 2]) results in differences in weight change over 48 weeks, compared to a strategy of remaining on current ART (INSTI + TAF/FTC [or TAF/3TC, Arm 3]).

1.3 Secondary Objectives

1.3.1 To assess if a switch to TDF/FTC (or TDF/3TC) from TAF/FTC (or TAF/3TC) results in differences in weight changes over 48 weeks by contrasting the 2 DOR-containing switch strategies (i.e., DOR+TAF/FTC [or TAF/3TC] versus DOR + TDF/FTC [or TDF/3TC] [Arm 1 versus Arm 2]).

1.3.2 To assess the effects of a switch from INSTI + TAF/FTC (or TAF/3TC) to DOR + TAF/FTC (or TAF/3TC), or DOR + TDF/FTC (or TDF/3TC) over 48 weeks on:

i. Safety and tolerability.
ii. Maintenance of virologic suppression.
iii. Minimum waist circumference.
iv. Fasting cardiometabolic parameters: glucose and insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and lipids (triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL]).
v. Dual-energy X-ray absorptiometry (DEXA) body composition measurements of total and regional fat and lean mass, and hip and lumbar spine bone mineral density.
vi. Change in categorization of bone mass (by WHO classification) from baseline to week 48 based on minimum reported T score from left/right femoral neck, left/right total femur/hip, and lumbar spine.

1.4 Exploratory Objectives

1.4.1 To assess the effects of a switch from INSTI + TAF/FTC (or TAF/3TC) to DOR + TAF/FTC (or TAF/3TC), or DOR + TDF/FTC (or TDF/3TC) over 48 weeks on:

i. Circulating immunologic parameters, including plasma biomarkers (e.g., high-sensitivity C-reactive protein, high-sensitivity interleukin-6, sCD163, and interleukin-18), and $CD4^+$ and $CD8^+$ T cell subsets (e.g., activated, senescent, and memory), and invariant NK T cells (iNKT cells).
ii. Circulating metabolic biomarkers, including adipokines (e.g., leptin, adiponectin), oxidized LDL, (1,3)-beta-D-glucan, and free fatty acids.

1.4.2 To assess relationships between blood concentrations of tenofovir diphosphate (TFV-DP) (both from TDF and TAF) and emtricitabine triphosphate (FTC-TP), measured from dried blood spots (DBS) testing, with changes in weight and metabolic markers over 48 weeks.

2.0 INTRODUCTION

2.1 Background

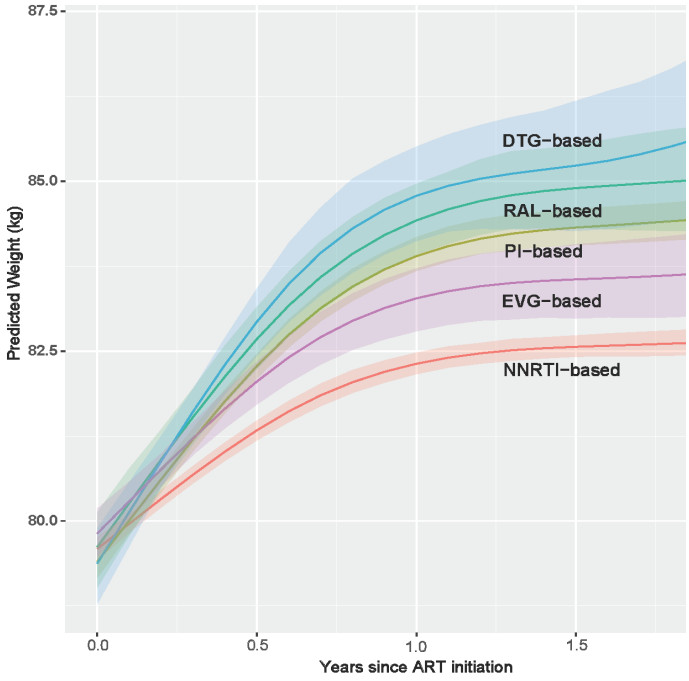
Early in the HIV epidemic, weight loss was a sign of more advanced disease, and weight gain following ART initiation was often regarded as a "return to health" phenomenon. In the current era, **however,** a rising proportion of people with HIV (PWH) are **obese** (body mass index [BMI] ≥30 kg/m^2), **which increases** the risk of **developing multiple comorbid conditions**. **In a multi-cohort analysis of over 14,000 PWH in the United States and Canada, the percentage of obese individuals at ART initiation increased from 9% to 18% between 1998 and 2010, and 18% of individuals overweight at the start of treatment became obese within 3 years after ART initiation [1]. Other studies have confirmed increasing prevalence of obesity in PWH [2, 3, 4], which parallels similar trends in the general population [5]. Women, minorities, and persons of lower socioeconomic status with HIV carry a disproportionate burden of obesity. The risk for metabolic diseases including diabetes mellitus, neurocognitive impairment, liver disease, and cardiovascular disease rises with increased body weight [6, 7, 8, 9]. Furthermore, weight gain in PWH confers greater risk of metabolic disease compared with HIV-negative individuals [6, 10, 11].**

Several prospective and retrospective studies report that PWH starting or switching to INSTI-containing ART regimens have significantly greater weight gain compared to protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens, which may be further compounded by the use of TAF as a second agent. At present, it is unknown whether **obese** PWH on INSTI + TAF/FTC (or TAF/3TC) could either attenuate their rate of weight increase over time or reduce body weight with a change to a different ART regimen.

In the prospective AIDS Clinical Trial Group (ACTG) study A5257, the use of RAL with TDF/FTC as an initial regimen was associated with greater increases in waist circumference and higher odds of a >10% weight gain at 96 weeks compared to ritonavir-boosted darunavir (DRV/r) and ritonavir-boosted atazanavir, each in combination with TDF/FTC [**12**]. In a large analysis of >22,000 treatment-naïve PWH in the multi-site North American AIDS Cohort Collaboration on Research and Design (NA-

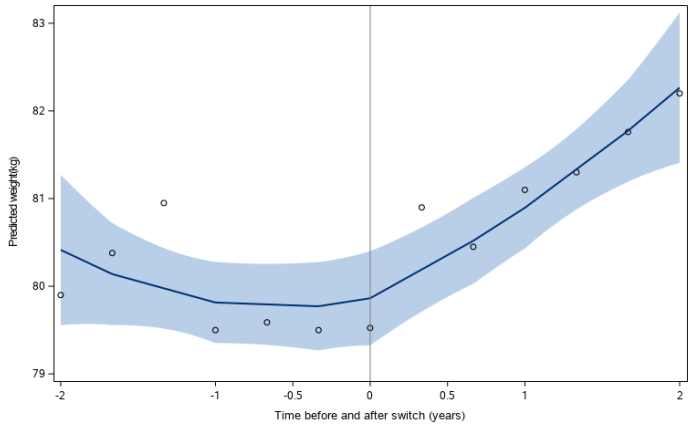
ACCORD), those initiating INSTI-containing regimens gained an estimated 5.9 kg after 5 years of treatment, compared to 3.7 kg for NNRTI, and 5.5 kg for PI [**13**]. However, most of this weight gain occurred in the first 2 years following ART initiation for all classes, and among INSTIs there was considerable heterogeneity: estimated weight gain at 2 years was 7.2 kg for DTG, 5.8 kg for RAL, and 4.1 kg for elvitegravir (EVG) (Figure 2.1-1). The NA-ACCORD analysis period was 2007-2016 and the first-line regimens primarily contained TDF, abacavir (ABC), FTC, and/or 3TC. Smaller observational studies also report greater weight gain among PWH initiating INSTI-containing regimens, which generally has been greater among women, African American/Black people, and those with lower pre-ART weight and CD4⁺ T cell counts [**13, 14, 15, 16**].

Figure 2.1-1: NA-ACCORD: Predicted weight at 2-years of ART among PWH starting INSTI-containing regimens compared to those starting PI- or NNRTI-class regimens.



A switch from an NNRTI- or PI-containing regimen to an INSTI-containing regimen may also be accompanied by weight gain. In a single-site report, PWH with virologic suppression on efavirenz (EFV)-containing regimens who switched to INSTI-containing regimens experienced significantly more weight gain compared to those who remained on EFV, and weight gain was greatest among those who switched to DTG [**17**]. Similarly, in ACTG protocols A5001 and A5322, women, African American/Black people, and persons age ≥ 60 who switched from PI- and NNRTI-containing regimens to INSTI-containing regimens while virologically suppressed had significantly greater weight gain in the 2 years following the switch versus the 2 years prior to switch (Figure 2.1-2) [**18**].

Figure 2.1-2: ACTG A5001 and A5322: Change in weight before and after switch to INSTI-containing regimens.



While initial studies focused on the relationship of INSTI-class medications and weight change, more recent data from prospective studies indicate the combination of an INSTI and TAF may have compounding effects on weight gain. TAF, approved in the US in November 2015, represented a low proportion of nucleoside(tide) reverse transcriptase inhibitor (NRTI) use in the above ART-naïve observational studies, but use of this agent is rapidly increasing given the lower incidence of bone loss and adverse renal effects compared to TDF. In the ADVANCE study, ART-naïve South African women randomized to DTG/TAF/FTC gained an average of 10 kg at 96 weeks of treatment (representing an average 16% weight gain), as compared to 5 kg on DTG/TDF/FTC and 3 kg on EFV/TDF/FTC (Figure 2.1-3) [**19**].

Figure 2.1-3: ADVANCE: Mean change in weight to week 96 in women.

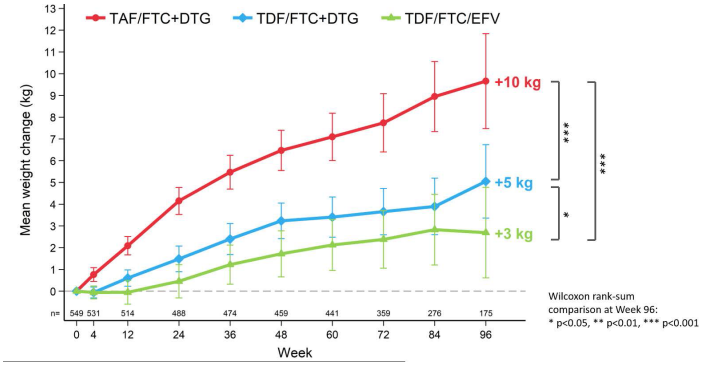
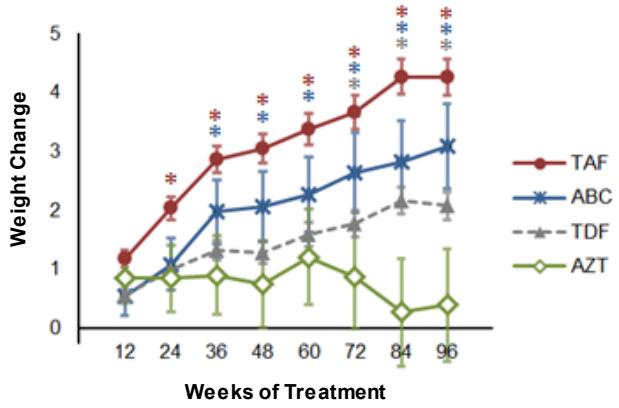


Figure 2.1-4: Analysis of pooled clinical RCT data: Estimated weight change over 96 weeks.



