



A5353

A Study to Evaluate Dolutegravir plus Lamivudine Dual Therapy for the Treatment of Naïve HIV-1-infected Participants

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

DAIDS ES # 12057

This file contains the current ACTG A5353 protocol, which includes the following documents, presented in reverse chronological order:

- Clarification Memorandum #2, dated 28 January 2016
- Clarification Memorandum #1, dated 12 January 2016
- Protocol Version 1.0, dated 14 August 2015

Clarification Memorandum #2 for:

ACTG A5353

A Study to Evaluate Dolutegravir plus Lamivudine Dual Therapy for the Treatment of Naïve HIV-1-infected Participants

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

DAIDS ES # 12057

Clarification Memo Date: 28 January 2016

This clarification memo 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 IRB/EC; however, as always, you must follow your IRB's/EC's policies and procedures. If IRB/EC review of clarification memos is required at your site, please submit this document for review.

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

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5353 protocol if it is amended at a future date.

The purpose of this memo is to clarify that integrase genotyping at screening does not have to be repeated if previously performed as part of clinical care.

The following are clarifications to protocol A5353, Version 1.0, dated 08/14/16:

4.1.4 No evidence of any RT, any integrase, or major protease resistance mutation (according to the 2014 IAS-USA drug resistance mutations list, available at <https://www.iasusa.org/sites/default/files/tam/22-3-642.pdf>) based on pre-ARV treatment genotype performed any time prior to study entry.

NOTE: Integrase genotyping must be performed at screening and will be provided by the study, **if not previously performed as part of clinical care.** RT and PR genotyping **must** be performed at screening as part of routine clinical care if not previously performed.

6.3.7 Virologic Studies

HIV Genotype

Genotypic resistance testing may be performed any time prior to study entry and results must be available prior to study entry. For the screening genotype, previous results verifiable by reports from a local CLIA-certified laboratory are acceptable as long as the results are available at entry. In the unlikely event that

the candidate has more than one prior genotype, consult with the protocol team before screening.

Integrase genotyping must be performed at screening and will be provided by the study through Quest Diagnostics-Baltimore, **if not previously performed as part of clinical care**. ~~since screening for integrase resistance before ART initiation is not standard of care.~~

NOTE: Plasma samples should be stored at screening per instructions in the Laboratory Processing Chart, regardless if integrase genotyping is performed.

RT and PR genotyping should be performed at screening as part of routine clinical care if not previously performed.

When a participant is suspected to have virologic failure or has HIV-1 RNA of 50-200 copies/mL at weeks 24 or 48, a plasma sample for real-time genotyping will be collected 7 to 28 days from the initial sample. The specimen collected for genotyping at this visit will be sent as per the instructions in the LPC for resistance testing if virologic failure is confirmed. Real-time results will be shared with sites.

Clarification Memorandum #1 for:

ACTG A5353

A Study to Evaluate Dolutegravir plus Lamivudine Dual Therapy for the Treatment of Naïve HIV-1-infected Participants

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

DAIDS ES # 12057

Clarification Memo Date: 12 January 2016

This clarification memo 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 IRB/EC; however, as always, you must follow your IRB's/EC's policies and procedures. If IRB/EC review of clarification memos is required at your site, please submit this document for review.

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

The protocol clarification contained in this memo should be implemented immediately. This update will be included in the next version of the A5353 protocol.

The main purpose of this memo is to clarify that in section 6.1, Schedule of Events, footnote #3, plasma HIV RNA, HIV genotype, stored plasma for minority viral variants, and stored plasma for random DTG levels, are required only if virologic failure is suspected or HIV RNA is \geq (greater than or equal to) 50 copies/mL at week 48 visit.

6.1 Schedule of Events

Evaluation	Pre-Treatment	Entry (Day 0)	On-Treatment Evaluations										Visit To Confirm HIV-1 RNA	Premature Treatment Discontinuation and Premature Study Discontinuation Evaluations
			Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48		
Day/Week	Screening (-45 Days)	Visit Window	± 3 Days	± 7 Days					± 14 Days				7-28 Days After Initial Sample	
Documentation of HIV	X													
Medical/ Medication History	X	X												
Complete Physical Exam		X												
Targeted Physical Exam	X		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X		X	X				X	X	X	X		X
Blood Chemistries	X	X		X	X				X	X	X	X		X
Creatinine Clearance	X	X		X	X				X	X	X	X		X
Liver Function Tests	X	X		X	X				X	X	X	X		X
Fasting Lipids		X									X			
Hepatitis B Surface Antigen	X													
Hepatitis C Antibody ¹		X												
Urinalysis		X									X			X
Pregnancy Test	X	X	Whenever pregnancy suspected											
CD4+ Cell Count		X		X	X	X	X	X	X	X	X	X		X

Evaluation	Pre-Treatment	Entry (Day 0)	On-Treatment Evaluations										Visit To Confirm HIV-1 RNA	Premature Treatment Discontinuation and Premature Study Discontinuation Evaluations	
			Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 52		
Day/Week	Screening (-45 Days)	Visit Window	± 3 Days	± 7 Days						± 14 Days			7-28 Days After Initial Sample		
Plasma HIV-1 RNA				X ²	X	X	X	X	X	X	X	X	X ³	X	X
HIV Genotype	X												X ³	X	
Stored Plasma for Minority Viral Variants		X	X	X	X	X	X	X	X	X	X	X	X ³	X	X
Stored Plasma for Random DTG Levels			X	X	X	X	X	X	X	X	X	X	X ³	X	X
Stored Blood for Pharmacogenomics		X													
Phone Call Reminder			Weeks 1 (± 3 days) , 6 and 10 (±7 days) and whenever non-adherence is suspected												
Adherence Questionnaire			X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		X		X	X	X	X	X	X	X	X	X			

1. Required only in participants with no prior positive hepatitis C antibody.

2. Screening HIV RNA within 90 days of entry.

3. Required only if virologic failure is suspected or HIV RNA is **≥ (greater than or equal to)** 50 copies/mL at week 48 visit. These evaluations are identical to the Visit to Confirm HIV-1 RNA.

A5353

A Study to Evaluate Dolutegravir plus Lamivudine Dual Therapy for the Treatment of Naïve HIV-1-infected Participants

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

**Sponsored by:
The National Institute of Allergy
and Infectious Diseases**

**Industry Support Provided by:
ViiV Healthcare Ltd.**

IND # or non-IND Protocol

The Antiretroviral Therapy Strategies (ARTS)

**Subcommittee of the Inflammation
Transformative Science Group:**

Babafemi Taiwo, MBBS, Chair

Protocol Co-Chairs:

**Roy Gulick, MD, MPH
Babafemi Taiwo, MBBS**

DAIDS Clinical Representative:

Catherine Godfrey, MD

Clinical Trials Specialist:

Elizabeth Hawkins, MA

**FINAL Version 1.0
August 14, 2015**



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APPENDIX I: SAMPLE INFORMED CONSENT

SITES PARTICIPATING IN THE STUDY

A5353 is open to all U.S. AIDS Clinical Trials Group (ACTG) clinical research sites (CRSs).

PROTOCOL TEAM ROSTER

Co-Chairs

Roy Gulick, MD, MPH
Division of Infectious Diseases
Weill Cornell Medical College Box 125
1300 York Avenue
New York, NY 10065
Phone: 212-746-6320
Fax: 212-746-8675
Email: rgulick@med.cornell.edu

Babafemi Taiwo, MBBS
Division of Infectious Diseases
Northwestern University CRS
Feinberg School of Medicine
645 N. Michigan Avenue, Suite 900
Chicago, IL 60611
Phone: 312-695-4994
Fax: 312-695-5088
Email: b-taiwo@northwestern.edu

DAIDS Clinical Representative

Catherine Godfrey, MD
HIV Research Branch
TRP, DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9E49
Rockville, MD 20852
Phone: 240-627-3074
Fax: 301-432-9282
Email: cgodfrey@niaid.nih.gov

Clinical Trials Specialist

Elizabeth Hawkins, MA
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
Phone: 301-628-3335
Fax: 301-628-3309
Email: ehawkins@s-3.com

Statistician

Lu (Summer) Zheng, PhD
Statistical and Data Analysis Center
Harvard School of Public Health
FXB Building, Room 613
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-3021
Fax: 617-432-2843
Email: szheng@sdac.harvard.edu

Data Manager

Melissa Mineo, MLS
Frontier Science and Technology
Research Foundation
4033 Maple Road
Amherst NY 14226
Phone: 716-834-0900 x7294
Fax: 716-834-8432
Email: mineo@fstrf.org

DAIDS Pharmacist

Oladapo Alli, PharmD
Pharmaceutical Affairs Branch
DAIDS/CSO/NIAID/NIH
5601 Fishers Lane
Room 9E16 MSC #9832
Rockville, MD 20892
Phone: 240-627-3593
Fax: 240-627-3112
Email: oladapo.alli@nih.gov

Virologist

Carole Wallis, Msc (MED), PhD
BARC-SA/Lancet Laboratories
11 Napier Road
Richmond
Johannesburg, Gauteng
SOUTH AFRICA
Phone: 27-11-358-0816
Email: carole.wallis@lancet.co.za

PROTOCOL TEAM ROSTER (Cont'd)

Investigators

David Haas, MD
 Vanderbilt Therapeutics CRS
 Vanderbilt Health-One Hundred Oaks
 719 Thompson Lane, Suite 47183
 Nashville, TN 37204
 Phone: 615-936-8594
 Fax: 615-936-2644
 Email: david.haas@vanderbilt.edu

Johnstone Kumwenda, FRCP
 College of Medicine-Johns Hopkins Project
 Chipatala Avenue
 P.O. Box 1131
 Blantyre
 MALAWI
 Phone: 265-1870132, ext 307
 Phone: 264-816454347
 Email: jkumwenda@jhul.medcol.mw

Amesika Nyaku, MD
 Division of Infectious Diseases
 Northwestern University
 Feinberg School of Medicine
 645 N Michigan Ave, Suite 900
 Chicago, IL 60611
 Phone: 312-695-2490
 Fax: 312-695-5088
 Email: a-nyaku@northwestern.edu

Paul Sax, MD
 Brigham and Women's Hospital, PBBA4
 75 Francis Street
 Boston, MA 02115
 Phone: 617-732-8881
 Fax: 617-732-6829
 Email: psax@partners.org

