A5372

Drug-Drug Interactions Between Rifapentine and Dolutegravir in HIV/LTBI Co-Infected Individuals

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

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AIDS CLINICAL TRIALS GROUP

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in HIV/LTBI Co-Infected Individuals

SIGNATURE PAGE

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

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Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5372 e-mail group. Include the protocol number in the e-mail subject line. Send an e-mail message to actg.user.support@fstrf.org.

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- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Rebecca Marshall (marshall@frontierscience.org) directly.
- For other questions, send an e-mail message to actg.teamA5372@fstrf.org (ATTENTION: [Rebecca Marshall]). Include the protocol number, PID, and a detailed question.

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

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

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Study Drug Orders
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IND (Investigational New Drug) Number or Questions
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Expedited Adverse Event (EAE) Reporting/Questions
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Telephone Calls
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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

1HP	4-week daily regimen of isoniazid and rifapentine
ARV	antiretroviral
AUC	area under the curve
BID	twice daily
DTG	dolutegravir
EFV	efavirenz
ICF	Informed Consent Form
IGRA	interferon gamma release assay
INH	isoniazid
INSTI	integrase strand transfer inhibitor
LTBI	latent TB infection
MDR TB	multi-drug-resistant tuberculosis
MTB	*Mycobacterium tuberculosis*
NRTI	nucleoside reverse transcriptase inhibitor
OHRP	Office for Human Research Protections
PGP	P-glycoprotein
PK	pharmacokinetics
QD	once daily
RAL	raltegravir
RFB	rifabutin
RHS	rifamycin hypersensitivity syndrome
RIF	rifampin
RPT	rifapentine
SAE	serious adverse event
SNP	single nucleotide polymorphism
TAF	tenofovir alafenamide
TB	tuberculosis
TST	tuberculin skin test
XDR TB	extensively drug-resistant tuberculosis

SCHEMA

A5372
Drug-Drug Interactions Between Rifapentine and Dolutegravir in HIV/LTBI Co-Infected Individuals

DESIGN

A5372 is an open-label, two-arm, multicenter pharmacokinetic (PK) study to investigate the potential interactions between dolutegravir (DTG) and steady state rifapentine (RPT) when RPT is given with isoniazid (INH) daily for 4 weeks (1HP) as part of treatment for latent TB infection (LTBI) in HIV-1 and LTBI co-infected individuals.

DURATION

The majority of participants will be on study for 6 weeks (a 4-week on-study treatment period and a 2-week follow-up period). The duration may be up to 8 weeks as participants will have up to 6 weeks from the time of study entry to complete 4 weeks of treatment.

Participants who are required to return for confirmation of virologic failure within 1 to 3 weeks after the follow-up visit may be on study for up to 11 weeks.

SAMPLE SIZE

Maximum of 72 participants – 36 in Arm 1 and 36 in Arm 2, to yield at least 32 evaluable participants in each arm.

Evaluable participants are defined as those who have completed 28 daily doses of RPT/INH within the 6 week time period from study entry and who have at least 6 plasma sample collections on each of the two intensive PK visits (6 of these collections must include trough DTG concentration collections at 23- and 24-hr post-dose collection time points). Participants who do not have the required PK will be replaced.

POPULATION

Adults living with HIV-1 on stable once daily DTG based ART with 2 nucleoside reverse **transcriptase** inhibitors (NRTI) and an indication for LTBI treatment.

REGIMEN

Participants will receive study-provided INH 300 mg and RPT 600 mg once daily for 4 weeks (1HP). During the 1HP treatment, DTG 50 mg will be administered twice daily (BID) in Arm 1, and 50 mg once daily (QD) in Arm 2. For Arm 1, the second dose of DTG will be provided by the study; NRTI therapy and pyridoxine (vitamin B6) will not be provided by the study. See details below.

The study will begin enrollment with Arm 1. Opening of Arm 2 will depend on assessment of DTG PK data from participants in Arm 1.

Arm 1

- DTG 50 mg orally BID (~12 hours apart)
  - 1st dose: DTG 50 mg each morning from non-study ARV supply
  - 2nd dose: DTG 50 mg each evening from study supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

Arm 2 (upon opening)

- DTG 50 mg orally each morning from non-study ARV supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

All participants must also be on once-daily DTG-based ARV treatment with 2 NRTIs (excluding TAF) during the study.

All participants must receive pyridoxine (vitamin B6) 25 or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines.