For men, average weight gain at 96 weeks was 5 kg, 4 kg, and 1 kg, respectively, on the same regimens. Over the 96 weeks, weight continued to increase in women, while plateauing in men. Lastly, a pooled analysis of weight gain in 8 randomized controlled clinical trials of treatment-naïve PWH initiating ART between 2003-2015, comprising over 5,000 participants and 10,000 person-years of follow-up, found greater weight gain over 96 weeks among those receiving TAF-containing regimens as compared to other NRTIs (Figure 2.1-4; error bars depict the 95% CI, and asterisks are color-coded to denote p≤0.05 compared to zidovudine [AZT]. At 96 weeks, mean weight gains by NRTI were: TAF 4.25 kg [95% CI 3.94-4.56], ABC 3.08 kg [95% CI 2.36-3.81], TDF 2.07 kg [95% CI 1.84-2.30]), and AZT 0.39 kg [95% CI -0.57-1.34] after adjusting for age, race, sex, baseline clinical factors, and additional ART agents [**20**].

Taken together, these studies suggest that NNRTI- and non-TAF-containing regimens are accompanied by lower weight gain among PWH [**13, 17, 20**], raising the possibility that a switch to this ART combination may offer a weight stabilization or reduction benefit among **obese** PWH on an INSTI/TAF regimen. DOR is an NNRTI that was approved by the Food and Drug Administration (FDA) in 2018 on the basis of phase 3 studies demonstrating non-inferiority compared to EFV- or DRV/r-containing regimens, in addition to a superior neuropsychiatric profile compared to EFV [**21, 22, 23**]. In the DRIVE-SHIFT trial, a switch to DOR with TDF/3TC among virally suppressed

participants demonstrated non-inferior maintenance of HIV-1 suppression compared with boosted PI, boosted EVG, and other NNRTI-containing regimens [**24**]. **D**ata presented at the 17th European AIDS Conference showed weight gain at 48 weeks among ART-naïve persons initiating DOR was similar to those initiating DRV/r (1.0 vs. 0.6 kg, p=0.12) in pooled phase 2 and 3 studies, but higher compared to EFV (1.0 vs. 0.0 kg, p<0.001). The difference in weight gain between DOR and EFV was smaller, though still significant, at 96 weeks (1.5 vs. 1.0 kg, p=0.02) [**25**].

This study will determine whether a switch to a DOR-based ART regimen results in less weight gain, weight stability or an overall weight loss at 48 weeks among **obese** persons **currently on** an INSTI + TAF/FTC **(or TAF/3TC)** regimen, and whether cardiovascular and metabolic health biomarkers improve. All study medications are FDA-approved for the treatment of HIV, but the study is not without risks to participants. Major risks include the potential for treatment failure on the new regimen, the development of side effects specific to the medications, and a reduction in bone density among those randomized to DOR + TDF/FTC (or TDF/3TC). The protocol includes procedures to exclude persons at higher risk of these adverse events, and to monitor participants for the development of adverse events during the study. Participants in the study may also derive potential benefits, including a stabilization or reduction in body weight, and/or improved cardiovascular and/or metabolic health. The risks and benefits of this study are described in more detail in the informed consent.

2.2 Rationale

Given that a 5% weight loss is associated with a substantial reduction in diabetes risk, a reduction in intrahepatic triglyceride content, and improved adipose tissue, liver, and muscle insulin sensitivity, interventions to reverse or attenuate weight gain among obese PWH exposed to INSTI/TAF regimens could improve cardiometabolic health outcomes.

3.0 STUDY DESIGN

A5391 is a phase IV, 48-week, three-arm, open label, randomized study of an ART regimen switch from BIC, DTG, or RAL + TAF/FTC (or TAF/3TC) to a DOR-containing regimen with TAF/FTC (or TAF/3TC depending on location) or TDF/FTC (or TDF/3TC depending on location) versus continuation of current ART.

Persons aged ≥18 years with a BMI ≥30 kg/m^2 and a minimum of 48 weeks of an INSTI + TAF/FTC **(**or TAF/3TC) **regimen** will be randomized 1:1:1 to switch to DOR + TAF/FTC (or TAF/3TC) (Arm 1) or DOR + TDF/FTC (or TDF/3TC) (Arm 2) versus continued current INSTI + TAF/FTC (or TAF/3TC) regimen (Arm 3).

NOTE: TAF and INSTI do not have to have been initiated simultaneously (see section 4.1.4).

The proposed sample size is 222 participants (74 per arm).

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Age ≥18 years.

4.1.2 Ability and willingness of participant or legal guardian/representative to provide informed consent.

4.1.3 HIV-1, 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, or plasma HIV-1 RNA viral load. If a rapid HIV test or any FDA-approved HIV-1 E/CIA test kit is not available, two HIV-1 RNA values ≥2000 copies/mL at least 24 hours apart may be performed by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or by any non-US laboratory that is DAIDS Good Clinical Laboratory Practice (GCLP) compliant and, if performing HIV-1 RNA testing, is Virology Quality Assurance (VQA)-certified.

NOTE: The term “licensed” refers to a US FDA-approved kit, 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.

World Health Organization (WHO) 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.

4.1.4 Currently on a BIC, DTG, or RAL + TAF/FTC (or TAF/3TC) regimen with ≥48 weeks dosing prior to study entry.

NOTE A: Participants who did not start TAF at the same time as they started an INSTI will be eligible if they started TAF/FTC (or TAF/3TC) ≥48 weeks prior to study entry.

NOTE B: Participants who underwent within-INSTI class substitutions (including from EVG to BIC, DTG, or RAL) will be eligible if substitution occurred ≥24 weeks prior to study entry.

NOTE C: Participants are permitted ART adherence gaps of ≤7 days (i.e., missed doses), with a maximum of 3 gaps in the 48 weeks prior to study entry.

4.1.5 Ability to acquire NRTIs (TAF/FTC or TAF/3TC, and TDF/FTC or TDF/3TC) and INSTI through usual care for the duration of the study.

4.1.6 A BMI ≥**30** kg/m^2 at screening.

4.1.7 No known plans to change or to initiate medications known to be associated with significant weight changes during study period.

NOTE: Complete list of medications known to be associated with significant weight changes will be maintained on the PSWP.

4.1.8 Agree to adhere to assigned ART during the study period

4.1.9 At least one HIV-1 RNA level <50 copies/mL (or below the lower limit of HIV-1 RNA detection available at the site if the lower limit of detection is >50) performed in the 48 weeks prior (≤48 weeks) to study screening, and at least one HIV-1 RNA level <50 copies/mL ≥48 weeks prior to study screening, using an FDA-approved assay performed by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that is VQA certified. HIV-1 RNA values prior to the screening visit will be assessed for eligibility by the site and assay dates and values do not need to be entered on an eCRF.

4.1.10 Screening HIV-1 RNA <50 copies/mL (or below the lower limit of HIV-1 RNA detection available if the lower limit of detection is >50) performed within 45 days prior to study entry by any US laboratory that possesses a CLIA certification or its equivalent, or at any network-approved non-US laboratory that is VQA certified.

4.1.11 For participants capable of becoming pregnant, negative serum or urine pregnancy test within 45 days prior to study entry 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 GCLP and participates in appropriate external quality assurance programs.

NOTE: Participants capable of becoming pregnant are defined as individuals who were assigned a female sex at birth and of reproductive potential (i.e., have reached menarche and who have not been post-menopausal for at least 24 consecutive months, and have not undergone surgical sterilization such as hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy). This includes transgender men who could become pregnant if menstruation were not suppressed. Participant-reported history is acceptable documentation of menopause.

4.1.12 Participants engaging in sexual activity and capable of becoming pregnant must agree to use contraception while on study drug (approximately 48 weeks) and for

8 weeks after the end of the study. At least one of the following contraceptive methods must be used:

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

NOTE: Participant report of partner sterilization is acceptable.

4.1.13 Transgender participants who are currently taking hormones must be on a stable hormone dose for >12 weeks prior to study entry. Transgender participants should not have active plans to change their hormone regimen or dose during the study period.

NOTE: As some transgender participants may also use hormones purchased outside of the medical system (e.g., street hormones), the medication history should include questions about the use of these agents.

4.1.14 The following laboratory values obtained within 45 days prior to study 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 males and >9 g/dL for females (based on sex at birth)
- Calculated creatinine clearance ≥50 mL/min as estimated by the CKD-EPI equation (a calculator is available at: https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi)
- Aspartate aminotransferase (AST) (SGOT) <3x ULN
- Alanine aminotransferase (ALT) (SGPT) <3x ULN

4.2 Exclusion Criteria

4.2.1 Historical or current evidence of the K65R/E/N or M184V/I mutations (for participants who have undergone HIV-1 genotyping), due to the potential for viral rebound after switch from an INSTI- to NNRTI-based regimen.

4.2.2 Historical or current evidence of major mutations associated with NNRTI resistance.

NOTE: Refer to the IAS-USA 2019 mutations list, including significant substitutions at positions 100, 101, 103, 106, 138, 179, 181, 188, 190, 221, 225, 227, 230, or 234 [**26**].

4.2.3 History of prior virologic failure in the opinion of the site investigator. For example, a confirmed plasma HIV-1 RNA >1000 copies/mL after having achieved viral suppression.

4.2.4 Prior exposure to single-dose nevirapine for the prevention of parent-to-child transmission of HIV.

4.2.5 Any history of significant renal toxicity while taking TDF (as determined by site investigator).

4.2.6 Currently breast-feeding or pregnant, or intending to become pregnant during the duration of the study.

4.2.7 Current use, use in the 4 weeks preceding study entry, or anticipated use of drugs specified in section 5.4.1 during the study period.