Field Representatives

Baiba Berzins, MPH
 Division of Infectious Diseases
 Northwestern University
 645 North Michigan Avenue, Suite 900
 Chicago, IL 60611
 Phone: 312-695-5012
 Fax: 312-695-5088
 Email: baiba@northwestern.edu

Field Representatives (cont'd)

Tanisha Sullivan, BA
 Infectious Disease/Dept of Medicine
 The Ponce de Leon Center CRS
 341 Ponce de Leon, Suite 331
 Atlanta, GA 30308
 Phone: 404-251-8942
 Email: tjorsli@emory.edu

Laboratory Technologist

Gerald Tegha, BSc, MSc
 Malawi CRS, UNC Project
 P.O. Box A-104
 100 Mzimba Road
 Kamzu Central Hospital
 Lilongwe 00000
 MALAWI
 Phone: 265 1 750 610
 Fax: 265-1755954
 Email: gtegha@unclilongwe.org

Community Scientific Subcommittee (CSS) Representative

Angel L. Hernandez, BA
 Puerto Rico-AIDS CRS
 Barrio Saltos
 Road 566 Int Road 593, KM 0.2
 Orocovis PR 00720
 Puerto Rico
 Phone: 787-919-6145
 Email: angelhdz2863@gmail.com

Industry Representatives

Belinda Ha, PhD
 GlaxoSmithKline
 5 Moore Drive
 Research Triangle Park, NC 27709
 Phone: 919-483-8284
 Fax: 919-483-8999
 Email: belinda.f.ha@gsk.com

Industry Representatives (cont'd)

Kimberly Y. Smith, MD, MPH
ViiV Healthcare Ltd.
Five Moore Drive
P.O. Box 13398
Durham, NC 27709
Phone: 919-491-2167
Email: kimberly.y.smith@viivhealthcare.com

Laboratory Data Manager

Adam Manzella, MA
Frontier Science and Technology
Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7418
Fax: 716-833-0655
Email: manzella@fstrf.org

STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.teama5353@fstrf.org. The appropriate team member will respond with a "cc" to actg.teamA5353@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol Email Group

Sites should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5353 email group. Include the protocol number in the email participant line.

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

Clinical Management

For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol team.

- Send an email message to actg.teama5353@fstrf.org. Include the protocol number, participant identification number (PID), and a brief relevant history.

Laboratory

For questions specifically related to virology laboratory tests, contact the protocol virologist or laboratory technologist.

- Send an email message to actg.teama5353@fstrf.org (ATTN: Carole Wallis).

Data Management

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at www.fstrf.org.

- For transfers, reference the Participant Transfer from Site to Site SOP 119, and contact [Melissa Mineo] directly.
- For other questions, send an email message to actg.teama5353@fstrf.org (ATTN: Melissa Mineo).
- Include the protocol number, PID, and a detailed question.

Participant Registration

For participant registration questions or problems and study identification number SID lists.

- Send an email message to rando.support@fstrf.org or call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at 716-834-0900, extension 7301.

Computer and Screen Problems

Contact the SDAC/DMC programmers.

- Send an email message to actg.support@fstrf.org or call 716-834-0900, extension 7302.

Protocol Document Questions

For questions concerning the protocol document, contact the clinical trials specialist.

- Send an email message to actg.teama5353@fstrf.org (ATTN: Elizabeth Hawkins).

Copies of the Protocol

To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via email. Electronic copies can be downloaded from the ACTG Web site (<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 email message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation

For questions related to protocol activation, contact the clinical trials specialist (Elizabeth Hawkins, ehawkins@s-3.com) or ACTG Site Coordination group at actgsitecoordination@s-3.com.

Study Product

For questions or problems regarding study product, dose, supplies, records, and returns, contact the DAIDS pharmacist (Oladapo Alli at 240-627-3593).

Study Drug Orders

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

IND (Investigational New Drug) Number or Questions

The IND number will be available on the PSWP within 30 days of the submission to the FDA. For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions

Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Phone Calls

Sites are responsible for documenting any phone calls made to A5353 team members. Send an email to actg.teama5353@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, Epivir
ATV	Atazanavir
BID	Twice a day
CrcI	Calculated creatinine clearance
DRV/r	Darunavir/ritonavir
DTG	Dolutegravir, Tivicay
E/CIA	Chemiluminescence immunoassay
EFV	Efavirenz
FTC	Emtricitabine
G-CSF	Granulocyte colony-stimulating factor
IAS	International Antiviral Society
INSTI	Integrase strand transfer inhibitor
LPV/r	Lopinavir/ritonavir
MVC	Maraviroc
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
PR	Protease
PrEP	Pre-exposure prophylaxis
PEP	Post-exposure prophylaxis
QD	Once a day
RAL	Raltegravir
RT	Reverse transcriptase
TAF	Tenofovir alafenamide
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir/emtricitabine
UDP	Uridine diphosphate
UGT	Uridine glucuronosyltransferases
VF	Virologic failure
ZDV	Zidovudine

SCHEMA

A5353

A Study to Evaluate Dolutegravir plus Lamivudine Dual Therapy for the Treatment of Naïve HIV-1-infected Participants

DESIGN	<p>This is a phase II, single-arm, open-label, pilot study of dolutegravir (DTG) plus lamivudine (3TC).</p> <p>All participants will undergo routine monitoring including plasma HIV-1 RNA levels, CD4+ cell count, hematology, chemistry, and urinalysis.</p> <p>Population-based protease (PR), reverse transcriptase (RT) and integrase genotyping will be done at the time of confirmed virologic failure. Plasma samples will be stored for potential future studies to assess the impact of adherence, drug-resistant minority viral variants, and DTG exposure on virologic and CD4+ cell count responses to DTG plus 3TC. All participants will also undergo UGT1A1 genotyping.</p>
DURATION	52 weeks
SAMPLE SIZE	120 participants
POPULATION	HIV-1 infected, antiretroviral (ARV) naïve men and women, 18 years and older, with plasma HIV-1 RNA \geq 1,000 copies/mL and $<$ 500,000 copies/mL, and with no evidence of a major PR mutation, any RT or any integrase mutations as defined by the 2014 International Antiviral Society (IAS)-USA drug resistance mutations list. At least 25% (N=30) of the participants will have screening HIV-1 RNA $>$ 100,000 copies/mL. The study will aim to enroll \geq 20% women.
REGIMEN	DTG 50 mg once a day (QD) plus 3TC 300 mg QD for 52 weeks

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

In treatment-naive participants, dual therapy with DTG plus 3TC is efficacious and well tolerated.

1.2 Primary Objective

To estimate the virologic success rate at week 24 after initiating DTG plus 3TC.

1.3 Secondary Objectives

- 1.3.1 To compare the efficacy of DTG plus 3TC in participants with baseline HIV-1 RNA \leq 100,000 versus $>$ 100,000 copies/mL
- 1.3.2 To estimate the virologic success rate of DTG plus 3TC therapy at weeks 12 and 48.
- 1.3.3 To describe emergent integrase and RT resistance in participants with virologic failure.
- 1.3.4 To evaluate the safety and tolerability of DTG plus 3TC.
- 1.3.5 To evaluate changes in CD4+ cell counts and serum lipids.
- 1.3.6 To store plasma samples for future studies of the impact of drug-resistant minority viral variants on response to DTG plus 3TC.
- 1.3.7 To describe the relationships between functional genetic variants in selected *UGT1A1* and other human genes relevant to the study drugs and responses (virologic and immunologic) as well as adverse events observed with DTG plus 3TC.
- 1.3.8 To store random-timed plasma samples that may be used to characterize associations between plasma DTG exposure, adherence, responses (virologic and immunologic) as well as adverse events observed with DTG plus 3TC.

2.0 INTRODUCTION

2.1 Background

All recommended first-line antiretroviral therapy (ART) regimens consist of three active antiretroviral (ARV) drugs, and some include a pharmacologic booster. While this strategy has saved millions of lives and slowed the spread of HIV, results of the recent GARDEL study [1] and advances in the potency, resistance profile and tolerability of ARV drugs provide new rationale for a reappraisal of the current paradigm for first-line

ART. In the GARDEL study of 217 treatment-naïve participants, 88% of those treated with lopinavir/ritonavir (LPV/r) plus lamivudine (3TC) and 84% of the LPV/r plus two-NRTI arm had HIV-1 RNA <50 copies/mL at week 48; the two-drug strategy was non-inferior to the three-drug comparator, regardless of baseline HIV-1 RNA. The efficacy of LPV/r plus 3TC in GARDEL surpassed the results from other experimental dual ART regimens.

Viral resistance during two-drug ART failure is linked to mutations associated with the ARVs that are being used. The main mutation associated with 3TC failure is M184V/I. The mutations linked to DTG are less well defined as a result of the low viral failures.

Table 2.1 Studies of two-drug ART

Trial	Sample Size	Design	Outcome
ACTG 5142 [2]	(N=757)	LPV/r + 2NRTIs vs EFV + 2NRTs vs LPV/r + EFV	LPV/r + EFV associated with NNRTI resistance and lipid abnormalities
PROGRESS [3]	(N=206)	LPV/r + RAL vs LPV/r + TDF/FTC	LPV/r + RAL was non-inferior but mean baseline HIV-1 RNA was low (~18,000 copies/mL)
ACTG 5262 [4]	(N=112)	DRV/r + RAL single arm	Increased virologic failure if baseline HIV-1 RNA > 100,000 copies/mL
SPARTAN[5]	(N=94)	ATV + RAL BID vs ATV/r +TDF/FTC	ATV + RAL was associated with increased virologic failure and jaundice
RADAR [6]	(N=85)	DRV/r + RAL vs DRV/r + TDF/FTC	More failure with DRV/r + RAL
NEAT [7]	(N=805)	DRV/r + RAL vs DRV/r + TDF/FTC	Non-inferior overall; Higher virologic failure when baseline HIV-1 RNA was >100,000 copies/mL or CD4+ < 200 cells/mm ³
GARDEL [1] (N=217)	(N=217)	LPV/r + 3TC vs LPV/r + 2NRTIs	LPV/r + 3TC non-inferior regardless of baseline HIV-1 RNA
MODERN [8]	(N=797)	MVC + TDF/FTC vs MVC + DRV/r	MVC + DRV/r inferior

2.2 Rationale

Dolutegravir (DTG) plus lamivudine (3TC) is a potential two-drug regimen. Desired attributes of a two-drug regimen include excellent efficacy regardless of baseline HIV-1 RNA, reliable long-term safety and tolerability, a resistance profile that preserves options for second-line therapy, potential for co-formulation into a single tablet, and relatively low cost. To realize the potentially dramatic impact of two-drug ART in resource-limited settings, the ideal two-drug regimen will need to be compatible with tuberculosis (TB) therapy, and safe in populations with high rates of opportunistic infections and immune reconstitution inflammatory syndrome. Such a regimen will also need to recapitulate other benefits of triple ART including efficacy in different anatomic compartments and control of systemic immune activation and inflammation.