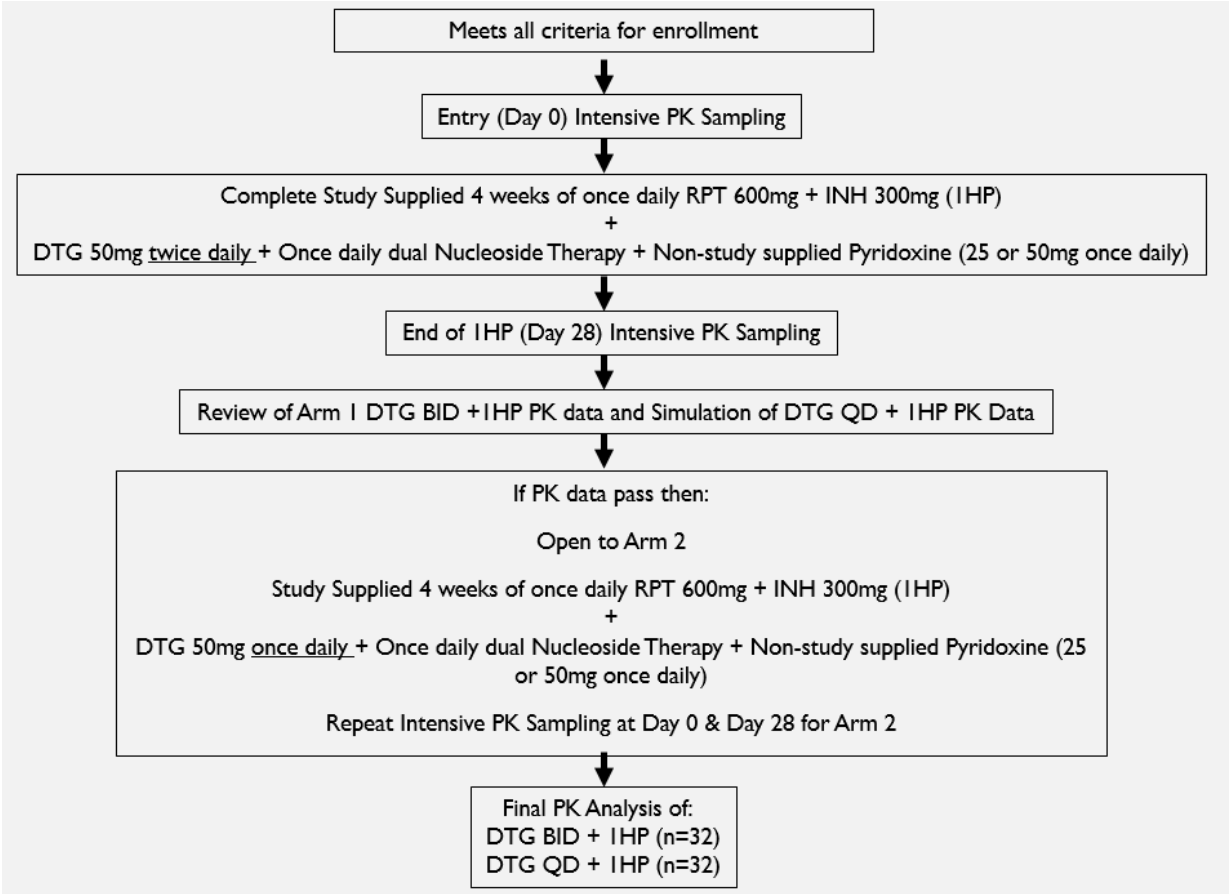

Figure 1: Schema

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

Dolutegravir (DTG) concentrations, when given twice daily (BID) or once daily (QD), with coadministration of 4 weeks daily rifapentine (RPT) (600 mg) and isoniazid (INH) (300 mg) [1HP], will maintain **steady-state plasma** trough **DTG concentrations** above 158 ng/mL **in 95% of study participants. The value 158 ng/mL is** the 5th percentile **steady-state** trough **concentrations** of DTG which has been demonstrated to be sufficient in maintaining viral suppression.

1.2 Primary Objectives

1.2.1 To determine the dosing for DTG that, when given together with 1HP, achieves target exposures (C_{trough}) of standard-dose DTG when it is given without RPT.

1.2.2 To estimate the steady state plasma pharmacokinetics (PK) of DTG when DTG 50 mg is dosed twice daily (BID) with 1HP.