4.2.8 Anticipated start or cessation of any of the following drugs during study period:

- Antipsychotics (e.g., clozapine, olanzapine, risperidone, etc.) and antidepressants (tricyclic antidepressants, e.g., amitriptyline, nortriptyline, etc.; selective serotonin reuptake inhibitors, e.g., fluoxetine, paroxetine, sertraline, etc.; and monoamine oxidase inhibitors, e.g., selegiline) associated with weight gain
- Anticonvulsants/mood stabilizers associated with weight gain (e.g., lithium, valproic acid) or weight loss (e.g., topiramate)
- Thyroid replacement hormones
- Anti-diabetic agents known to cause weight loss (e.g., GLP-1 receptor agonists such as exenatide, dulaglutide, semaglutide, metformin, and SGLT-2 inhibitors such as canagliflozin, dapagliflozin, etc.).

NOTE A: Participants currently receiving antipsychotics, antidepressants, anticonvulsants/mood stabilizers, and thyroid replacement hormones with no dose modifications for at least 12 weeks prior to entry are eligible.

NOTE B: Participants currently receiving anti-diabetic agents known to cause weight loss with no dose modifications for at least 24 weeks prior to entry are eligible.

4.2.9 Planning to undergo bariatric surgery or initiate significant dietary or exercise changes within the study period (e.g., structured weight loss programs such as Weight Watchers), as determined by participant report.

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

4.2.11 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with ability to adhere to study requirements, or cessation of **regular** methamphetamine use**, as determined by the site investigator,** within 60 days prior to study entry.

4.2.12 Acute or serious illness requiring systemic treatment and/or hospitalization within 30 days prior to entry.

4.2.13 A history of a diagnosis of osteoporosis or osteopenia.

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 approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all 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 approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific 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 issued by the DAIDS PRO 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 potential participant has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form prior to the initiation of study procedures.

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 Data Management Center (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 Randomization/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 Results 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 Plans for Enrollment of Women

Given the greater weight gain observed among women receiving INSTI-containing regimens, the study will enroll a greater number of women (defined as female sex assigned at birth) compared to men (>50%).

NOTE A: Since the numbers of transgender men enrolling are expected to be small, requiring a minimum of 50% persons assigned female sex at birth at enrollment will guarantee the population of women in our study, which includes both cis and transgender women, will be >50% of all participants. Enrollment based on sex assigned at birth was selected to account for study sites that do not record gender, or settings where participants may be hesitant to report gender.

NOTE B: The protocol team **may** assign study enrollment limits for sex assigned at birth **as needed** (see section 7.4).

4.5 Plans for Enrollment of Minorities

Given the greater weight gain observed among persons of African American/Black race receiving INSTI-containing regimens, the study will enroll a greater number of African American/Black participants compared to non-African American/Black participants (>50%) at US (i.e., non-international) sites. The over-enrollment of African American/Black participants at US sites (relative to their representation in the general US population) is justified as these individuals comprise >40% of new HIV **acquisitions** in the US annually, and may disproportionately benefit from a switch to DOR. Increasing the representation of African American/Black participants in the trial will facilitate the assessment of race as a factor in the response to ART switch.

NOTE: The protocol team **may** assign study enrollment limits for race at US sites **as needed** (see section 7.4).

4.6 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 A5391 protocol chairs.
- Participants in A5332 REPRIEVE can be co-enrolled in A5391.
- 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 A5391 protocol chairs.
- **US and non-US sites are encourage to co-enroll participants in A5379, “B-Enhancement of HBV Vaccination In Persons Living With HIV (BEe-HIVe): Evaluation of HEPLISAV-B.” Co-enrollment in A5379 does not require permission from the A5391 protocol chairs.**
- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as DOR + TAF/FTC (or TAF/3TC), DOR + TDF/FTC (or TDF/3TC), or BIC, DTG, or RAL + TAF/FTC (or TAF/3TC).

DOR will be provided to Arms 1 and 2 participants through the study, NRTIs and INSTIs will not be provided by the study and participants will receive them from their regular care provider.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens/Administration

Participants on BIC, DTG, or RAL-containing regimens with TAF/FTC (or TAF/3TC) will be randomized 1:1:1 to:

- Arm 1: DOR 100 mg + TAF/FTC (or TAF/3TC, depending on location) by mouth daily with or without food
- Arm 2: DOR 100 mg + TDF/FTC (or TDF/3TC, depending on location) by mouth daily with or without food
- Arm 3: Continuation of entry INSTI+TAF/FTC (or TAF/3TC)

5.1.2 Duration

Total study duration for all arms will be 48 weeks (a brief extension may be required for some participants to complete all study evaluations).

5.2 Study Product Formulation and Preparation

DOR is supplied as white film-coated tablets, each containing 100 mg of doravirine.

Store DOR at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] in the original bottle.

Keep the bottle tightly closed to protect from moisture; do not remove the desiccant.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

DOR will be supplied through the study.

NRTIs for all arms (TAF/FTC, TAF/3TC, TDF/FTC, or TDF/3TC) and INSTIs for Arm 3 will be acquired through standard of care locally.

DOR will be provided by Merck & Company and is available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product 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 DOR received from the NIAID CRPMC and subsequently dispensed. At US CRSs, all unused DOR 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 Prohibited Medications

1. Rifampin/rifabutin
2. Enzalutamide
3. Anticonvulsants contraindicated in co-administration with any of the study drugs (carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramide)
4. Mitotane
5. St. John's wort
6. FDA-approved weight loss agents (e.g., bupropion-naltrexone, liraglutide, orlistat, lorcaserin, phentermine-topiramate)
7. Non-prescription weight loss drugs (e.g., Hydroxycut; additional non-prescription agents at the discretion of the site investigator)
8. Chronic oral steroid use (prednisone equivalent of ≥5 mg for >2 weeks)
9. Bisphosphonates or other treatments for osteoporosis
10. Any antiretrovirals not included in the study treatment

5.4.2 Precautionary Medications

A list of precautionary medications is provided on the PSWP.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: Schedule of Evaluations

Evaluation	Screening	Entry	Post-Entry Evaluations (Weeks)					Prem. Disc.	Confirmation of virologic failure
			4	12	24	36	48, Study Completion		
Visit Window	*<45 days and ≥24 hours prior to entry*	*Day 0*	*-3/+7 days*	*±14 days*					
Documentation of HIV	X								
Medical History	X	X							
Medication History	X	X							
Complete Physical Exam		X							
Targeted Physical Exam			X	X	X	X	X	X	
Concomitant Medications			X	X	X	X	X	X	
Height Measurement	X								
Weight Measurement	X	X	X	X	X	X	X	X	
Waist Circumference		X			X		X	X	
Body Mass Index	X								
Hematology	X	X			X		X	X	

Evaluation	Screening	Entry	Post-Entry Evaluations (Weeks)					Prem. Disc.	Confirmation of virologic failure
			4	12	24	36	48, Study Completion		
Visit Window	*<45 days and ≥24 hours prior to entry*	*Day 0*	*-3/+7 days*	*±14 days*					
Liver Function Tests	X	X	X	X	X		X	X	
Fasting Lipid Profile		X			X		X	X	
Chemistry	X	X	X	X	X		X	X	
Fasting glucose		X			X		X	X	
Calculated Creatinine Clearance	X	X	X	X	X		X	X	
Dipstick Urinalysis		X			X		X	X	
Pregnancy Testing	X	X					X		
CD4+/CD8+ T cells		X			X		X	X	
Plasma HIV-1 RNA	X	X	X[a]	X[a]	X[a]		X[a]	X[a]	X
HIV-1 viral genotype									X
Hemoglobin A1c		X			X		X	X	
Stored plasma and serum (fasting) for insulin, immunologic, and cardiometabolic testing		**X**			**X**		**X**	**X**	
D**ried Blood** S**pot** for drug concentration measurements		X			X		X	X	

Evaluation	Screening	Entry	Post-Entry Evaluations (Weeks)					Prem. Disc.	Confirmation of virologic failure
			4	12	24	36	48, Study Completion		
Visit Window	*<45 days and ≥24 hours prior to entry*	*Day 0*	*-3/+7 days*	*±14 days*					
Stored PBMCs		X					X	X	
Adherence Assessment			X	X	X	X	X	X	
DEXA Scan		X					X	X	
Food Security and Physical Activity Questionnaires		X							
Exercise and Diet Education		X							

[a.] Plasma HIV-1 RNA >200 copies/mL will have an additional visit with repeat viral load testing within 2 weeks of receipt of the result. The specimen for the HIV-1 viral genotype will be drawn at the same time as the second HIV-1 RNA level; if virologic failure is confirmed the reserved specimen will be sent for genotype

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations to determine eligibility must be completed within 45 days, but at least 24 hours, prior to study entry unless otherwise specified. In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

Participants must arrive fasting for the entry visit. Fasting is defined as nothing to eat or drink except for prescription medications and water for at least 8 hours before the visit. If the study participant is not fasting, the participant should return to the clinic for fasting evaluations within 7 days. Entry evaluations must occur *at least 24 hours* after screening evaluations unless otherwise specified. All entry evaluations must occur after randomization. **Study treatment should be initiated as soon as possible after entry evaluations have been completed and within 14 days of entry. If study treatment is initiated more than 7 days post randomization, please consider scheduling the week 4 post-entry visit near the end of the allowed visit window.**

Entry evaluations (excluding DEXA imaging) must be completed prior to the initiation of study medications. Refer to section 6.3.17, DEXA Scan, for scheduling guidance for the DEXA scan at entry (baseline).

6.2.3 Post-Entry Evaluations

Participants must arrive fasting for the weeks 24 and 48 visits, or at a premature discontinuation visit. Fasting is defined as nothing to eat or drink except for prescription medications and water for at least 8 hours before the visit. If the study participant is not fasting, the participant should return to the clinic within the visit window per the SOE.

If a participant experiences an acute inflammatory condition within 14 days prior to a scheduled visit, any scheduled blood collection evaluation should be postponed for an additional 7 days from the initial scheduled visit. Examples of inflammatory conditions that would justify delaying blood collection evaluation 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 A5391 CMC via email (actg.cmcA5391@fstrf.org) with any questions regarding whether a specific situation would require a delay in blood collection, and determination of whether the inflammatory condition has resolved.

Because of diurnal variations in values that may be measured on stored samples, all blood collections should be collected prior to 11:00 AM local time. If this is not possible, then participants' 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 target visit.

NOTE: If treatment initiation was 7 or more days post-randomization, please schedule this visit towards the end of the visit window.