Despite its virologic efficacy in GARDEL, LPV/r plus 3TC is not an acceptable two-drug regimen since LPV/r is associated with dyslipidemia, lipodystrophy, insulin resistance, and treatment-limiting drug interactions including with rifampin, a key drug for TB treatment. Additional trials are studying darunavir/ritonavir plus 3TC (or emtricitabine [FTC]), but this regimen also has the drawbacks of gastrointestinal side effects, elevated lipids, and drug-drug interactions with ritonavir. In contrast, DTG plus 3TC has the potential to be an acceptable two-drug ART regimen.

Dolutegravir (DTG)

DTG is a highly potent integrase strand transfer inhibitor (INSTI). In a phase I study, monotherapy with DTG 50mg once-daily for 10 days resulted in a mean plasma HIV-1 RNA decline of $2.46 \log_{10}$ copies/mL and 7/10 (70%) of the participants achieved HIV-1 RNA <50 copies/mL [9]. DTG is now approved for both treatment-naïve and treatment-experienced HIV-1-infected individuals. DTG has a high barrier against resistance with no mutations emerging in large clinical trials of treatment-naïve individuals [10-12]. Multiple mutations in the major INSTI resistance pathways (positions 143, 148 and 155), or in the 148 pathway plus other INSTI mutations, are needed for significant loss of activity to occur [13, 14]. This is a higher resistance barrier than raltegravir and elvitegravir [15]. DTG selects the R263K mutation, which confers low-level resistance while simultaneously compromising viral fitness [16, 17]. However, in a study of ART-experienced integrase-naïve HIV-infected adults, minority codon changes in a subject suggested evolving resistance in the presence of R263K during continued DTG exposure [18]. Other mutations described in association with DTG (e.g., G118R and H51Y) also decrease viral replicative fitness [19], which may explain the relative rarity of DTG-related mutations in clinical trials. The reduced replicative fitness of viruses selected by DTG is consistent with findings suggesting that integrase mutations selected by DTG may attenuate the emergence of resistance to some reverse transcriptase inhibitors including lamivudine [16]. Transmitted resistance to DTG has not been reported to date.

Virologic failure and emergence of INSTI resistance during DTG exposure has been associated with non-adherence [18]. The metabolic, renal, bone, and drug interaction profiles of DTG are favorable. The cerebrospinal fluid (CSF) concentrations of DTG achieved with 50 mg daily dose exceed the in vitro IC_{50} against wild-type viruses (0.2

ng/mL) and are similar to unbound DTG concentrations in plasma [20]. Consistent with this, DTG-containing three-drug ART effectively suppresses CSF HIV-1 RNA.

Pharmacogenetics of DTG

Dolutegravir undergoes hepatic metabolism by uridine diphosphate (UDP) glucuronosyltransferases (UGT) 1A1. Frequent polymorphisms in UGT1A1 affect hepatic expression of UGT1A1. The most frequent genetic variant that affects *UGT1A1* function is a dinucleotide TA_n repeat polymorphism (rs8175347) in a TATAA element in the UGT1A1 promoter. This varies from 5 to 8 TA repeats. In all populations, TA₆ (UGT1A1 *1) and TA₇ (UGT1A1 *28) are most frequent, while TA₅ (UGT1A1 *36) and TA₈ (UGT1A1 *37) are infrequent or absent [21-23]. The UGT1A1 *28 allele is a causative genetic variant of Gilbert syndrome, a form of mild unconjugated hyperbilirubinemia that affects ~5% of individuals of European ancestry [24]). The TA₈ repeat (UGT1A1 *37) appears to cause even slower transcription than TA₇, while TA₅ (UGT1A1 *36) appears to cause even faster transcription than TA₆. Genome-wide association studies [25-27] have consistently associated a nearby single nucleotide polymorphism, rs887829 (UGT1A1 *80), with indirect hyperbilirubinemia in the general population. The rs887829 T allele is in almost complete linkage disequilibrium with TA₇ and TA₈, while rs887829 C is in almost complete linkage disequilibrium with TA₅ and TA₆ ($r^2 \sim 0.99$) [22]. Thus, either rs887829 or rs8175347 may be used to interrogate UGT1A1 expression. In a study of 88 volunteers, UGT1A1 loss-of-function genotypes were associated with significantly increased plasma dolutegravir clearance, plasma area-under-the-concentration-time-curve (AUC) values, and maximal plasma concentrations [28]. Homozygosity for the rs887829 T loss-of-function allele varies in frequency by race/ethnicity, and is present in ~19% of African Americans, ~8% of European Americans, and ~16% of Hispanic Americans. UGT1A1 polymorphisms are not known to exert significant impact on response to DTG hence pre-screening is not needed.

Lamivudine (3TC)

3TC is a potent ARV drug with an outstanding safety and tolerability record and low in vitro and in vivo mitochondrial toxicity. The M184V/I mutation confers resistance to 3TC and FTC; while also reducing the viral replicative capacity. Transmitted resistance to 3TC is well described, although rarely observed at a population genotyping level as a result of the poor viral fitness of M184V/I viruses, and the clinical impact is variable.

DTG plus 3TC

A small pilot study of DTG plus 3TC in treatment-naïve individuals (PADDLE) is ongoing in Argentina [29] and demonstrates preliminary virologic activity [Pedro Cahn, personal communication], but the study is inadequate to estimate the virologic efficacy of DTG plus 3TC and determine whether a phase III study of this combination is warranted. PADDLE was designed to include only 20 participants with baseline HIV-1 RNA $\leq 100,000$ copies/mL and CD4+ count ≥ 200 cells/mm³. As such, there is an urgent need to evaluate DTG plus 3TC in a larger, more representative population of treatment-naïve HIV-1-infected individuals.

To better understand the ideal population and consequences of DTG plus 3TC dual therapy, it will be important to evaluate whether variables such as UGT1A1 polymorphisms and minority drug resistant variants may affect responses to DTG plus

3TC, particularly in individuals with high pre-treatment viremia. Minority variants have been associated with reduced response to NNRTI and CCR5 antagonists [30-35] while studies of the effects of INSTI [36-38] and NRTI [39-42] resistant minority variants have produced mixed results. In the ACTG A5262 study, only one of the five participants with raltegravir resistance during darunavir/ritonavir plus raltegravir failure had evidence of baseline minority variants bearing a raltegravir resistance mutation [38]. There is no evidence that PI resistant minority variants have any clinical consequence [39, 43].

An important consideration in the use of a DTG plus 3TC regimen is the development of resistance mutations (i.e., M184V/I) that confer resistance to 3TC as these may be more clinically significant than in a triple-therapy regimen where the presence of a M184V/I mutation can increase susceptibility to zidovudine (ZDV) and TDF [44]. Current guidelines and a recent meta-analysis [45, 46] support the clinical equivalence of 3TC and FTC in terms of efficacy and safety. Some data however suggest a lower rate of M184V/I resistance mutations when FTC is used [47-49] potentially related to the greater potency or longer half-life of FTC compared to 3TC [50-52]. Importantly, the use of 3TC is supported by World Health Organization (WHO) guidelines and many countries have turned to its use because of significant cost savings. Identifying emergence of M184V/I in the setting of this clinical trial could have significant policy implications internationally.

Potential impact of DTG plus 3TC

The two main potential benefits of DTG plus 3TC are reduced adverse effects and lower cost. Despite the established efficacy of triple ART, cumulative exposure to some of the constituent NRTIs have been associated with adverse effects that may be avoided with dual therapy. Tenofovir disoproxil fumarate (TDF) has well-established deleterious bone and renal effects [53-56], and there are continued concerns about possible cardiovascular adverse effects of abacavir [57]. Tenofovir alafenamide (TAF) is a potent tenofovir prodrug that achieves approximately 90% lower plasma levels of tenofovir than TDF, hence improved renal and bone profiles. TAF also achieves 5 fold higher cellular levels of tenofovir diphosphate compared to TDF [58, 59]. It is unknown whether concentrating tenofovir diphosphate in cells will predispose to untoward effects such as reduced telomerase activity [60, 61]. The combination of DTG and 3TC is expected to have a favorable safety and metabolic profile [10-12]. Given the large number of individuals on life-long ART, even small reductions in side effects could have a tremendous impact globally.

Another potential benefit of two-drug ART is lower cost of therapy, which may improve access to ART, particularly in resource-limited settings. A major driver of the reduced cost of DTG plus 3TC is availability of generic 3TC. ViiV Healthcare has submitted an abbreviated New Drug Application (NDA) to the Food and Drug Administration (FDA) for the generic version of DTG. If approved, this would allow provision of DTG to PEPFAR-supported countries and dramatically enhance availability of a DTG plus 3TC regimen globally. Based on pricing listed in the RED BOOK and applicable MEDICAID discounts, the cost of DTG plus generic 3TC is approximately 60% of the cost of branded DTG/3TC/abacavir (Triumeq, ViiV Healthcare, Research Triangle Park, NC). This potential cost saving from DTG plus 3TC is much greater than what is expected from another DTG-based two-drug combination (DTG plus rilpivirine) since rilpivirine is not available in generic formulation. The need for effective, scalable ART will inevitably

increase as the 19 million people who are currently unaware of their HIV infection globally get diagnosed and seek care [62].

3.0 STUDY DESIGN

A5353 is a phase II, single-arm, open-label, pilot study designed to estimate the efficacy of DTG plus 3TC as initial combination ART in HIV-1-infected treatment-naïve participants. Participants with plasma HIV-1 RNA \geq 1000 copies/mL and $<$ 500,000 copies/mL obtained within 90 days prior to study entry are eligible. Participants are ineligible if the screening HIV PR/RT and integrase genotype or any previous genotype shows any RT, any integrase, or major protease resistance mutation according to the 2014 International Antiviral Society (IAS)-USA drug resistance mutations list. There is no CD4+ cell count restriction.