1.2.3 If Arm 2 opens, to estimate the steady state plasma PK of DTG when DTG 50 mg is dosed once daily (QD) with 1HP.

1.3 Secondary Objectives

1.3.1 To evaluate the safety of coadministration of DTG based ART with 1HP.

1.3.2 To evaluate the tolerability of coadministration of DTG based ART with 1HP.

1.3.3 To estimate the proportion of participants who maintain virologic suppression when DTG based ART is coadministered with 1HP.

1.4 Exploratory Objectives

1.4.1 To evaluate the steady state PK parameters of DTG in the presence or absence of 1HP, taking into account relevant pharmacogenetics across diverse populations (single nucleotide polymorphisms [SNPs] to be determined).

1.4.2 To evaluate the steady state PK parameters of RPT achieved from 1HP dosing in people living with HIV and explore relevant pharmacogenetics associated with RPT exposures (SNPs to be determined).

1.4.3 To develop a joint pharmacokinetic model of RPT and DTG PK and its drug-drug interaction (DDI) where relationship and interaction between dynamic RPT and DTG concentrations is modelled, quantified, and described.

2.0 INTRODUCTION

2.1 Background

2.1.1 Dolutegravir

Dolutegravir (DTG) is now included in preferred regimens for antiretroviral (ARV)-naïve individuals by the Department of Health and Human Services (DHHS), World Health Organization (WHO), and International AIDS Society (IAS) USA guidelines panels [1, 2, 3]. Moreover, the drug is being rolled out into resource poor settings (RPS) and was recently launched in South Africa. The drug combines high potency, excellent tolerability, and a high barrier to resistance (Tivicay Package Insert, ViiV, 2017) [4].

The SPRING-1 study was a Phase IIb dose ranging trial of DTG given with two nucleoside reverse transcriptase inhibitors (NRTI) in antiretroviral naïve adults living with HIV. Data from this multicenter trial showed that DTG was well tolerated in the doses studied from 10 mg to 50 mg once daily. Efficacy analysis (% participants with viral load <50 copies mL) showed that at 48 weeks 90% of individuals in the 50 mg arm achieved virologic suppression while 91% achieved this same endpoint in the 10 mg dosing arm (difference non-significant) [5]. The geometric mean (%CV) values for DTG trough concentrations in SPRING-1 were 0.3 ug/mL (71%) and 1.2 ug/mL (62%) for the 10 and 50 mg doses of DTG, respectively. The efficacy and PK data from the SPRING-1 study are reassuring in that the 50 mg dose of DTG is the current standard of care, while efficacy data from the 10mg daily dose of DTG may provide insight into acceptable DTG trough thresholds that may arise when encountering drug-drug interactions such as those in the treatment of HIV/TB co-infection when using rifamycin antibiotics in combination with DTG. To this end, this evaluation will target achieving 95% of DTG trough values above 158 ng/mL, the 5^{th} percentile DTG trough value in the DTG 10 mg dosing arm of SPRING-1 and above the protein adjusted DTG IC_{90} of 64 ug/mL.

Primarily metabolized by UGT1A, with CYP3A as a minor route, DTG has been studied with rifampin and rifabutin in healthy HIV-uninfected volunteers [6]. Given twice daily with standard-dose, daily rifampin, DTG total daily exposures were similar to or higher than those achieved with DTG given once daily alone. Overall plasma concentrations of DTG were only modestly reduced when DTG was given with (versus without) rifabutin, and no DTG dose adjustment is required. One out of 27 healthy volunteers (in the rifabutin arm) experienced a serious adverse reaction consistent with rifamycin hypersensitivity syndrome (RHS).

In the INSPIRING study, a Phase IIIb trial of people living with HIV with drug susceptible TB receiving a rifampin based TB treatment, DTG given at a dose of 50 mg twice daily was both effective and well tolerated. At week 48 the proportion of participants with HIV-1 RNA <50 copies/mL was 75%. No patients randomized to the DTG ARV arm discontinued DTG due to adverse events. Importantly, there were no reports of treatment emergent resistance in participants receiving

combined DTG and rifampin (n=69) based TB treatment. Rates of treatment related IRIS were low (6%) and no participant discontinued due to IRIS or liver events [7].