Evaluations at weeks 12, 24, 36, and 48 must occur ±14 days of the target visit.

Study Completion
The week 48 evaluations will be the participant's final scheduled study visit. Participants must arrive fasting for the study completion visit. Fasting is defined as nothing to eat or drink except for prescription medications and water for at least 8 hours before the visit. If the study participant is not fasting, the participant should return to the clinic for fasting evaluations within the visit window (±14 days). If additional HIV-1 RNA testing for virologic failure visit is not necessary (i.e., plasma HIV-1 RNA is determined to be ≤200 copies/mL at week 48), participants should discontinue the study and study treatment once they complete their week 48 visit evaluations. Refer to the Discontinuation Log in the A5391 electronic case report form (eCRF) completion guideline.

If additional HIV-1 RNA testing for virologic failure visit is necessary (i.e., plasma HIV-1 RNA is determined to be >200 copies/mL at week 48 visit), participants should discontinue the study only after a repeat HIV-1 RNA is determined to be ≤200 copies/mL or virologic failure is confirmed and a genotype is sent. In this circumstance, the participant should continue on his or her randomized regimen until HIV-1 RNA and/or viral genotype results are obtained. Additional DOR can be provided to participants in Arms 1 and 2 to ensure continued administration until all required testing is completed. Refer to the Discontinuation Log in the A5391 eCRF completion guideline.

6.2.4 Event-Driven Evaluations

Confirmation of virologic failure

- Participants with HIV-1 plasma RNA >200 copies/mL **on a post-entry sample** should receive repeat viral load testing within 2 weeks of site receipt of the initial result. A genotype can be drawn with the blood for the second viral load, but not sent to the lab until virologic failure is confirmed with a second viral load >200.
- If virologic failure is confirmed with second HIV-1 plasma RNA >200, then the participants will undergo HIV-1 viral genotyping. Participants will discontinue treatment after this specimen has been collected.

Evaluations for Randomized 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 prematurely discontinue/modify any component of their study regimen should ideally complete the premature discontinuation evaluations (listed in the (SOE)) prior to treatment discontinuation or within 7 days of discontinuation. Participants must arrive fasting for the treatment discontinuation visit. Fasting is defined as nothing to eat or drink except for prescription medications and water for at least 8 hours before the visit. If the study participant is not fasting, if possible, the participant should return to the clinic for fasting evaluations within 7 days. The premature discontinuation evaluations are listed in the SOE. Participants who discontinue the study treatment will still be encouraged to remain in study follow-up through 48 weeks. **Refer to section 6.3.17, DEXA Scan, for scheduling guidance for the DEXA scan at premature discontinuation.**

Premature Study Discontinuation
Participants who prematurely discontinue from the study will have the study discontinuation evaluations performed prior to being taken off the study (listed in the SOE). **Refer to section 6.3.17, DEXA Scan, for scheduling guidance for the DEXA scan at premature discontinuation.**

6.3 Instructions for Evaluations

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

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 **AE Grading Table** and AE reporting of adverse events requirements.

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

6.3.1 Documentation of HIV-1

Section 4.1.3 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 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 prior 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (non-traumatic and in adulthood; verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Bariatric or other weight loss surgery

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

6.3.3 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Complete ART history, as available
Immune-based therapy	Within 2 years prior to entry
Blinded study treatment	Complete history
HIV-1-related vaccines	Complete history
Prescription drugs for treatment of opportunistic infections	Within 4 weeks prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	Within 4 weeks prior to study entry
Prescription drugs (other)	Within 4 weeks prior to study entry
Alternative therapies	Within 4 weeks prior to study entry
Dietary supplements	Within 4 weeks prior to study entry
Diet or weight loss therapy, either prescribed or over the counter	Within 48 weeks prior to study entry
Sex-hormone medications or sex-hormone analogues or antagonists*	Last 48 weeks except as noted below
Growth hormones	Complete history
Other category	Within 4 weeks prior to study entry

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); 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. Also includes hormones purchased outside the medical system (i.e., “street hormones”).

6.3.4 Weight History

If/as documentation is available: Weight prior to initiating/switching to INSTI-based ART; and annual weight over the following 3 years (i.e., approximately 1, 2, and 3 years after initiating or switching to INSTI-based ART). Recalled values will not be accepted as documentation. If/as available, documentation of known medical reason for weight changes (as per investigator opinion), during the time period above—for example, concomitant medication use, Cushing’s disease, prolonged hospitalization, and so forth.

6.3.5 Clinical Assessments

Complete Physical Examination
A complete physical examination at entry to include at a minimum 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 complete physical examination will also include signs and symptoms, diagnoses, and vital signs (temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Examination
A targeted physical examination at study visits after entry is to include vital signs (temperature, pulse, respiration rate, and blood pressure), and is to be driven by any previously identified or new adverse event, that the participant has experienced since the last visit or at this visit.

Post entry, see section 8.2 for collection requirements for pregnancy.

Refer to section 7.2 for AE collection requirements.

Concomitant Medications
Post-entry, the following new or discontinued concomitant medications must be recorded:

- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.3 for examples).
- Anti-diabetic medications, antipsychotics, antidepressants, anticonvulsants/mood stabilizers, smoking cessation treatments (including over the counter), dietary supplements, and weight loss agents (including over the counter)

- Growth hormone or growth hormone-releasing analogs
- Any drugs with anti-inflammatory properties
- Any weight loss drugs (including non-prescription)
- Any drugs expected to increase weight
- Thyroid hormones

Study Treatment Modifications
Record all study drug modifications including initial doses, participant-initiated, site investigator-initiated, and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than 5 consecutive days since the last visit**, and overdose**. Record any permanent discontinuation of treatment.

6.3.6 Height Measurement

Height in centimeters should be measured per the SOE.

6.3.7 Weight Measurement

All weight measurements should be conducted with the participant wearing an examination gown or a minimum amount of additional clothing (e.g., socks, light pants/dress, and thin blouse/shirt are acceptable, but no shoes, outer coat, or sweatshirt), and after removal of heavy jewelry (e.g., large necklace) or belt buckle, and removal of contents of pockets. Weight should be measured per the SOE and with approximately the same type (examination gown) or amount of clothing (as described above) on each time.

6.3.8 Waist Circumference

Minimum waist circumference in centimeters should be measured with a flexible tape on bare skin at the smallest horizontal circumference above the umbilicus and below the xiphoid process per the SOE.

6.3.9 Body Mass Index

Body mass index should be calculated using weight and height collected at screening and the formula: BMI = (weight in kilograms)/(height in meters, squared). A BMI calculator is available on the Frontier Science Portal.

6.3.10 Laboratory Evaluations

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

At screening and entry, all laboratory values must be recorded on the eCRF. For post-entry assessments, record on the eCRF all laboratory values for ALT, AST, serum creatinine, calculated creatinine clearance, alkaline phosphatase, total bilirubin, total cholesterol, HDL, calculated LDL, triglycerides, WBC cell count and differential and glucose regardless of grade as indicated on SOE; record abnormal laboratory findings per section 7.2.

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

Liver Function Tests
Total and direct bilirubin, AST [SGOT], ALT [SGPT], alkaline phosphatase, total protein, albumin

Fasting Lipid Profile
Total cholesterol, triglycerides, HDL, calculated LDL

Chemistry
Sodium, potassium, chloride, phosphate, bicarbonate, serum creatinine, and blood urea nitrogen

Fasting Glucose
Glucose

Calculated Creatinine Clearance
Calculated creatinine clearance will be estimated by the CKD-EPI equation (a calculator is available at: https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi).

Dipstick Urinalysis
Total protein.

Pregnancy Test
For participants capable of becoming pregnant: serum or urine β-HCG (urine test must have a sensitivity of <25 mIU/mL) performed at Screening, Study Entry, and Study Completion visits. Record pregnancy and pregnancy outcome per section 8.0.

NOTE: Additional pregnancy testing should be performed by the site investigator if there is concern for pregnancy after study entry.

6.3.11 Immunologic Studies

CD4+/CD8+ T cells
Obtain absolute CD4+/CD8+ count and percentages **at entry and post-entry evaluations** from a laboratory that possesses a CLIA certification or equivalent (US sites) or Immunology Quality Assurance (IQA) certification (non-US sites).

For entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

6.3.12 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 45 days prior to study entry by a laboratory that possesses a CLIA certification or equivalent, or at any network-approved non-US laboratory that is VQA-certified. Eligibility will be determined based on the screening value.

HIV-1 RNA testing will occur at entry, weeks 4, 12, 24, and 48, or at premature discontinuation. Participants with one plasma HIV-1 RNA >200 copies/mL **on a post entry sample** will have an additional visit with repeat viral load testing within 2 weeks of site receipt of the result (refer to Event-Driven Evaluations in section 6.2.4). Screening HIV-1 RNA tests will be performed by the site, while entry and post-entry HIV-1 RNA measurements will be performed centrally.

HIV-1 viral genotype
Participants with two sequential **post-entry** plasma HIV-1 RNA >200 copies/mL measurements will have HIV-1 viral genotype performed (refer to Event Driven Evaluations in section 6.2.4). The specimen for the HIV-1 viral genotype will be drawn at the same time as the second HIV-1 RNA level; if virologic failure is confirmed the reserved specimen will be sent for genotype (refer to laboratory processing chart [LPC]).

6.3.13 Metabolic Studies (refer to LPC)

Hemoglobin A1c
Hemoglobin A1c will be collected at entry, week 24, and week 48 or premature discontinuation.

Fasting stored plasma and serum for insulin, immunologic and cardiometabolic assays
Fasting plasma will be collected at entry, week 24, and week 48 or at premature discontinuation.

- Insulin will be measured at the end of the study from batched stored samples. HOMA-IR (incorporates fasting glucose and insulin levels) to be calculated during data analysis, not by the site.

- Measurement of metabolic, cardiovascular, and immunologic biomarkers will be performed at central laboratories. Collection, processing, and shipping instructions are provided in the current A5391 LPC, which is posted on the PSWP.

If a participant arrives for a fasting visit (entry, week 24, and week 48) in a non-fasting state, the visit should be re-scheduled within the visit window noted in the SOE. Participants should be fasting for premature discontinuation visits if possible.

Samples will be stored according to the LPC and are expected to be used for measurement of immune biomarkers. **Separate samples will be collected (in fasting state) to measure insulin, 1,3 beta-glucan, and free fatty acids, in addition to stored plasma for immunologic and cardiometabolic testing, and stored serum for immunologic and cardiometabolic testing**.