A total of 120 participants will be enrolled and followed for 52 weeks. The study will enroll \geq 25% (i.e., at least 30 participants) with screening HIV-1 RNA $>$ 100,000 to $<$ 500,000 copies/mL and will aim to enroll \geq 20% women.

All participants will undergo routine monitoring including plasma HIV-1 RNA, CD4+ cell counts, hematology, chemistry, and urinalysis. All participants will also undergo *UGT1A1* genotyping. Adherence to all study drugs will be monitored by self-report and phone call reminders.

Integrase genotyping will be performed in all participants at screening to assess drug resistance. Since integrase genotyping is not standard of care, it will be provided by the study. Population-based sequencing of entire protease (PR) and partial reverse transcriptase (RT) will be performed at screening through standard of care if results are not available through pre-treatment resistance testing. Population-based sequencing of entire protease, partial RT, and integrase will be performed in participants with confirmed virologic failure.

Plasma samples will be stored for future studies to determine the impact of adherence, drug-resistant minority variants and DTG exposure on responses to DTG plus 3TC.

Participants with suspected virologic failure (defined in section 6.2.3) or HIV-1 RNA of 50-200 copies/mL at weeks 24 or 48 will have a confirmatory HIV-1 RNA obtained within 7 to 28 days after the initial sample was drawn. A plasma sample will be collected at the confirmation visit and sent for real-time population-based integrase, PR, and RT sequencing if virologic failure is confirmed.

To allow for confirmation if there is a suspected failure at week 48, all participants will receive therapy and be followed until week 52. Only those participants with HIV-1 RNA levels $>$ 50 copies/mL at week 48 will have a plasma HIV-1 RNA measurement (and other laboratory evaluations) at week 52. Participants who experience confirmed virologic failure or treatment-limiting adverse effects may be switched to another ART regimen by their HIV care provider, in consultation with the study team and guided by the results of genotyping.

Participants who modify or permanently discontinue the study regimen or miss doses are expected to stay on study and will be followed to contribute to the intent-to-treat analysis.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Men and women ≥ 18 years of age.

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

NOTE: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies.

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.

4.1.3 Plasma HIV-1 RNA ≥ 1000 copies/mL and $< 500,000$ copies/mL obtained within 90 days prior to study entry using any FDA-approved assay by any US laboratory that has a CLIA certification or its equivalent.

4.1.4 No evidence of any RT, any integrase, or major protease resistance mutation (according to the 2014 IAS-USA drug resistance mutations list, available at <https://www.iasusa.org/sites/default/files/tam/22-3-642.pdf>) based on pre-ARV treatment genotype performed any time prior to study entry.

NOTE: Integrase genotyping must be performed at screening and is provided by the study. RT and PR genotyping should be performed at screening as part of routine clinical care if not previously performed.

4.1.5 ARV treatment drug-naïve (defined as no previous ARV treatment at any time prior to study entry, with the exception of successful post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP)).

NOTE: Participants who were diagnosed with HIV while on PrEP or within a year of PrEP (unless documented seronegative in the interim) are not eligible.

4.1.6 The following laboratory values obtained within 45 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent:

- ANC $\geq 750/\text{mm}^3$
- Hemoglobin $\geq 10.0 \text{ g/dL}$
- Platelets $\geq 50,000/\text{mm}^3$
- Calculated creatinine clearance (CrCl) $\geq 50 \text{ mL/min}$, as estimated by the Cockcroft-Gault equation
- AST $< 5 \times \text{ULN}$ (upper limit of normal)
- ALT $< 5 \times \text{ULN}$
- Total bilirubin $< 1.5 \times \text{ULN}$

4.1.7 Hepatitis B surface antigen negative within 45 days prior to study entry performed by a CLIA-certified laboratory.

4.1.8 For women with reproductive potential, negative serum or urine pregnancy test at screening and within 48 hours 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). Reproductive potential is defined as women who have not been postmenopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, salpingectomy, tubal ligation or tubal micro-inserts). The urine test must have a sensitivity of $\leq 50 \text{ mIU/mL}$.

NOTE: Women who report 12 months of amenorrhea and have a follicle-stimulating hormone (FSH) level in the menopausal range should be considered as NOT having reproductive potential.

4.1.9 If participating in sexual activity that could lead to pregnancy, female participants with reproductive potential must use one form of contraceptive as listed below while receiving protocol-specified medications and for 30 days after stopping the medications. At least one of the following methods must be used appropriately:

- Condoms (male or female) with or without a spermicidal agent. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission.

NOTE: In the setting of condom failure, emergency contraception (plan B) is an appropriate backup method of contraception.

- Diaphragm or cervical cap with spermicide.
- Intrauterine device.
- Hormone-based contraceptive.

4.1.10 Ability and willingness of participant or legal representative to provide informed consent.

4.2 Exclusion Criteria

4.2.1 Serious illness requiring systemic treatment and/or hospitalization

NOTE: Participant is eligible if the participant completes therapy 7 days prior to study entry or is clinically stable on therapy in the opinion of the site investigator for 7 days prior to study entry.

NOTE: Participants with oral candidiasis, vaginal candidiasis, mucocutaneous herpes simplex, and other minor illnesses (as judged by the site investigator) are eligible.

4.2.2 Treatment within 30 days prior to study entry with immune modulators such as systemic steroids, interleukins, interferons, granulocyte colony-stimulating factor (G-CSF), erythropoietin, or any investigational therapy.

NOTE: Participants receiving stable physiologic glucocorticoid doses (defined as prednisone \leq 15 mg/day or equivalent as a stable or tapering dose) are eligible. Participants receiving corticosteroids for acute therapy for PCP or asthma exacerbation, or receiving a short course (defined as \leq 2 weeks of pharmacologic glucocorticoid therapy) are eligible.

4.2.3 Pregnancy or breastfeeding.

4.2.4 Requirement for any medication that is prohibited with a study medication (see Section 5.4).

4.2.5 Known allergy/sensitivity to any of the study drugs or their formulations.

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

4.2.7 Active hepatitis C virus (HCV) treatment or anticipated need for treatment within study period.

NOTE: HCV infection alone is not exclusionary.

4.2.8 Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

4.2.9 Severe hepatic impairment (Class C) as determined by Child-Pugh classification.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s)

approved, as appropriate, by 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 of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all 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 should be retained in the site's regulatory files.

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

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the legal representative if the participant is under guardianship) will be asked to read and sign the approved protocol consent form.

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

4.3.2 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 Coenrollment 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."
- Coenrollment in A5128 does not require permission from the A5353 protocol chairs.
- For specific questions and approval for coenrollment in other studies, sites should first check the PSWP or contact the protocol team via email as described in the Study Management section.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

Study treatment is defined as dolutegravir (DTG) and lamivudine (3TC), both of which will be provided through the study.

5.1.1 Regimen

Participants will receive:

Dolutegravir (DTG) 50mg PO daily plus

Lamivudine (3TC) 300mg PO daily.

Participants should begin study treatment within 72 hours after entry and continue on study treatment for a maximum of 52 weeks.

Participants should return remaining medication at each study visit.

5.1.2 Administration

Dolutegravir will be administered orally as one 50 mg tablet daily, with or without food.

Dolutegravir should be taken at least 2 hours before or 6 hours after taking calcium, iron, or magnesium containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.

Lamivudine will be administered orally as one 300 mg tablet daily, with or without food.

5.1.3 Duration

Participants will take study medications for 52 weeks.

5.2 Study Product Formulation and Preparation

- 5.2.1 Dolutegravir (DTG, Tivicay ®) 50 mg tablets. Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°-86°F) [See USP Controlled Room Temperature].
- 5.2.2 Lamivudine (3TC, Epivir ®) 300 mg tablets. Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°-86°F) [See USP Controlled Room Temperature].

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply/Distribution

Dolutegravir will be supplied by ViiV Healthcare Ltd.

Lamivudine will be supplied by ViiV Healthcare Ltd.

Study products will be available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, in the section Study Product Management Responsibilities.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

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 updated ACTG Precautionary and Prohibited Medications Database located at:
http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

Prophylaxis for those who are at risk of opportunistic infections is strongly recommended. Investigators should refer to the current version of the U.S. Public

Health Service/Infectious Diseases Society of America “Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons.”

5.4.2 Prohibited Medications

The following are prohibited while the participant is on study drugs:

- Systemic cytotoxic chemotherapy
NOTE: Topical 5FU and treatments for human papilloma virus disease are allowed.
- Dofetilide is prohibited with DTG as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity.
- There are no prohibited medications with 3TC.

5.5 Adherence Assessment

Adherence to the study drugs DTG and 3TC will be monitored by self-report. Sites will provide adherence reinforcement according to local standard practice and phone call reminders between visits and whenever poor adherence is suspected. Participants with poor adherence will be provided counseling by the site.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

Evaluation	Pre-Treatment	Entry (Day 0)	On-Treatment Evaluations											Visit To Confirm HIV-1 RNA	Premature Treatment Discontinuation and Premature Study Discontinuation Evaluations
			Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 48	Week 52		
Day/Week	Screening (-45 Days)	Visit Window	± 3 Days	± 7 Days						± 14 Days				7-28 Days After Initial Sample	
Urinalysis		X									X				X
Pregnancy Test	X	X	Whenever pregnancy suspected												
CD4+ Cell Count		X		X		X			X			X			X
Plasma HIV-1 RNA	X ²	X	X	X	X	X	X	X	X	X	X	X	X ³	X	X
HIV Genotype	X												X ³	X	
Stored Plasma for Minority Viral Variants		X	X	X	X	X	X	X	X	X	X	X	X ³	X	X
Stored Plasma for Random DTG Levels			X	X	X	X	X	X	X	X	X	X	X ³	X	X
Stored Blood for Pharmacogenomics		X													
Phone Call Reminder			Weeks 1 (± 3 days) , 6 and 10 (±7 days) and whenever non-adherence is suspected												
Adherence Questionnaire			X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		X		X	X	X	X	X	X	X	X	X			

1. Only required in participants with no prior positive hepatitis C antibody.

2. Screening HIV RNA within 90 days of entry.

3. Only required if virologic failure suspected or HIV RNA >50 copies/mL at week 48 visit. These evaluations are identical to the Visit to Confirm HIV-1 RNA.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening

Screening evaluations to determine eligibility must be completed within 45 days prior to study entry, unless otherwise specified. The site may use documentation of HIV infection and the HIV resistance genotype obtained any time prior to study entry provided test results are available prior to study entry.