A similar study of DTG twice daily in combination with rifampin based TB treatment in adults living with HIV and TB has provided additional virologic and PK data on DTG use in this population. In 10 participants from Cameroon with a median baseline HIV-1 RNA of 520,440 copies/mL, patients started on DTG 50 mg BID within the study all had HIV-1 RNA <200 copies/mL at week 48 with a median DTG trough (C_{12}) value of 1,123 ng/mL (Inhibitory Quotient approximately 17.5) [8].

A recent study explored the PK of DTG when dosed as 100 mg once daily in combination with daily rifampin. In this healthy volunteer study, participants sequentially received DTG 50 mg and DTG 100 mg once daily, both with and without rifampin. The GMR of the C_{max}, AUC, and C_{24} of DTG for DTG 100 mg once daily + rifampin:DTG 50 mg alone were: 1.09, 0.74, and 0.24. DTG trough concentrations were substantially reduced, while overall dosing interval exposures of DTG decreased to a lesser extent [9].

There are less data when DTG is given with RPT as compared to rifampin. In a small study assessing the PK and safety of DTG when given at a dose of 50 mg once-daily together with once-weekly INH and RPT (each dosed at 900 mg, 3HP) in HIV-uninfected healthy volunteers, DTG trough (C_T) concentrations were reduced by 43%, 74%, and 53% 2, 3, and 6 days after the dose, respectively, compared to when DTG was given alone [10]. The lowest average C_T, though, remained 5.3 times higher than the protein-adjusted IC_{90} for DTG, suggesting that even with these reductions in exposure, virologic suppression was likely to be maintained in individuals with HIV taking standard-dose DTG. The combination, however, was poorly-tolerated, with flu-like syndrome seen in two of three volunteers. Brisk immune responses have been seen in healthy volunteers given rifamycins previously [6, 11-13] and in individuals with TB. Rifamycin hypersensitivity is most common when rifamycins are dosed intermittently [14, 15].

In a similar study of 3HP in HIV/latent TB infection (LTBI) co-infected individuals, Dooley and colleagues conducted PK sampling of patients receiving 50 mg DTG in combination with once weekly RPT and INH. The geometric mean (GM) trough concentration of DTG pre-HP treatment was 1003 ug/mL (5th-95th percentile: 500-2080), and during HP treatment 546 (134-1616) with all trough concentrations except for one above the DTG IC_{90} of 64 ug/mL. Overall, although weekly HP decreased DTG bioavailability, which was associated with a modest decrease in trough concentrations, all trough concentration except for one were above the DTG IC_{90}, and DTG clearance remained unchanged after the 8th weekly dose of RPT/INH. Notably, with regard to safety, co-administration of DTG and weekly HP was well-tolerated, with no HP-related Grade >3 AEs. All viral loads were suppressed [16]. These data, combined with the week 48 results of the INSPIRING study [7] add to the evidence in that safety events such as those seen in the Brooks et al. study [10] present differently in healthy volunteers versus HIV/LTBI co-infected individuals.

The safety and tolerability of DTG plus *daily* RPT remains to be established in individuals living with HIV and LTBI; moreover, the dose of DTG required to maintain HIV virologic suppression among patients with LTBI-HIV receiving RPT 600 mg daily for 4 weeks within the 1HP LTBI regimen (standard DTG dose of 50 mg once a day versus 50 mg twice a day) must be determined before these drugs can be safely used together. In Arm 2 of the present study, we will investigate DTG PK when DTG is given daily at the standard dose of 50 mg and RPT is administered daily as 600 mg for 28 days as part of the 1HP regimen. Recent data in healthy volunteers combining DTG 100 mg with rifampicin 600 mg daily yielded an approximate 28% and 75% reduction in plasma AUC and C_{trough} values, respectively. However, reassuringly, these mean DTG trough values remained ~5-fold higher than the protein binding adjusted IC_{90} DTG plasma concentration of 64 mg/mL [17]. These data, combined with the Brooks et al. DTG PK data when using DTG 50 mg together with weekly RPT/INH each at 900 mg showing similar maximum DTG trough reductions of ~75%, remaining 5.3 times higher than the protein-adjusted IC_{90} for DTG, along with PK and efficacy data from the dose finding studies of DTG (SPRING-1) and data from Dooley et al. of 3HP+ DTG based ART (NCT 03435146) form the rationale for DTG dosing in Arm 2 of our study [5]. While overall RPT exposures are higher with daily RPT dosing, it remains to be studied what effect RPT dose and frequency (600 mg daily vs 900 weekly) has on DTG bioavailability and CYP enzyme induction and ultimately any subsequent drug interactions arising from this induction. Additionally, the participant population within the present study will be virologically suppressed prior to entering the study, suggesting the possibility of a lower threshold for DTG exposure and C_{trough} values than what may be needed in HIV treatment-naïve individuals presenting with high viral loads. To date, there are no PK data available when combining DTG (either QD or BID) with daily RPT, at any dose.