6.3.14 Dried Blood Spots (DBS) for drug concentration measurements

DBS cards will be stored to measure concentrations of TFV-DP, both from TDF and TAF, and FTC-TP at entry, week 24, week 48, and also at any premature discontinuation. Refer to section 11.0.

6.3.15 Stored Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs will be collected and stored at entry and week 48 or premature discontinuation.

PBMCs will be stored according to the LPC and are expected to be used for the following advanced flow assays:

- $CD4^+$ and $CD8^+$ T cell subsets (e.g., activated, senescent, and memory)
- Invariant NK T cells (iNKT cells)

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

6.3.16 Adherence Assessment

The adherence questionnaire **will be administered per the SOE and** is posted on the DMC Portal in the Forms Management Utility. Responses will be recorded on an eCRF in Rave.

6.3.17 DEXA Scan

A whole body DEXA scan for body composition and bone mineral density will be obtained. Sites will record requested DEXA scan findings on an eCRF. **Additional information about reporting requirements and expected evaluations is provided in the Manual of Procedures (MOPS).**

The DEXA imaging evaluation at entry (baseline) should be completed within 14 days prior to or 14 days after the initiation of study treatment. If a participant prematurely discontinues the study, the second DEXA imaging evaluation should be completed within 14 days prior to or 14 days after the premature discontinuation visit.

6.3.18 Food Security and Physical Activity Questionnaires

Food security will be assessed using the USDA Adult Food Security Questionnaire. Physical activity will be assessed using the International Physical Activity Questionnaire. The questionnaires will be collected from all participants at entry only, as indicated in the SOE. The questionnaires are posted on the DMC Portal in the Forms Management Utility. Responses will be recorded on an eCRF in Rave.

6.3.19 Exercise and Diet Education

At the time point indicated in the SOE, participants will receive general recommendations on a balanced diet and regular exercise. Educational materials are posted on the PSWP.

Documentation of exercise and diet education is not recorded on the eCRF.

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 condition.

7.2 Adverse Event Collection 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
- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting serious adverse event (SAE) definition or expedited adverse event (EAE) reporting requirement

NOTE **A**: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

NOTE B: Creatinine and eGFR should be graded using the categorical mL/min values from the DAIDS AE Grading Table. The percent change criteria will not apply to A5391.

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 AEs to DAIDS

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

DAERS, an internet-based reporting system, must be used for 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: DOR, TAF, TDF, FTC, and 3TC.

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 as per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the 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

Members of the protocol team will monitor the conduct and safety of the study via regular pooled summaries of accrual, baseline characteristics, treatment and study discontinuation, and data completeness.

The study will enroll >50% women and >50% African American/Black participants. For the purpose of enrollment limits, a woman is defined as someone assigned female sex at birth. The protocol team **may** assign overall study enrollment limits for sex at all sites and race at US sites, **or** site-specific enrollment limits.

The protocol team will monitor enrollment by sex and race, with periodic updates issued to sites to inform on current study enrollment by sex and race, as needed. At the outset of the study, sites will be encouraged to prioritize enrollment of women and African American/Black participants, and will be alerted that restrictions on enrollment may later be enacted to achieve enrollment targets. The protocol team, in consultation with the Statistical and Data Management Center, will review the sex and race distributions after approximately 25%, 50%, and 75% of enrollment has occurred.

The DAIDS Clinical Representatives will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct per DAIDS policies, guidance documents, and Standard Operating Procedures (SOPs), as applicable. Additionally, the DAIDS clinical representatives and the protocol monitoring team will review aggregated AE summaries and virological failures pooled across treatment arms prepared quarterly by the SDAC.

The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC). The SMC will review unblinded, by-arm summaries of accrual, baseline characteristics, study and treatment status (including premature

discontinuations), data availability/completeness, virologic failures, and AEs. The first interim review will occur no more than 1 year after the enrollment of the first study participant. An interim review may also be convened if a concern is identified by the DAIDS clinical representatives, the study chairs, or study statisticians in consultation with the team. See section 10.0 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring are outlined in a Study Progress, Data, and Safety 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

Only toxicities related to antiretroviral drugs (study-provided or participant-supplied) will be considered in the toxicity management section. The grading system is located in the DAIDS AE Grading Table, corrected Version 2.1, July 2017: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The general guidelines presented in sections 8.1.1, 8.1.2, and 8.1.3 apply to toxicities that are not specifically discussed elsewhere.

8.1.1 Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue study treatment without alteration of the dosage. For participants experiencing Grade 1 or 2 AEs who choose to discontinue all study treatment, the site investigator should complete premature treatment discontinuation evaluations, contact the study leadership team (actg.cmca5391@fstrf.org), and the participant should be encouraged to stay in study follow-up until 48 weeks.

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

8.1.2 Grade 3

Grade 3 AEs or toxicity should be evaluated and managed by the site investigator. The A5391 CMC should be notified at actg.cmca5391@fstrf.org regarding AEs or toxicities that result in a change of study treatment. If the site investigator has compelling evidence that the AE or toxicity was NOT caused by the study treatment, dosing may continue.

If the study treatment is temporarily held, the participant should be re-evaluated frequently until the AE or toxicity returns to Grade ≤2, at which time the study treatment may be reintroduced at the discretion of the site investigator or according to standard practice.

If the site investigator determines that an isolated Grade 3 laboratory abnormality (lab abnormality without a clinical AE) is related to study treatment, the site has the option of confirming the AE or toxicity before holding the study treatment.

If the same Grade 3 AE or toxicity recurs within 4 weeks of reintroducing the study treatment and is thought to be related to the study treatment (per the site investigator), the study treatment must be permanently discontinued. However, if the same Grade 3 AE or toxicity recurs after 4 weeks, and is not thought to be related to the study treatment (per the site investigator), the management scheme outlined above may be repeated.

If a participant permanently discontinues study treatment as a result of the Grade 3 AE, the site should complete the premature study treatment discontinuation evaluations as defined in the SOE as soon as possible and the participant should be followed frequently until resolution of the AE. See section 6.2.4 for management of participants who prematurely discontinue study treatment. Participants should be encouraged to stay in study follow-up until week 48.

8.1.3 Grade 4

Participants who develop a Grade 4 symptomatic AE (clinical or laboratory) related to study drug will have all study treatment permanently discontinued. The study leadership team (actg.cmca5391@fstrf.org) must be notified by e-mail regarding these toxicities to discuss further management. If participants experience Grade 4 AEs requiring permanent discontinuation of all study medications, the site should ideally complete the premature study treatment discontinuation evaluations as soon as possible per the SOE and the participants should be followed frequently until resolution of the AE. See section 6.2.4 for management of participants who prematurely discontinue study treatment. Participants should be encouraged to stay in study follow-up until week 48.

The participant should be re-evaluated frequently until the AE returns to Grade ≤2 or baseline.

8.1.4 Creatinine Clearance

Creatine clearance should be calculated at screening, entry, and weeks 4, 12, 24, and 48 weeks (or premature discontinuation). Any participant experiencing a calculated CrCl <50 mL/min should have the value repeated within 7 days.

8.1.4.1 FTC/3TC

All study participants will be on FTC or 3TC as part of their regimen. Participants who experience a confirmed (two consecutive) reduction in CrCl to <50 mL/min should have their FTC or 3TC dose reduced as indicated on the package insert, at the discretion of the site investigator.

8.1.4.2 TDF

Participants who experience a confirmed (two consecutive) reduction in CrCl to <50 mL/min on TDF should have their TDF dose reduced as indicated on the package insert, at the discretion of the site investigator.

8.1.4.3 TAF

Participants who experience a confirmed (two consecutive) reduction in CrCl to <30 mL/min on TAF should have their TAF dose reduced as indicated on the package insert, at the discretion of the site investigator.

8.1.5 Hyperlactatemia/Lactic Acidosis

The following case definition of symptomatic hyperlactatemia/lactic acidosis will be used in this protocol:

New, otherwise unexplained and persistent (≥2 weeks) occurrence of one or more of the following symptoms:

- Nausea and vomiting
- Abdominal pain or gastric discomfort
- Abdominal distention
- Elevated liver function tests
- Unexplained fatigue
- Dyspnea
- Concern for hyperlactatemia/lactic acidosis should be confirmed by measurement of serum lactate level at the discretion of the site investigator. If a lactate level >2 x ULN is confirmed, participants should immediately discontinue their study medications and the team (actg.cmca5391@fstrf.org) should be contacted to plan further treatment.

8.2 Pregnancy

Participants in Arm 1 or 2 who become pregnant on study must discontinue DOR and should receive a new regimen in accordance with current WHO guidelines for treatment of PWH who become pregnant while on ART. Participants who become pregnant may remain in follow-up off study treatment. All participants who become pregnant while on study will be followed through the end of pregnancy to determine the effects of the study regimens on outcomes in the exposed infants. For participants who become pregnant while receiving DTG please see the MOPS for further management.

Participants who become pregnant, and who have access to an International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) trial site, should be encouraged to enroll in appropriate IMPAACT studies.

The intrapartum complications, 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. Phone: 1-800-258-4263; Fax: 1-800-800-1052.

Pregnancy Reporting

Participants who become pregnant while on study drugs and discontinue DOR due to their pregnancy will be asked to remain on study, off study treatment. Sites will complete the premature discontinuation visit within 7 days after stopping treatment (except for DEXA scan and any aspects deemed by the site investigator to be potentially harmful). If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should complete a study discontinuation visit within 7 days and request permission to contact the participant regarding pregnancy outcome at the end of the pregnancy. Any intrapartum complications, pregnancy, and pregnancy outcome for the participant and infant (if known) should be recorded on the eCRFs.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see section 8.1 Toxicity).
- Requirement for concomitant medications (see section 5.4).
- Request by participant to terminate treatment.
- Clinical reasons believed life-threatening by the physician, even if not addressed in the Toxicity section of the protocol.
- Pregnancy

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Failure/inability of participant to attend study visits.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

The study's primary objective is to evaluate if a switch to either DOR + TAF/FTC (or TAF/3TC) or DOR + TDF/FTC (or TDF/3TC) results in a difference (less weight gain or overall weight loss) in weight change over 48 weeks compared to continued use of RAL, DTG, or BIC + TAF/FTC (or TAF/3TC). It is of secondary interest to compare the two

switch arms (DOR + TAF/FTC [or TAF/3TC] versus DOR + TDF/FTC [or TDF/3TC]) to assess if there are additional weight benefits with a switch to TDF/FTC (or TDF/3TC) from TAF/FTC (or TAF/3TC).