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 log and entered into the ACTG database.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluations and be completed prior to the initiation of study medications. Participants should begin study treatment within 72 hours after entry.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations

The visit window for evaluations at week 2 is ± 3 days after treatment initiation. The visit window for evaluations at weeks 4 to 24 is ± 7 days after treatment initiation. The visit window for subsequent study visits is ± 14 days.

Virologic failure is defined as follows:

- Weeks 16 or 20:
 - Confirmed plasma HIV-1 RNA >400 copies/mL,
- Week 24 or later:
 - Confirmed value >200 copies/mL

Visit to Confirm HIV-1 RNA

A confirmatory plasma HIV-1 RNA measurement will be done within 7-28 days of the initial sample when a participant has any of the following:

- Suspected virologic failure, OR
- HIV-1 RNA 50-200 copies/mL at week 24, OR
- HIV-1 RNA 50-200 copies/mL at week 48

If the initial sample was collected during a treatment interruption, sites are encouraged to address toxicity or adherence issues before taking the confirmatory sample, if possible, within the allowed window. If the visit for HIV-1 confirmation coincides with a regularly scheduled visit, the evaluations should be combined.

If virologic failure is confirmed, sites must email the protocol core team at actg.corea5353@fstrf.org. Management of ART will be left to the discretion of the site investigator. If stopping study treatment, the participant will complete the Premature Treatment Discontinuation evaluations and continue to be followed on study/off study treatment per Section 6.2.4.

Study Completion Evaluations

Week 52 evaluations will be completed as the participant's final on-study visit.

6.2.4 Discontinuation Evaluations

Evaluations for Registered Participants Who Do Not Start Study Treatment

Participants who do not begin study treatment within 7 days after study entry will be discontinued from the study, and will be replaced. No evaluations beyond the entry visit are required. All CRFs must be completed and keyed for the period up to and including week 0.

Premature Treatment Discontinuation Evaluations

Participants who discontinue the study treatment prior to the week 52 visit will have the Premature Treatment Discontinuation evaluations done within 14 days after stopping study drugs, or as soon as possible thereafter.

Participants who prematurely discontinue study treatment will be encouraged to continue on study/off study treatment and receive all study evaluations per the schedule of events, with the exception of plasma storage and adherence questionnaires, through completion of the study.

Premature Study Discontinuation Evaluations

Participants who prematurely discontinue from the study prior to the week 52 visit will have the Premature Study Discontinuation evaluations performed within 14 days after discontinuing the study as per Section 6.1.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS Web site for information about what must be included in the source document:

<http://www.niaid.nih.gov/labsandresources/resources/daidsclinsrch/documents/sourcedocappndx.pdf>

All stated evaluations are to be recorded on the case report form (CRF) and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the events listed above).

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, which can be found on the DAIDS RSC Web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.3.1 Documentation of HIV-1

Section 4.1.2 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

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

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis B
- Chronic hepatitis C

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.

Medication Category	Complete History or Timeframe	Record in CRFs
Antiretroviral therapy	Complete history	Yes
Immune-based therapy	Within 30 days prior to entry	Yes
Prescription drugs for treatment of opportunistic infections	Within 30 days prior to entry	Yes

Medication Category	Complete History or Timeframe	Record in CRFs
Other prescription drugs, including hormonal contraceptives	Within 30 days prior to entry	Yes
Non-prescription drugs	Within 30 days prior to entry	No
Complementary and alternative medicines	Within 30 days prior to entry	No

6.3.4 Clinical Assessments

Complete Physical Exam

A complete physical examination performed at study entry is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, height, weight, and vital signs (temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam

A targeted physical examination is to be driven by any previously identified or new signs or symptoms and diagnoses that the participant has experienced since the last visit. This examination includes weight and vital signs (temperature, pulse, respiration rate, and blood pressure).

Signs and Symptoms

At entry, record all signs/symptoms occurring within 30 days prior to entry. After entry, record all Grade ≥ 2 rash and all other Grade ≥ 3 signs and symptoms. Any signs or symptoms that lead to a change in study treatment, regardless of grade, must be recorded.

Diagnoses

Record all diagnoses identified by the ACTG criteria for clinical events and other diseases. Refer to the study CRFs for the appropriate appendix used for current ACTG criteria.

Concomitant Medications

Record any new or discontinued prescription medications including lipid-lowering agents, contraceptives, systemic steroids, other immune modulatory drugs, investigational drugs, and study-prohibited medications taken since the last study visit, including actual or estimated start dates and stop dates.

Study Treatment Modifications

During the study, all study drug modifications (DTG and/or 3TC) including participant-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation of treatment will be recorded on the CRFs at each

visit. Participant-initiated and protocol-mandated interruptions include both inadvertent and deliberate interruptions of study drugs for a period of >3 days. The protocol core team (actg.corea5353@fstrf.org) must be notified of the addition of any ARV drug or permanent discontinuation of any study medication.

6.3.5 Laboratory Evaluations

At screening and entry, record all protocol-required laboratory values, regardless of grade, on the CRFs. For post-entry assessments, record all grades of creatinine and fasting lipid values and all other Grade ≥ 3 laboratory values. All laboratory toxicities that lead to a change in treatment, regardless of grade, must be recorded.

All grade 3 or higher laboratory values, any laboratory value that led to a change in treatment or that met ICH, EAE, or SAE guidelines are defined by the protocol as reportable events that will require more detailed event reporting.

Hematology

Hemoglobin, hematocrit, white blood cell count (WBC), differential WBC, ANC, and platelet count.

Blood Chemistries

Blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, and CO_2 /bicarbonate), and glucose.

Creatinine Clearance (CrCl)

CrCl should be calculated using Cockcroft-Gault method. A program for calculating CrCl is available on the DMC website at: <http://www.fstrf.org/>. All values will be recorded in the CRFs.

Liver Function Tests

Total bilirubin, direct bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase.

Fasting Lipids

Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides

NOTE: Participants must fast for 8 hours prior to this test. Fasting is defined as no food or drink, except for sips of water with medications. If a participant is not fasting at the time of the visit, the sample should be drawn and labeled non-fasting. The date and time of the participant's last food or drink will not be recorded on the CRF.

Hepatitis B Surface Antigen

Documentation of hepatitis B surface antigen negative status within 45 days prior to study entry. This will not be recorded on the CRF.

Hepatitis C Antibody

Only required in participants with no prior positive hepatitis C antibody.

Urinalysis

Dipstick or microscopic exam may be done; if dipstick results are abnormal, microscopic exam is required.

Pregnancy Test

All women of reproductive potential must have a negative serum or urine beta-human chorionic gonadotropin (β -HCG) pregnancy test result at screening and within 48 hours prior to study entry and any time thereafter when pregnancy is suspected. The urine test must have a sensitivity ≤ 50 mIU/mL.

6.3.6 Immunologic Studies

Refer to the A5353 Lab Processing Chart (LPC) for collection, processing and shipping instructions.

CD4+ Cell Count

Evaluations for CD4+ cell counts and percentages should be performed at the same laboratory, if possible, for all on-study evaluations. The laboratory must have CLIA certification, or equivalent, and be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

Because of the diurnal variation in CD4+ cell counts, determinations for individual participants should be obtained consistently in either the morning or the afternoon throughout the study if possible.

6.3.7 Virologic Studies

Refer to the A5353 LPC for collection, processing and shipping instructions.

Plasma HIV-1 RNA

Screening HIV-1 RNA must be performed within 90 days prior to study entry using any FDA-approved assay by a laboratory that possesses a CLIA certification or equivalent. Entry and post-entry plasma HIV-1 RNA quantification will be measured in real time using the Abbott Realtime assay at Quest Diagnostics-Baltimore.

HIV Genotype

Genotypic resistance testing may be performed any time prior to study entry and results must be available prior to study entry. For the screening genotype, previous results verifiable by reports from a local CLIA-certified laboratory are acceptable as long as the results are available at entry. In the unlikely event that the candidate has more than one prior genotype, consult with the protocol team before screening.

Integrase genotyping must be performed at screening and will be provided by the study through Quest Diagnostics-Baltimore since screening for integrase resistance before ART initiation is not standard of care.

RT and PR genotyping should be performed at screening as part of routine clinical care if not previously performed.

When a participant is suspected to have virologic failure or has HIV-1 RNA of 50-200 copies/mL at weeks 24 or 48, a plasma sample for real-time genotyping will be collected 7 to 28 days from the initial sample. The specimen collected for genotyping at this visit will be sent as per the instructions in the LPC for resistance testing if virologic failure is confirmed. Real-time results will be shared with sites.

6.3.8 Stored Plasma for Minority Viral Variants

Plasma samples will be stored for possible evaluation of the impact of minority variants and on responses to DTG plus 3TC. Individual participant results will not be shared with sites.

6.3.9 Stored Plasma for Random DTG Levels

Plasma samples will be stored for evaluation of random-timed DTG levels. Individual participant results will not be shared with sites. The time and date of the last three doses of DTG, and the time and date the plasma samples were obtained will be documented.

6.3.10 Stored Blood for Pharmacogenomics

At entry, a single whole blood sample will be obtained from all participants for human genotyping of UGT1A1 and other selected polymorphisms relevant to the study drugs. If blood for pharmacogenomics is not obtained at entry, it may be obtained at any subsequent study visit.

6.3.11 Phone Call Reminders

Study staff will contact participants by telephone between visits to provide adherence reinforcement. Phone call reminders will not be recorded on the CRF.

6.3.12 Adherence Questionnaire

An adherence questionnaire will be used to document participant adherence to the study medications. Sites will provide adherence reinforcement, according to local standard practice throughout the study. Participants with poor adherence will be provided counseling by the site.

6.3.13 Dispense Study Drug

Study drug will be dispensed as indicated per the Schedule of Events.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity Management

Criteria for participant management, dose interruptions, modifications, and discontinuation of study treatment are delineated only for toxicities attributable to study drugs (i.e., DTG and 3TC). The goal is to maintain participant safety while continuing therapy, if possible. If any individual study drug must be interrupted or discontinued due to toxicity, then the entire regimen must be interrupted or discontinued.

The grading system for drug toxicities is located in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, which can be found on the DAIDS web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>

NOTE: The protocol core team must be notified at actg.corea5353@fstrf.org regarding toxicities that result in regimen interruption or discontinuation. The protocol does not allow drug substitution for toxicity management.

The general guidelines presented in sections 7.1.1 to 7.1.3 apply to toxicities that are not specifically discussed further below.

7.1.1 Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue DTG and 3TC. If the participant chooses to discontinue study treatment, the site should complete the Premature Treatment Discontinuation evaluations, notify the A5353 protocol core team at actg.corea5353@fstrf.org and encourage the participant to attend all remaining study visits.

7.1.2 Grade 3

Grade 3 abnormalities must be evaluated and managed by the site investigator according to the standard of care. It may be necessary to discontinue both study drugs. The A5353 protocol core team must be notified at actg.corea5353@fstrf.org regarding toxicities that result in a change of regimen. If the site investigator has compelling evidence that the AE was NOT caused by a study drug, dosing may continue. If study drugs are temporarily held, the participant should be re-evaluated closely until the AE returns to Grade ≤ 2 , at which time study treatment may be reintroduced at the discretion of the site investigator or according to standard practice.

If the site investigator determines that a Grade 3 AE or toxicity is an isolated event, the site has the option of confirming the toxicity before holding study treatment.

If the same Grade 3 AE recurs within 4 weeks of reintroducing study drugs, the implicated study regimen must be permanently discontinued. However, if the same Grade 3 AE recurs after 4 weeks, but is not thought to be related to DTG or 3TC, the management scheme outlined above may be repeated.

Participants experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed closely until resolution of the AE. The A5353 protocol core team must be notified at actg.corea5353@fstrf.org. The participant should be encouraged to attend all remaining study visits and continue other study evaluations according to the protocol.

7.1.3 Grade 4

Participants who develop a Grade 4 AE or toxicity thought to be related to study treatment must have both DTG and 3TC temporarily held. If the site investigator has compelling evidence that the AE has NOT been caused by DTG or 3TC, dosing may resume when the AE has resolved to Grade ≤ 2 . Notify the A5353 protocol core team at actg.corea5353@fstrf.org.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study treatment should be followed closely until resolution of the AE to Grade ≤ 2 , and the protocol team must be consulted. The participant should be encouraged to attend all remaining study visits and continue other study evaluations according to the protocol.

7.2 Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first 10 weeks of treatment, rarely require interruptions or discontinuations of therapy, and tend to resolve within 2 to 3 weeks. A single case of hypersensitivity with DTG involved a profuse, purpuric, and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme have been reported for DTG in clinical trials.

Participants with an isolated Grade 1 rash (defined as having no systemic symptoms) may continue study medications at the site investigator's discretion. The participant should be advised to contact the site investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Participants may continue study medications for an isolated Grade 2 rash. However,

study medications (and all other concurrent medication(s) suspected in the site investigator's causality assessment) should be permanently discontinued for any \geq Grade 2 rash that is associated with an increase in ALT. The participant should be advised to contact the site investigator immediately if rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Participants should permanently discontinue study medications (and all other concurrent medication(s) suspected in the site investigator's causality assessment) for an isolated Grade 3 or 4 rash, and the participant will be followed on study/off study treatment. Participants should be treated as clinically appropriate and followed until resolution of the AE.

If the etiology of the rash can be definitely diagnosed as being unrelated to study medications and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided. Study treatment should be continued.

7.3 Nausea/Vomiting

Nausea/vomiting of any grade may be treated symptomatically with oral antiemetics or antiemetic suppositories. For Grade \geq 3 nausea or vomiting thought to be secondary to study drugs that fails to improve on antiemetics to Grade \leq 2, all study drugs must be held until Grade \leq 2. If Grade \geq 3 nausea or vomiting recurs with reinstitution of study drugs or persists beyond 14 days despite symptomatic management, then study treatment must be discontinued and the protocol team consulted.

7.4 AST/ALT Elevations

All study medications may be continued for asymptomatic \leq Grade 3 AST/ALT elevations at the discretion of the site investigator.

For symptomatic Grade 3 (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia) or any Grade 4 elevations in AST or ALT, all study medications should be held and the protocol core team should be consulted actg.corea5353@fstrf.org. In addition, for Grade 3 ALT and bilirubin \geq 2 x ULN (attempts should be made to fractionate the bilirubin), the study medications should be held and the core team consulted as this will likely result in permanent study medication discontinuation.

Participants who develop symptomatic Grade 3 or any Grade 4 AST or ALT should be followed weekly until resolution to \leq Grade 2. Participants will be followed on study/off study treatment after study medication discontinuation.

Participants with Grade 3 or 4 AST or ALT with fever, rash, or eosinophilia should stop all study medications and not be re-challenged. Participants should be followed weekly until resolution to \leq Grade 2 and should be followed on study/off study treatment.

Careful assessments should be done to rule out the use of alcohol, non-study medication-related toxicity, or viral hepatitis (including viral hepatitis complicated by immune reconstitution inflammatory syndrome) as the cause of Grade 3 or 4 AST/ ALT elevations. Evaluations to be considered (but are not required) include:

- Viral hepatitis serology including: Hepatitis A IgM antibody, Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (IgM), Hepatitis C RNA, Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test);
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging to evaluate liver disease.

7.5 Calculated Creatinine Clearance (CrCl)

3TC requires dose adjustment for CrCl <50 mL/min per the standard of care.

7.6 Allergic Reaction

Participants may continue study medication for Grade 1 or 2 allergic reactions at the discretion of the site investigator. The participant should be advised to contact the investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed at the discretion of the site investigator.

Participants with \geq Grade 3 allergic reactions that are considered to be possibly or probably related to the study medications should permanently discontinue study medications and continue to be followed on study/off study treatment. Participants should be treated as clinically appropriate and followed until resolution of the AE.

7.7 Suicidal Ideation

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some participants being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation

and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

7.8 Pregnancy

Women who become pregnant while on study treatment must immediately discontinue study treatment and consult with their primary care physicians. Participants should have the Premature Treatment Discontinuation evaluations completed within 2 weeks after stopping study treatment.

Participants will be encouraged to remain in the study to be followed on study/off study treatment until study completion and will be followed by telephone contact thereafter to determine the pregnancy outcome. Pregnancy-related outcomes (health of the infant) and any pregnancy-related complications (e.g., fetal loss/abnormalities) and obstetrical history must be reported on the CRF. Sites are encouraged to prospectively register pregnant women in the Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052.

NOTE: Pregnant participants will be considered on study until the outcome of the pregnancy has been obtained and reported on the CRF.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Study Treatment Discontinuation

- Drug-related toxicity requiring permanent study treatment discontinuation (see section 7.0)
- Requirement for prohibited concomitant medications (see Section 5.4)
- Pregnancy
- Breastfeeding
- Completion of treatment as defined in the protocol
- 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
- Failure by the participant to attend three consecutive clinic visits

8.2 Premature Study Discontinuation

- Request by the participant to withdraw
- Request of the primary care provider or investigator if s/he thinks the study is no longer in the best interest of the participant
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results

- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, or pharmaceutical supporters.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is single arm, open-label study to evaluate the safety and virologic efficacy of DTG plus 3TC in treatment-naïve HIV-1-infected participants. A total of 120 participants will be enrolled and followed for 52 weeks. The study will enroll $\geq 25\%$ (i.e., at least 30 participants) with screening HIV-1 RNA $> 100,000$ copies/mL, and will aim to enroll $\geq 15\%$ women. Efficacy of the study regimen will be assessed using FDA Snapshot definition. Participants who experienced study-defined virologic failure will have real-time population-based sequencing done on plasma sample obtained at confirmation visit.

The primary efficacy outcome measure is at week 24 while the study follow-up is week 52. Final analysis will commence after all participants complete week 52 follow-up. Preliminary analysis will be conducted after all participants complete required follow-up for evaluation of primary efficacy outcome measure at week 24.

9.2 Outcome Measures

9.2.1 Primary Outcome Measure

Virologic success at week 24

NOTE: virologic success is defined as HIV-1 RNA < 50 copies/mL and on study treatment (FDA Snapshot definition). Participants with HIV-1 RNA ≥ 50 copies/mL or who discontinued study treatment or did not have HIV-1 RNA data are counted as non-success.

9.2.2 Secondary Outcome Measures

9.2.2.1 Virologic success at weeks 12 and 48

9.2.2.2 Virologic failure (as defined in Section 6.2.3)

NOTES:

1. Participants are evaluated for virologic failure regardless of whether on study treatment.
2. Confirmation will be determined based on any two consecutive evaluations meeting the virologic failure definition regardless of the time between them.

3. Participants discontinuing the study (for any reason, including death and lost to follow-up) will be considered a virologic failure if their last measurement meets the definition of virologic failure but no confirmatory measurement was obtained. All other participants' follow-up will be censored immediately after the last available plasma HIV-1 RNA measurement.

9.2.2.3 Plasma HIV-1 RNA level

9.2.2.4 CD4+ cell count

9.2.2.5 HIV-1 drug resistance mutations in participants with virologic failure

9.2.2.6 Lipid values

9.2.2.7 Sign/symptoms or laboratory toxicities of Grade 3 or higher, or of any grade which led to a permanent change or discontinuation of study treatment

9.2.3 Exploratory Outcome Measures

HIV-1 minority variants in participants with virologic failure

9.3 Randomization and Stratification

There is no randomization or stratification in this study.

Since a key secondary objective of the study is to determine if the regimen works in participants with high viral loads ($>100,000$ copies/mL) as well as in participants with lower viral loads ($\leq 100,000$ copies/mL). Participants with high viral loads will constitute at least one-fourth (1/4) of the study population. Hence, the enrollment of participants with screening HIV-1 RNA $\leq 100,000$ copies/mL will be capped at $\frac{3}{4}$ of the entire study population (N=90).