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 to be listed under "Other Outcome Measures."

10.2.1 Primary Outcome Measures

Change (percent) in body weight (kg) from entry to week 48.

10.2.2 Secondary Outcome Measures

10.2.2.1 Change (percent) in body weight (kg) from entry to week 24.

10.2.2.2 Change (absolute) in waist circumference from entry to weeks 24 and 48.

10.2.2.3 Change (absolute) in fasting cardiometabolic parameters (glucose, insulin, HOMA-IR, triglycerides, LDL, HDL) from entry to weeks 24 and 48.

10.2.2.4 Occurrence of confirmed plasma HIV-1 RNA >200 copies/mL.

10.2.2.5 Occurrence of Grade ≥3 AEs or >10% reduction in CrCl as estimated by the CKD-EPI equation.

10.2.2.6 Occurrence of premature discontinuation of study treatment.

10.2.2.7 Change (percent) in DEXA body composition measures (total fat and lean mass, trunk fat, limb fat, appendicular lean mass) from entry to week 48.

10.2.2.8 Change (percent) in DEXA hip and lumbar spine bone mineral density from entry to week 48.

10.2.2.9 Change in categorization of bone mass (by WHO classification) from baseline to week 48 based on minimum reported T score from left/right femoral neck, left/right total femur/hip, and lumbar spine.

10.2.3 Other Outcome Measures

10.2.3.1 Change (absolute) in immunologic parameters from entry to weeks 24 and 48.

10.2.3.2 Change (absolute) in plasma adipokines from entry to weeks 24 and 48.

10.2.3.3 Change in blood concentrations of TFV-DP both from TDF and TAF, and FTC-TP, measured from DBS, from entry enrollment to weeks 24 and 48.

10.3 Randomization and Stratification

All eligible participants will be randomized using a 1:1:1 ratio to one of three study arms: switch to DOR + TAF/FTC (or TAF/3TC), switch to DOR + TDF/FTC (or TDF/3TC), or continued INSTI + TAF/FTC (or TAF/3TC), using permuted blocks with institutional balancing. Participants will be stratified at randomization by sex assigned at birth and race (African American/Black vs. non-African American/Black). Participant enrollment targets are >50% participants assigned female sex at birth across all sites and >50% African American/Black participants at US sites.

10.4 Sample Size and Accrual

The proposed sample size is 222 participants (74 per arm). It is anticipated that participants will accrue to the study at a rate of 20 participants per month at an estimated 14 sites (12 US and 2 non-US); at this rate, the study should fully accrue in approximately 11-12 months.

A total of 222 participants will be randomized at a 1:1:1 ratio to the three arms. Allowing for 15% loss to follow-up this will yield 189 evaluable participants (63 per arm). This sample size will provide 80% power to detect an absolute difference of 5% at week 48 between each switch arm and the control arm (continuing INSTI), assuming the standard deviation (SD) of within-participant changes is 9%, using two-sided t-tests with 2.5% alpha level. Each switch arm will be compared to the control arm using a 2.5% alpha level to control the overall type-I error rate. The study is powered to detect a 5% difference in weight between arms, as a 5% absolute difference is considered clinically meaningful.

At present, prospective, randomized controlled trial data on weight changes on INSTI + TAF/FTC are only available from sub-Saharan African studies (ADVANCE trial, see above), which may differ from the majority of ACTG sites by clinical, social, behavioral, genetic, and other factors. There are also limited data on DOR aside from recent abstract data, which showed a median 1.0 kg (IQR -1.2 to 3.9) weight gain at 48 weeks among ART-naïve persons initiating DOR in pooled phase 2 and 3 studies [**25**]. Therefore, the sample size, and specifically the assumed SD, for A5391 is based on ACTG A5257 trial data comparing INSTI + TDF/FTC vs non-INSTI + TDF/FTC.

In A5257, among individuals who remained on RAL and who had BMI ≥**30** at **48** weeks, the SD for the change in weight from week **48** to week **96** (i.e., approximately 48 weeks) was **7**% (mean change **-**0.**03**%). During the first 96 weeks, however, where larger changes in weight occurred, the SD for the change in weight was 1**1**%. The 9% SD chosen for this study is intermediate of the SDs observed from A5257 and is a conservative approach to ensure that A5391 is well powered to detect differences between arms.

The table below provides a summary of statistical power based on a range of possible SD estimates.

Table 10.4-1: Statistical Power under Different Scenarios Assuming: N=63 Evaluable per Arm

Two Sample T-test with Two-sided 2.5% Alpha		
Power	Mean Difference between arms	Standard Deviation for change within arm
99%	5%	5%
96%	5%	7%
80%	5%	9%
61%	5%	11%

10.5 Data and Safety Monitoring

An ACTG-appointed Study Monitoring Committee (SMC) will undertake reviews of interim data to ensure safety of study participants and to possibly recommend termination or modification of the study. At SMC reviews, data will be considered as detailed in section 7.4.

At each interim review, the SMC will review unblinded summaries, by randomized arm, of study status and, including loss to follow-up (LTFU), treatment discontinuations and cross-over, and safety, including virologic failures and adverse events. Interim efficacy analyses are not planned.

There are no pre-specified stopping guidelines for this study, but the SMC should consider possible modifications or termination on bases of safety concerns or operational futility. With regards to safety, if 10% or more of participants on the DOR-containing arms experienced virologic failure or treatment-related AEs, this would be concerning to the study team. However, the DRIVE-SHIFT phase 3, open-label, randomized noninferiority trial showed comparable maintenance of virologic suppression among ART-treated persons switched from INSTI-based regimens to DOR/3TC/TDF. With respect to operational futility the SMC should consider the overall and within arm LTFU rates, and treatment cross-over rates (particularly those switching from DOR-containing arm back to an INSTI-containing arm). As a benchmark, an overall LTFU rate of 20% or higher would be cause for concern, particularly if a higher rate is observed in the INSTI-containing arm where participants are not switched to DOR.

10.6 Analyses

The primary analysis will contrast each switch arm (DOR + TAF/FTC [or TAF/3TC] or DOR + TDF/FTC [or TDF/3TC]), separately, with the control arm (remaining on INSTI + TAF/FTC [or TAF/3TC]). A secondary analysis will then compare the two switch arms with each other to determine if there are added effects of switching from TAF/FTC (or TAF/3TC) to TDF/FTC (or TDF/3TC); the switch arms will be compared regardless of the observed results for the primary comparisons. Figure 10.6-1 depicts the planned comparisons.

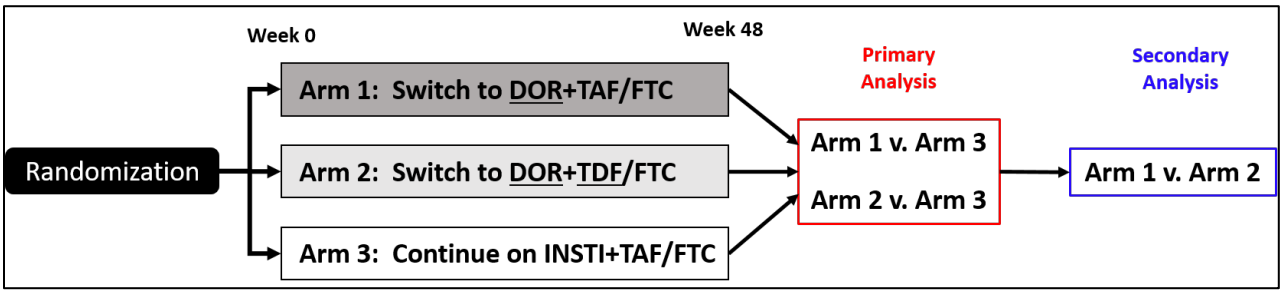


Figure 10.6-1: Planned comparisons.

NOTE: Analyses will be conducted on the entire **trial sample, irrespective of history of weight gain (i.e., protocol version at enrollment). History of** >10% **weight gain will be a prespecified subgroup, but this subgroup analysis could be limited by the availability of historical weight information among participants enrolling to the trial under the current version, when this information is not required.**

10.6.1 Primary Analysis

The primary analysis will compare the percent change in weight (kg) from entry to week 48. The mean percent change in weight at week 48 will be compared separately between each of the investigational switch arms and the control arm using linear regression adjusting for stratification factors, with a 2.5% type-I error rate; corresponding 97.5% confidence intervals (CIs) will also be provided. It is of secondary interest to contrast the two switch arms (see below). The primary analysis will be conducted using intent-to-treat (ITT) principles, in which participants will be analyzed according to their randomized study arm, regardless of whether they changed treatment during study follow-up. A supplemental analysis will restrict the analysis population to only those who remained on their randomized regimens through week 48.

In the event that participants discontinue the study prior to week 48, imputation methods will be used to estimate weight at week 48. Modern statistical methods to account for loss to follow-up will be considered, such as multiple imputation, global sensitivity analysis, or inverse probability of censoring weighting; specific details will be discussed in the Statistical Analysis Plan.

10.6.2 Secondary Analysis

To further understand the effect of TAF on weight gain, the two switch arms will be compared to each other. The mean percent change in weight at week 48 will be compared between the DOR + TAF/FTC (or TAF/3TC) arm and the DOR + TDF/FTC (or TDF/3TC) arm using linear regression adjusting for stratification factors with a 5% type-I error; corresponding 95% CI will be provided.

Changes in weight from entry to week 24, changes in minimum waist circumference, and fasting cardiometabolic parameters from entry to weeks 24 and 48, and changes DEXA measures from entry to week 48 will be analyzed in a similar manner as the analyses of weight changes. Sensitivity analyses of changes in triglycerides, LDL, and HDL will consider on-study use of lipid-lowering medications by participants.

Safety, tolerability, and maintenance of virologic suppression will be evaluated by estimating the proportion of participants who experienced any Grade 3 or higher AE or >10% reduction in CrCl, who prematurely discontinued study treatment, or who have confirmed **post-entry** plasma HIV-1 RNA > 200 copies/mL, and will be compared separately between each switch arm and the control arm via two-sided mid-p Fisher's exact test, each evaluated with 2.5% type-I error.

Additional longitudinal analyses will evaluate changes in weight across all study visits. Details will be provided in the Statistical Analysis Plan.