9.4 Sample Size and Accrual

Virologic success at week 24 (HIV-1 RNA <50 copies/mL and on study treatment, using FDA Snapshot definition) will be estimated with a two-sided 95% confidence interval (CI) using exact binomial probability. With a sample size of 120 participants, if the observed virologic success rate is between 85% and 90%, the 95% CI will have a width of $\pm 5.75\%$ to $\pm 6.75\%$. The estimated virologic success rate is based on results of dolutegravir arms from SPRING-2 (93% at week 24), SINGLE (92% at week 24) and FLAMINGO (90% at week 24), as well as the raltegravir arm from A5257 (84% at week 24).

For subgroup analysis of participants with higher viral load, assuming N=30 and the observed virologic success rate between 85% and 90%, the 95% CI will have a width of (-12.2%, +10%) to $\pm 14.1\%$. Similarly for subgroup analysis of female participants,

assuming N=20 and the same observed virologic success rates, the 95% CI will have a width of (-15.3%, +10%) to (-17.4%, +15%).

It is anticipated that the study will meet its accrual target in 4 to 6 months after sites are enrolling. While accrual is ongoing, participants who are enrolled but never started treatment will be replaced. Each participant will be followed for 52 weeks. Only participants those with plasma HIV-1 RNA levels >50 copies/mL at week 48 visit will undergo confirmatory plasma HIV-1 RNA quantification at the week 52 visit.

9.5 Monitoring

The team will routinely monitor accrual, baseline characteristics, toxicities and premature treatment and study discontinuation. The study will be reviewed by an independent Study Monitoring Committee (SMC) on study conduct, safety and efficacy annually. The first SMC review will occur 6 months after the enrollment of the 40th participant.

At the interim review, to help assess regimen efficacy, the SMC will be provided with a two-sided 95% CI for the estimated week 24 virologic success (HIV-1 RNA <50 copies/mL and on study treatment, FDA Snapshot definition) rate. Table below shows examples of observed number of success and the corresponding 95% CIs for the initial SMC review.

Number of participants evaluated	Observed number of virologic success	Observed virologic success rate	95% CI
N=40	27	67.5%	[51%, 81%]
	28	70%	[54%, 83%]
	29	72.5%	[56%, 85%]
	30	75%	[59%, 87%]

An upper bound of the 95% CI for the virologic success rate that is smaller than 85% at this interim review would be consistent with a lower success rate than expected. For example, at the SMC review of 40 participants, if 28 participants had virologic success at week 24, the observed success rate is 70% with 95% CI of [54%, 83%], which excludes 85%. In this situation, the SMC may want to consider modifying the study on the basis that the virologic success rate is lower than desirable.

In addition, to ensure participants' safety, virologic success at weeks 12 and 24 (at each increment of 20 participants) will be monitored by the team throughout accrual and follow-up. The team will immediately inform the SMC and may request a formal review at any time when the upper bound of the nominal 95% CI for the virologic success rate at week 12 excludes 80% or at week 24 excludes 85%.

The table below shows the largest number of participants with virologic success where 95% CI excludes the threshold at week 12 and 24, respectively, at various evaluation

times. For example, if 11 participants are observed to have virologic success at week 12 among the first 20 participants who reached week 12, the observed virologic success rate is 55% with 95% CI of [32%, 77%] which excludes 80%, the team will consider requesting a formal SMC review prior to the initial scheduled review.

Number of participants evaluated	Week 12		Week 24	
	Largest number of virologic success where 95% CI exclude 80%	95% CI	Largest number of virologic success where 95% CI exclude 85%	95% CI
20	11	[32%, 77%]	13	[41%, 84.6%]
40	26	[48%, 79%]	28	[54%, 83%]
60	41	[55%, 79.7%]	44	[60%, 84%]
80	56	[59%, 79.7%]	60	[64%, 84%]
100	71	[61%, 79.6%]	76	[66%, 84%]

Since the monitoring procedure will evaluate the interim CI at multiple times, a simulation study (iteration=500) was carried out to assess the properties of the monitoring procedure. Table below presents the probability of at least one interim 95% CI excluding threshold (80% at week 12 and 85% at week 24) and triggering an unscheduled SMC review for various true virologic success rates at weeks 12 and 24. For example, if the true virologic success rate is 70% at week 12 and 82% at week 24 (lower than desirable), the study will have 68% of probability to observe an interim 95% CI excluding the threshold and trigger an unscheduled SMC review. On the contrary, if the true rate is 85% at week 12 and 88% at week 24, the probability of triggering an unscheduled SMC review is only 1%.

True virologic success rate		Probability of at least one interim 95% CI excluding threshold
Week 12	Week 24	
65%	79%	0.93
70%	82%	0.68
75%	84%	0.34
80%	86%	0.08
85%	88%	0.01

9.6 Analyses

9.6.1 Primary Analyses

The proportion of participants with virologic success (plasma HIV-1 RNA <50 copies/mL and while on study treatment, FDA Snapshot definition) at week 24 will be estimated with 95% CI. Participants with last HIV-1 RNA <50 copies/mL while on study treatment in the analysis window (i.e., week 24 ± 6 weeks) are

counted as success. The two-sided 95% CI will be calculated using the exact binomial distribution.

Participants who enrolled but never started study treatment will be excluded from all analyses.

9.6.2 Secondary Analyses

Virologic success at scheduled visit weeks will be analyzed using the same approach for the primary analysis and summaries of plasma HIV-1 RNA results will be provided. The cumulative proportion of participants experiencing virologic failure at or prior to week 48 will be estimated using the method of Kaplan and Meier with 95% CI calculated using the Greenwood variance.

Participant-specific changes in CD4+ count and lipid measures from baseline to scheduled week(s) will be summarized by descriptive statistics and longitudinal plots. Patterns of drug resistance mutations at study entry and failure will be summarized for participants who experienced virologic failure.

Reported signs/symptoms or laboratory toxicities will be tabulated. Premature treatment discontinuation will be summarized with detailed reasons provided.

10.0 PHARMACOLOGY PLAN

See section 6.3.9.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the participant identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 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.

11.3 Clinical Site Monitoring and Record Availability

- 11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.
- 11.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, the FDA, the NIAID, the OHRP, and the industry supporter or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The suspected unexpected serious adverse reactions (SUSAR) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study from the time of enrollment through week 52.
- The study agents for which expedited reporting are required are:
 - Dolutegravir
 - Lamivudine

Liver Events: Any liver toxicity that results in discontinuation of study medications, based on liver stopping criteria in 7.4, will be reported as an EAE regardless of seriousness.

Suicidal Ideation or Behaviors: If the participant expresses suicidal ideation or intent, the data will be captured as an AE on the CRF. Any suicide thought or attempt that qualifies as an SAE will be reported as an EAE.

11.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, must be used and is available on the DAIDS RSC Web site at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

11.4.4 Expedited AE Reporting Period

The EAE reporting period for this study is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

After the protocol-defined AE reporting period, unless otherwise noted, only 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 (e.g., from publicly available information).

12.0 PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant or legal representative. The consent form will describe the purpose of the study, the

procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant or legal representative and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other government agencies as part of their duties, or the industry supporter or designee.

12.3 Study Discontinuation

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

13.0 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.

14.0 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 Centers for Disease Control and Prevention and the National Institutes of Health.

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

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DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol A5353

FINAL Version 1.0: A Study to Evaluate Dolutegravir plus Lamivudine Dual Therapy for the Treatment of Naïve HIV-1-infected Participants

SHORT TITLE FOR THE STUDY: (A5353) Dolutegravir plus Lamivudine in Treatment Naïve HIV-1-infected Participants

INTRODUCTION

You are being asked to take part in this research study because you:

- are infected with HIV (the virus that causes AIDS)
- have never taken any medicine for the treatment of HIV

This study is sponsored by the National Institutes of Health. 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?

This study is being done to see if the combination of two anti-HIV medicines, dolutegravir (DTG, Tivicay) and lamivudine (3TC, Epivir) taken once a day, will provide a safe, effective, and well-tolerated treatment for HIV. DTG is a type of HIV medicine called an integrase inhibitor; 3TC is a type of HIV medicine called a reverse transcriptase inhibitor. DTG works by blocking integrase and 3TC works by blocking reverse transcriptase, two HIV proteins (enzymes). This prevents HIV from multiplying and lowers the viral load (amount of HIV in the blood). Both DTG and 3TC are currently part of Food and Drug Administration (FDA) recommended regimens along with a third active drug. Since some HIV medicines have side effects and are costly, there is interest in whether HIV can be successfully controlled with fewer than three HIV drugs.

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

If you decide to take part in this research study, you will be asked to sign this consent form and schedule a screening visit to determine if you are eligible to enter this study. If screening visits determine that you are eligible and you agree to be in this study, you will take DTG and 3TC once a day for 52 weeks. While you are in this study, you will be seen in the clinic about 13

times. The study staff will tell you about how long each visit will last. During the study, you will get the results from any routine tests that are done during the study when they are available.

Screening visit

- Your HIV infection will be confirmed if there is no record available. You have another HIV test and may have to sign a separate consent form before having this test
- You will be asked about your medical history and any medicines you have taken.
- You will have a brief physical exam and be asked about your health.
- You will have blood drawn for routine safety tests to check your blood count, kidney and liver function, to measure your HIV viral load (the amount of HIV in your blood).
- You will have blood drawn to test for hepatitis B (infection caused by a virus that attacks the liver).
- You will have blood drawn to determine your HIV integrase genotype (genetic makeup of the virus that will show if there is any evidence of HIV drug resistance). You will have blood drawn to determine your HIV protease and reverse transcriptase genotype as part of your routine medical care if this was not already done.
- If you are a woman who could become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will not be able to enroll in this study if you are pregnant or breastfeeding.

If you do not enroll into the study

If you do not qualify to take part in this study or you decide not to take part in this study, we will still use some of your information. As part of the screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4+ cell count, HIV viral load) information is being collected from you so that ACTG researchers may see if there are patterns or common reasons why people do not join a study.

Entry visit

- If the screening evaluations show that you are eligible for the study, you will return to the clinic for the entry visit.
- You will have a physical exam. The study staff will check the different systems in your body and your vital signs such as temperature, pulse, blood pressure, and respiratory rate.
- You will be asked about medicines you have taken in the past or are taking now.
- You will have blood drawn for routine safety tests to check your blood count, kidney and liver function, and to measure your CD4+ cell count and HIV viral load. Some of your blood will be stored for future testing.
- You will have blood drawn to test for hepatitis C (infection caused by a virus that attacks the liver).
- You will have a fasting lipid blood test to measure the level of cholesterol in your blood. Fasting means no food or drink, except for sips of water with medications for 8 hours before the test. If you are not fasting at the time of the blood draw, your blood will still be drawn.
- You will be asked to provide a urine sample.
- If you are a woman who could become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will not be able to enroll in this study if you are pregnant.

- Some of your blood will be stored to check your genetic makeup which may be useful in understanding your response to the study drugs. The way medication affects a person is often varied and depends to a certain degree on genes and variations in those genes. Blood will be stored with the usual protectors of identity.
- You will begin taking DTG and 3TC by mouth once a day for the next 52 weeks.
 - There are no food restrictions with this combination so you may take these drugs with or without food. If you are taking some antacids, laxatives, or iron or calcium supplements you will need to take the DTG 2 hours before or 6 hours after these medications. Alternatively, you may take iron or calcium supplements at the same time as DTG if taken with food.
 - You will be given DTG and 3TC at your study visits to take home, and you will need to store them in a safe place at room temperature
 - Both DTG and 3TC will be supplied by the study.

During the study visits:

After the entry visit, your study visits will be on weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. All (or some) of the following tests will be done at each visit, depending on the week you come to the clinic:

- You will have a brief physical examination performed at each study visit.
- At each study visit, you will be asked questions about any medicines you are taking now and about any signs or symptoms that you are experiencing and any changes in other medications that you have had since your last visit.
- You will have blood drawn for routine safety tests to check your blood count, cholesterol level and kidney and liver function and to measure your CD4+ cell count.
- Blood will be drawn to check your HIV viral load at each study visit.
- You will have a fasting lipid blood test taken to measure the level of cholesterol in your blood.
- You will have a urine sample collected.
- If you are a woman who could become pregnant, you will have a pregnancy test whenever pregnancy is suspected.
- The study staff will contact you between some of your study visits to remind you of your appointment and to take your study medications.
- You will be asked about how well you take the study medicines at each study visit. The study staff will give you information and encouragement to help you take your medications as prescribed.
- Some of your blood will be stored to check the level of study drugs in your blood. Blood will be stored with the usual protectors of identity. You will not be told the results of these tests.

Confirmation of Viral Load

You will be asked to return to the clinic to have blood drawn if your HIV viral load gets too high and it is suspected that the study drugs might be failing to fight your HIV. You will have a brief physical exam and be asked about how well you have been taking your study medications. You will have blood drawn to measure your viral load and to do HIV-1 genotype resistance testing if virologic failure is confirmed. Your study doctor will talk to you about the plan for future treatment. This visit may be combined with another study-scheduled visit.

Pregnancy

If you are a woman and you become pregnant, you will have to stop taking the study drug but we will ask you to stay in the study to be followed on study/off treatment until study completion. If you do not wish to continue to be followed on study/off treatment, the study staff will ask your permission to contact you regarding the outcome of your pregnancy. Your pregnancy will be reported to the Antiretroviral Pregnancy Registry, an international database that collects information about pregnancies in women taking anti-HIV drugs. These reports will not use your name or other information that could be used to identify you.

Premature Treatment/Study Discontinuation

If you stop taking the study drug before the study-defined treatment period, you will be asked to return to the clinic to complete some evaluations:

- You will have a brief physical exam and be asked about any medicines you have been taking.
- You will be asked about how well you took the study medicines.
- You will have blood drawn for routine safety tests to check your blood count, liver and kidney function, CD4+cell count, and viral load.
- You will be asked to provide a urine sample.
- Some of your blood will be stored for future testing.

Other Information

As stated above, some of your blood will be stored for study-required testing which is part of your participation in this study. If you agree to be in this study, you are also agreeing to have blood stored for study-required tests.

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protectors of identity) and used for future ACTG-approved HIV-related research.

Please indicate below "yes" or "no" and initial and date whether you approve the use of these extra stored samples for future testing. Note that you can withdraw your consent for research on stored specimens at any time you want and the specimens will be discarded. Your refusal or withdrawal of consent for the storage of these samples will not affect your study participation since storage of leftover samples is not a requirement for the study.

_____ Yes, I agree.

_____ No, I do not agree.

A5353 Study Visits

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference.

Study Schedule

Evaluation or test	Screen	Entry	Post-Entry Visits		Confirm virologic failure	Early discontinuation
			On treatment (Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48)	End of treatment (Week 52)		
Consent	✓					
Complete physical examination		✓				
Brief physical examination	✓		✓	✓	✓	
Medical/medication history	✓	✓	✓	✓	✓	✓
Blood sample collection and laboratory testing	✓	✓	✓	✓	✓	✓
Urinalysis		✓		✓		✓
Stored blood samples		✓	✓	✓	✓	✓
Phone call reminder			Between study visits			
Adherence questionnaire			✓	✓	✓	
Approximate amount of blood	30 mL	30 mL	15 to 25 mL/visit	30 mL	22 mL	25 mL

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 120 people (men and women) will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 52 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.

- A Study Monitoring Committee (SMC) recommends that the study be stopped early (An SMC is an outside group of experts who monitor the study).
- Your doctor thinks the study is no longer in your best interest.
- The site investigator thinks that you are at significant risk of failing to comply with the requirements of the protocol.
- Your primary care physician requests you be taken off the study.

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

- Continuing the study medicine may be harmful to you.
- You need a treatment that you may not take while on the study.
- You become pregnant or are breastfeeding.
- Your viral load worsens.
- You are not able to take the study medicine as required by the study.
- You miss three consecutive clinic visits.

If you must stop taking the study drug before the study is over, the study doctor will 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 drugs through the study, or once I leave the study, how can I get study drugs?

If you must permanently stop taking DTG and 3TC before the study is over, the study staff will talk with you about other treatment options. After you have finished the study, you will not be able to get DTG or 3TC through the study.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm

Although the study site will make every effort to protect your privacy and confidentiality, it is possible that others could find out that you are participating in this study and that social harm may result (because you could become labeled as being infected with HIV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community. Poor adherence (failing to take HIV medications as prescribed) can increase the risk of drug resistance, HIV treatment failure, and a risk of HIV transmission to others.

Risks of Drawing Blood

Drawing blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection.

Risks of Study Drugs

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. It is very important that you tell your study doctor of 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 on 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 approval for taking any new medication while you are on the study.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome:

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.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Integrase Inhibitor

Dolutegravir, (DTG, Tivicay®)

The following serious and potentially life-threatening side effects have been associated with the use of dolutegravir. These include allergic reactions and liver problems.

Contact your health care provider right away if you develop a rash while taking dolutegravir, especially if it's associated with any of the following symptoms:

- Fever
- General ill feeling
- Extreme tiredness
- Muscle or joint aches
- Blisters or sores in your mouth
- Blisters or peeling skin
- Redness or swelling of your eyes
- Swelling of your mouth, face, lips, or tongue
- Trouble breathing

Contact your health care provider right away if you have any of the following symptoms that could be signs of liver problems:

- Yellowing of your skin or whites of your eyes (jaundice)
- Dark or tea-colored urine
- Pale-colored bowel movements
- Nausea or vomiting
- Loss of appetite
- Pain, aching, or tenderness on your right side below your ribs

People with pre-existing history of depression or other psychiatric illness may be at greater risk for suicidal thoughts, or attempts, which may lead to death. If your psychiatric condition worsens, or if you develop suicidal thoughts, call your healthcare provider right away.

Other side effects include:

- Changes in liver test results, more common in people with hepatitis B or C
- Trouble sleeping
- Tiredness
- Headache

Nucleoside Analogue

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or 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, weakness, dizziness and shortness of breath.

Lamivudine (3TC, Epivir®)

The following side effects have also been associated with use of lamivudine:

- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
- Upset stomach, vomiting, nausea, loose or watery stools
- 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

If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if lamivudine is stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if drug combinations in this study harm unborn babies. If you are a woman and having sex that could lead to pregnancy, you must agree not to become pregnant.

If you are a woman participating in sexual activity that could lead to pregnancy, you and/or your male partner must use one form of birth control that you discuss with the study staff. You must start one method of birth control before you start taking the study drugs, while you are taking the study drugs, and for 30 days after stopping study drugs.

- Condoms (male or female) with or without a spermicidal agent. Condoms are recommended because their appropriate use is the only contraceptive method effective for preventing HIV transmission.
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

If you can become pregnant, you must have a pregnancy test before you enter this study and before you start taking DTG and 3TC. The test must show that you are not pregnant. Pregnancy tests will also be performed whenever pregnancy is suspected. If you think you may be pregnant at any time during the study, tell your study staff right away. Pregnancy will result in immediate discontinuation of the study drugs.

BREASTFEEDING

It is unknown whether the study drugs pass through breast milk and may cause harm to your infant. You must not breastfeed while you are in this study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you but no guarantee can be made. Your health may be watched more closely than usual while you are on the study, which may help you to feel better. It is also possible however that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:

- Treatment with FDA-approved HIV prescription drugs available to you.
- Treatment with HIV experimental drugs, if you qualify.
- No HIV treatment.

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

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your

participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protections, FDA, your site's institutional review board (a committee that makes sure that your rights and safety are protected while in the study), National Institutes of Health (NIH), study staff, study monitors, and other government agencies as part of their duties, and the pharmaceutical company supporting this study and its 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 www.ClinicalTrials.gov. 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?

There will be no cost to you for the study drugs (DTG and 3TC), the study visits, physical examinations, laboratory tests or other tests required by the study. You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study.

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.

WILL I RECEIVE ANY PAYMENT?

Compensation for participating in this study will be at site's discretion.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of taking part in this study, you will be given treatment right away for your injuries and be referred for further treatment, if necessary. However, you or your insurance company may have to pay for this care. There is no program for compensation either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if

you decide not to take part. Your decision will not affect other studies done by NIH in which you may be taking part, and will not lead to any penalty or loss of benefits that you have the right to expect.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

- name of the investigator or other study staff
- telephone number of above

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

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5353

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 Legal Representative (print)
(As appropriate)

Legal Representative's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff's Signature and Date

Witness's Name (print)
(As appropriate)

Witness's Signature and Date