11.0 PHARMACOLOGY PLAN

DBS cards will be stored to measure concentrations of TFV-DP, both from TDF and TAF, and FTC-TP at entry, week 24, and week 48 (or at premature discontinuation). Interpretation of the FTC-TP levels requires information on the timing of ART doses over the preceding 3 days. Therefore, the date/time of INSTI, DOR, TDF, TAF, and FTC (or 3TC) doses, depending on study arm, for the three days preceding the entry, week 24, and week 48 study visits should be recorded on the eCRF.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

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 randomization.

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

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity [27]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solutions. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12.4 Reporting Protocol Deviations

The site principal investigator and staff are responsible for identifying and reporting deviations. If protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be reported to the IRB/EC per their guidelines.

Refer to the MOPS for the definition of protocol deviation and instructions for completing the study protocol deviation eCRF.

13.0 PARTICIPANTS

13.1 IRB Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or *parent,* legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant 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, NIAID, OHRP, other local, US, and non-US regulatory entities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

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

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

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 US CDC and the US 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

1. Koethe JR, Jenkins CA, Lau B, et al. Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res Hum Retroviruses 2016;32:50-8.
2. Hasse B, Iff M, LedergerberB, et al. Obesity trends and body mass index changes after starting antiretroviral treatment: the Swiss HIV Cohort Study. Open Forum Infect Dis 2014;1(2):ofu040. PMID: 25734114
3. Ilozue C, Howe B, Shaw S, et al. Obesity in the HIV-infected population in Northeast England: a particular issue in Black-African women. Int J STD AIDS 2017;28:284-9.
4. Tate T, Willig AL, Willig JH, et al. HIV infection and obesity: where did all the wasting go? Antivir Ther 2012;17:1281-9. PMID: 22951353
5. Amorosa V, Synnestvedt M, Gross R, et al. A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia. J Acquir Immune Defic Syndr 2005;39:557-61.
6. Herrin M, Tate JP, Akgun KM, et al. Weight Gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals. J Acquir Immune Defic Syndr 2016;73:228-36. PMID: 27171741
7. Yuh B, Tate J, Butt AA, et al. Weight change after antiretroviral therapy and mortality. Clin Infect Dis 2015;60:1852-9. PMID: 25761868
8. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al.; CHARTER Group. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. Neurology 2012;78:485-92. PMID: 22339412
9. Mohammed SS, Aghdassi E, Salit IE, et al. HIV-positive patients with nonalcoholic fatty liver disease have a lower body mass index and are more physically active than HIV-negative patients. J Acquir Immune Defic Syndr 2007;45:432-8. PMID: 17558337
10. Achhra AC, Mocroft A, Reiss P, et al.; D:A:D Study Group. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. HIV Med 2016 ;17:255-68. PMID: 26216031
11. Rebeiro PF, Jenkins CA, Bian A, et al. Risk of incident diabetes mellitus, weight gain, and their relationships with integrase inhibitor-based initial antiretroviral therapy among persons with human immunodeficiency virus in the United States and Canada. Clin Infect Dis 2021;73:e2234-e2242. PMID: 32936919
12. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in waist circumference in HIV-infected individuals initiating a raltegravir or protease inhibitor regimen: effects of sex and race. Open Forum Infect Dis 2018;5:ofy201. PMID: 30465010
13. Bourgi K, Jenkins C, Rebeiro P, et al. Greater weight gain among treatment-naive persons starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc 2020;23:e25484. PMID: 32294337
14. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J Antimicrob Chemother 2018;73:2177-85.

15. Rizzardo S, Lanzafame M, Lattuada E, et al. Dolutegravir monotherapy and body weight gain in antiretroviral naive patients. AIDS 2019;33:1673-4. PMID: 31305333
16. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis 2020;70:1267-74.
17. Norwood J, Turner M, Bofill C, et al. Brief Report: Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr 2017;76:527-31. PMID: 28825943
18. Erlandson KM, Wu K, Lake JE, et al.; A5501, A5322 Protocol Teams. Mitochondrial DNA haplogroups and weight gain following switch to integrase strand transfer inhibitor-based antiretroviral therapy. AIDS 2021;35:439-45. PMID: 33252493
19. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med 2019;381:803-15. PMID: 31339677
20. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis 2020;71:1379-89. PMID: 31606734
21. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018;5:e211-e20.
22. Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial. Clin Infect Dis 2019;68:535-44. PMID: 30184165
23. Gatell JM, Morales-Ramirez JO, Hagins DP, et al. **Doravirine dose selection and 96-week safety and efficacy versus efavirenz in antiretroviral therapy-naive adults with HIV-1 infection in a Phase IIb trial. Antivir Ther 2019;24:425-35. PMID: 31355775**
24. Johnson M, Kumar P, Molina JM, et al.; DRIVE-SHIFT Study Group. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial. J Acquir Immune Defic Syndr 2019;81:463-72. PMID: 30985556
25. Orkin C, Elion RA, Thompson M, et al. **Changes in weight and BMI with first-line doravirine-based therapy. AIDS 2021;35:91-9. PMID: 33048879**
26. IAS-USA drug resistance chart 2019. Available at https://www.iasusa.org/wp-content/uploads/2019/07/2019-drug-resistance-mutations-figures.pdf. Accessed December 26, 2019.
27. **FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards. March 2020; Updated on January 27, 2021. Accessed at:** https://www.fda.gov/media/136238/download**.**

APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol: A5391

Doravirine for **Obese** Persons on Integrase Inhibitors and Tenofovir Alafenamide
(The Do IT Study)
FINAL Version 2.0, dated 19Aug2022

SHORT TITLE FOR THE STUDY: The Do IT Study

SUMMARY

PURPOSE

This is a research study, and your participation in this study is voluntary.

The purpose of this study is to see whether **obese (body mass index ≥30 kg/m^2)** people living with HIV **who are receiving an** antiretroviral therapy (ART) regimen that include**s** an integrase strand transfer inhibitor (INSTI) in combination with tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir alafenamide/lamivudine (TAF/3TC) could gain less weight, or might lose weight, after an ART regimen switch. The study will also assess if a switch in ART leads to differences in metabolic conditions (i.e., how the body stores and uses energy), cardiovascular health (i.e., the heart and blood vessels), and bone health.

NUMBER OF PARTICIPANTS

There will be 3 treatment groups of 74 people each, for a total of 222 participants.

LENGTH OF STUDY

The study will last for 48 weeks (about 1 year). Following the first visit, you will need to come back to the clinic after about 4, 12, 24, 36, and 48 weeks. You will need to fast for 8 hours before a few visits. Each visit may take up to 3 hours. You will not need to stay overnight.

STUDY TREATMENT

Participants age ≥18 years on bictegravir (BIC), dolutegravir (DTG), or raltegravir (RAL) with TAF/FTC or TAF/3TC (depending on location) will be assigned by chance 1:1:1 (i.e., equally) to:

- Doravirine (DOR) with TAF/FTC (or TAF/3TC)

- DOR with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (or TDF/3TC)
- Continue on their current regimen

DOR will be provided to study participants through the study but nucleoside reverse transcriptase inhibitors (TAF/FTC [or TAF/3TC] and TDF/FTC [or TDF/3TC]) and the INSTI medications for those remaining on their current regimen will not be provided by the study.

REQUIRED ACTIVITIES

Blood and urine collections
At most visits, some blood **(about 2 to 6 tablespoons)** will be collected from a vein in your arm.
At a few visits, you will be asked to provide a urine sample.

Questionnaires
At the Entry Visit, you will complete questionnaires on food security and physical activity. At each visit **after entry** you will complete a questionnaire on medication adherence.

Special procedures
You will have a dual-energy X-ray absorptiometry (DEXA) scan at two visits to measure your lean muscle and body fat, and your bone density.

RISKS

Risks of participating in this study include side effects from drugs used in this study or the risk of loss of HIV-1 viral suppression (i.e., a rise in the level of virus in the blood, which may require a change in your HIV medications).

BENEFITS

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

You may have weight loss, but no guarantee can be made.

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 have HIV (the virus that causes AIDS)**, you have a body mass index that is in the obese range, and you are taking an** antiretroviral therapy (ART) **regimen that contains** an integrase strand transfer inhibitor (INSTI; a class of drug that includes bictegravir, dolutegravir, and raltegravir) combined with tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir alafenamide/lamivudine (TAF/3TC).

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?

Weight gain after starting ART is common, but recent studies have found that some people with HIV who are taking an INSTI combined with TAF/FTC (or TAF/3TC) may gain more weight than people taking other drug combinations. Weight gain on ART can be healthy for persons who are underweight when they start treatment. However, an increasing number of people with HIV (PWH) are obese**, which may** increase their risk for cardiovascular (heart) and metabolic diseases (such as diabetes).

It is currently unknown whether people who **are obese and taking** an INSTI + TAF/FTC (or TAF/3TC) regimen could either slow the rate of weight gain or could actually lose weight by changing their ART.

The primary purpose of this study is to see if **obese** PWH who **are taking an** INSTI + TAF/FTC (or TAF/3TC) regimen could either slow their rate of weight gain or lose weight within about 1 year if they switch to a regimen containing doravirine (DOR; a newer, non-nucleoside reverse transcriptase inhibitor medication). The study will also try to see if participants changing from TAF/FTC (or TAF/3TC) to TDF/FTC (or TDF/3TC) will experience less additional weight gain or a reduction in overall body weight at 48 weeks compared to persons continued on an INSTI + TAF/FTC (or TAF/3TC) combination. Additionally, the study will see whether a change in ART can affect things like waist circumference, metabolic and cardiovascular health, fat and lean mass body composition, bone health, and maintenance of virologic suppression. Finally, the study will look at the safety and tolerability of DOR plus either TAF/FTC (or TAF/3TC) versus TDF/FTC (or TDF/3TC).

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

When you enter this study, you will be randomized (assigned by chance, as if by roll of dice) to one of three study groups. Because the randomization is equal, you will have a 33% chance of being in any of the following study groups:

1. Group 1: You will continue taking TAF/FTC (or TAF/3TC) but will stop your INSTI and take DOR; your ART will be DOR + TAF/FTC (or TAF/3TC) for 48 weeks.
2. Group 2: You will stop your INSTI and TAF/FTC (or TAF/3TC) and will switch to DOR + TDF/FTC (or TDF/3TC) for 48 weeks.
3. Group 3: You will continue your current ART of an INSTI + TAF/FTC (or TAF/3TC) for 48 weeks.

DOR will be provided to study participants in Groups 1 and 2 through the study. Nucleoside reverse transcriptase inhibitors (TAF/FTC [or TAF/3TC] and TDF/FTC [or TDF/3TC]) will not be provided by the study.

The study will last 48 weeks (approximately 1 year). After the Entry Visit, you will return to the clinic at 4, 12, 24, 36, and 48 weeks. Each visit may take up to 3 hours. You will not need to stay overnight for any of the visits.

You must fast (have nothing to eat or drink other than medications and water for at least 8 hours) before the first visit. You will be asked to fast again before the visits 24 and 48 weeks later.

You will remain on your study group ART for the entire study unless your usual health provider or the study doctor makes a change. If you leave the study early, you will have a final study visit which may take up to 3 hours.

At most visits, some blood **(about 2 to 6 tablespoons)** will be collected from a vein in your arm, you will have a brief physical exam including measurement of weight and waist circumference, and you will be asked a series of questions about your health, how you are taking your study treatment, what you have been eating and drinking while in the study, and your recent physical activity. At a few visits, you will be asked to provide a urine sample. At the Entry Visit you will also have a complete physical exam, medication and medical histories, and exercise and diet education. At the Entry Visit and then again after 48 weeks, you will have a dual-energy X-ray absorptiometry (DEXA) scan to measure your lean muscle and body fat, and your bone density. This will take approximately 30 minutes.

Persons capable of becoming pregnant will have serum or urine pregnancy testing at the Screening, Entry, and Study Completion Visits, and if there is a concern for pregnancy after study entry.

The level of HIV virus in your blood will be measured at Study Entry and at 4, 12, 24 and 48 weeks. Participants found to have **more than** 200 copies of HIV virus per milliliter of blood will have an additional visit **to repeat the test measuring HIV virus** within 2 weeks of the study site receiving the first result.

<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, gender, race), clinical (for example, disease condition, diagnosis, height, and weight), and laboratory (for example, CD4 cell count, viral load) information will be collected from you. We also will collect information on whether you use (or have used) injection drugs.

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

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

Some of your blood will be stored as what we call “samples” and used for study-required metabolic, cardiovascular, immunologic, study drug levels, and virologic testing.
Identifiers (for example, your name and date of birth) 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.

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.

More information about the storage of extra samples and use in other studies are provided in Attachment A.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 222 people will take part in this study (3 treatment groups of 74 people each).

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 48 weeks.

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

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

- Continuing the study treatment may be harmful to you
- You need a drug that you may not take while on the study
- You are not able to take the study treatment as required by the study
- You become pregnant
- Your doctor **(primary care provider)** requests that you come off the study **because they think that the study is no longer in your best interest**

If you must stop taking the study treatment before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

If I have to permanently stop taking study-provided drug, or once I leave the study, how would that drug be provided?

During the study:

If you must permanently stop taking DOR before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you have completed your study participation, the study will not be able to continue to provide you with DOR. If continuing to take this or similar drugs would be of benefit to you, the study staff will discuss how you may be able to obtain them through your usual health care.

WHAT ARE THE RISKS OF THE STUDY?

Risks from participating in this study include risks from the study procedures and risks associated with a switch to different ART.

Study procedures:

- Blood collection: The study staff will use a standard-sized blood-drawing needle, but this may still cause pain, redness, soreness, bruising, or infection at the needle entry point. Rarely, some people faint.
- Whole body DEXA scan: This test requires exposure to x-rays. The amount of exposure is approximately equal to the exposure you would receive over a period of about 9 days from natural background sources.

Study medications:

Participation in this study may include changing one or two of your current anti-HIV medications. All medications used in this study have obtained regulatory approval by the Food and Drug Administration (US sites) or appropriate national regulatory bodies (non-US sites). This means that regulators have reviewed the existing evidence and concluded that the medications' clinical benefits (i.e., how much the medications improve health) for patients outweigh the risks. The drugs in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship to the study drugs. It is very important that you tell your study doctor about any changes in your medical condition while taking part in the study. At any time during the study, if you believe you are experiencing any of these side effects, you have the right to ask questions about possible and/or known risks.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and you must ask for approval before taking any new medication while you are on the study. If you have questions about additional side effects, please ask the medical staff at your site.

Adverse Reactions Related to All Combination Antiretroviral Drugs

Treatment failure:
When people with viral suppression switch to a different ART regimen, there is a risk that the HIV virus will become detectable again in the blood. This is called “treatment failure,” and it is usually caused by the virus’ resistance to the new drug. This type of resistance is usually caused by mutations (or changes) in the virus that can be found by analyzing the genetic information of the virus (i.e., the molecular ‘code' which is copied each time the virus replicates, and determines how a virus affects the body and responses to treatment). This is known as performing an HIV genotype (i.e., a test that determines the molecular code of the HIV virus to predict which medications will be effective against it). HIV genotypes are often performed when someone’s ART regimen appears to fail. Sometimes, the genotype does not find a resistance mutation, but this is rare. Before enrollment, the study staff will review any prior genotypes in your record to check for mutations that are known to affect how well DOR or TDF might work for you. If any are found, you will be told about them. You will not be eligible for the study if you have any of these mutations. If you are at a site that does not perform routine HIV genotypes, the study staff will review your record for any suspected instances of treatment failure; if these are present, you will be informed that you do not qualify to participate in the study.

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning additional study drug side effects please ask the medical staff at your site.

Use of Combination Antiretroviral Drugs:
In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

Adverse Reactions Related to all Nucleoside Analogues
Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, and other complications and death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include:

- Unexplained weight loss
- Stomach discomfort
- Nausea
- Vomiting
- Fatigue
- Cramps
- Muscle pain
- Cold or blue hands and feet
- Weakness

- Dizziness
- Shortness of breath

Please contact your provider if any of these symptoms occur.

Rarely, TDF, TAF, 3TC and FTC are associated with severe liver problems that can cause death. Some symptoms associated with this include:
- Skin or the white part of your eyes turns yellow
- Dark “tea-colored” urine
- Light-colored stools
- Loss of appetite for several days or longer
- Nausea, or stomach-area pain

If you are infected with both hepatitis B and HIV, the use of 3TC, FTC, TDF, and TAF have an additional risk related to liver problems. Your liver function tests may increase, and symptoms (listed above) associated with hepatitis (an acute inflammation of the liver) may worsen if these drugs are stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

Risks of doravirine (DOR), tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and Lamivudine (3TC)
The most common adverse reactions reported with use of any of these drugs are:
- Nausea
- Upset stomach
- Headache
- Fatigue or feeling tired
- Diarrhea
- Abdominal pain
- Dizziness

Less common adverse reactions reported with use of DOR, FTC, and 3TC are:
- Sleeping problems such as insomnia or sleepiness during the day
- Elevation of liver function tests, which indicates some degree of liver inflammation

Other Adverse Reactions Associated with DOR
- Abnormal dreams or nightmares
- Distraction
- Rash

Other Adverse Reactions associated with TDF
- Worsening or new kidney damage or failure
- Bone pain
- Bone changes such as thinning and softening (this may increase the risk of breakage)
- Muscle pain and muscle weakness

Less common adverse reactions to TDF include:
- Shortness of breath
- Rash
- Allergic reaction. Symptoms may include:
  - Fever
  - Rash
  - Upset stomach
  - Vomiting
  - Loose or watery stools
  - Abdominal pain
  - Body achiness
  - Shortness of breath
  - A general feeling of illness
  - Swelling of the face, lips, and/or tongue.

Other side effects associated with Lamivudine (3TC) or Emtricitabine (FTC):
- Numbness, tingling, and pain in the hands or feet
- Depression
- Rash
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal pancreatic and liver function blood tests

ARE THERE RISKS RELATED TO PREGNANCY?

Persons who are pregnant, intend to become pregnant during the duration of the study, or are currently breast-feeding are not eligible to enroll. Anyone who is participating in sexual activity that could lead to the participant becoming pregnant must agree to use contraception while on DOR (approximately 48 weeks) and for 8 weeks after the end of the study.

Acceptable forms of contraception are:
- Intrauterine device (IUD)
- Hormone-based contraceptive
- Partner/s's sterilization (in other words, vasectomy, and sterilized partner must be the sole partner of the participant)

If you become pregnant while on study, the study staff would like 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 ART when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in persons taking ART. 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, you may have weight loss, but no guarantee can be made. It is likely that you will not receive any benefit from being in this study. Information learned from this study may help others who have HIV and have experienced unintentional weight gain on ART.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- Treatment with prescription drugs available to you
- Treatment with experimental drugs, if you qualify

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

WHAT ABOUT CONFIDENTIALITY?

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

Your records may be reviewed by the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and non-US regulatory entities as part of their duties, institutional review boards (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a 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 **http://www.ClinicalTrials.gov**, as required by US law. This **Web site** will not include information that can identify you. At most, the **Web site** will include a summary of the results. You can search this **Web site** 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. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and non-US 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, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

A description of this clinical trial will be available on **http://www.ClinicalTrials.gov**, as required by US law. This **Web site** will not include information that can identify you. At most, the **Web site** will include a summary of the results. You can search this **Web site** at any time.

WHAT ARE THE COSTS TO ME?

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

Only DOR will be provided by the study. If you are randomized to one of the two treatment arms receiving DOR you will have that medication provided without charge.

You must obtain TAF/FTC (or TAF/3TC) or TDF/FTC (or TDF/3TC) through your regular source of medications. If you are randomized to remain on your current ART, you should continue to get it through your regular source.

WILL I RECEIVE ANY PAYMENT?

You will receive monetary compensation for your time as a participant in this study *(sites to insert amount here*). **This money can be used for transportation to study visits, meals, childcare, medication co-pays, or other expenses.**

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the results of routine lab tests (for example, blood glucose, liver and kidney tests, hemoglobin A1c test, pregnancy test, viral load, and CD4 count) that are performed at the study visits. You have the option to receive the results of your DEXA scans, either at the time of the procedure or at a later date.

You will not receive results from some of the testing that your blood is used for. This testing includes:

- The levels of proteins and other compounds related to the risk of diabetes and heart disease
- The levels of immune system proteins and immune cells in the blood
- The levels of ART medications
- Other research tests that will be done in the future on stored blood samples

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of your time in the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

WHAT HAPPENS IF I AM INJURED?

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

[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.

- ***There is no program for compensation through the NIH. 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. OR***
- *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. 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:

- *[**N**ame of the investigator or other study staff]*
- *[**T**elephone number of above]*

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

- *[**N**ame or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[**T**elephone 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
Participant's Legally Authorized Representative (print) (As appropriate)	Legally Authorized Representative 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

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 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 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, his or her research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review his or her 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>
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.

Your extra samples will not be used for human genetic testing unless you sign and date a consent form for A5128 or A5243.