In an ongoing birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to DTG compared to non-DTG-containing antiretroviral regimens taken at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking DTG-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-DTG-containing regimens at the time of conception (prevalence difference 0.09%; 95% CI -0.03, 0.30) [20].

Reproductive toxicology studies have not shown any relevant findings. DTG has been shown to cross the placenta.

Data available from other sources including the Antiretroviral Pregnancy Registry (APR), other cohorts and clinical trials are insufficient to confirm or refute this potential risk.

Women will be counselled regarding the unknown risks that could be associated with DTG exposure to the foetus should they fall pregnant. All women will be given additional information on the potential risk of neural tube defects (NTDs) of infants born to women on DTG.

2.1.2 Isoniazid and rifapentine (1HP)

Tuberculosis is the leading cause of death in individuals living with HIV. Preventive therapy (treatment of latent tuberculosis infection) has been shown to significantly reduce development of active TB. Recently, an ultra-short course of isoniazid+rifapentine given daily for 1 month (1HP) was shown to be non-inferior to 9 months of daily isoniazid therapy (9H) at preventing TB in people living with HIV [21]. Additionally, the 1HP regimen had fewer adverse events, and was more likely to be completed than 9H in adults and adolescents living with HIV. Rifapentine in preventive treatments including 1HP treatment has been dosed according to weight bands, however, the rationale for this weight-banded approach has been lacking. A comprehensive analysis of RPT population pharmacokinetics in more than 400 TB patients receiving various daily doses of RPT confirmed the absence of any impact of weight on RPT pharmacokinetics, therefore justifying flat RPT dosing. Based on this scientific evidence, we will use a flat dose of RPT in this study, to avoid underdosing of lighter participants [22].

2.2 Rationale

Drug-drug interaction studies with daily RPT and DTG are still lacking and are urgently needed given that DTG is quickly becoming a first-line agent in the global context and it is important that 1HP treatment be available to patients with HIV/LTBI co-infection receiving DTG based ART. Combined regimens with the lowest pill burden and convenience of once daily dosing provide an ideal option for management of co-infected patients. Additionally, having a one month regimen (1HP) available for co-infected patients receiving DTG based ART will significantly reduce LTBI treatment duration, in which the only current option is 9 months of daily INH. The design of A5372 allows for a staged approach to achieving the most simplified DTG based ART regimen safely and effectively used in combination with 1HP LTBI treatment. Safety and efficacy data from both QD and BID DTG dosing will be collected so as to provide an ideal ultra-short course RPT containing treatment regimen for HIV/LTBI. Interactions in the other direction (e.g., effects on RPT/INH) are not anticipated given our knowledge of the metabolic pathways of RPT/INH and the effects of DTG on metabolizing enzymes and transporters. Thus, DTG is not expected to affect exposure of RPT/INH.

Although safety concerns have arisen when combining rifamycin-based LTBI treatments with DTG-based ART [10], these studies have been conducted in healthy volunteers and rates of adverse events in HIV/LTBI co-infected individuals have been shown to be far less. The safety data from the INSPIRING study, which included 69 participants receiving DTG- and RIF-based TB treatment showed that no individuals stopped study drugs due to drug-related AEs [7]. In a study by Dooley et al., of HIV/LTBI co-infected individuals on DTG-based ART and 3HP LTBI treatment showed that of the 60

participants who started 3HP dosing, all 60 completed all 12 weekly doses of RPT/INH while none of the 60 participants discontinued study medications due to AEs [16]. The study population of A5372 largely mimics the study population enrolled in the Dooley et al. study, and provides an opportunity to develop safety data on HIV/LTBI co-infected individuals receiving an ultra-short course LTBI regimen of 1HP in combination with DTG-based ART.

3.0 STUDY DESIGN

A5372 is an open-label, two-arm, multicenter PK study to investigate the potential interactions between DTG and steady state RPT when RPT is given with INH daily for 4 weeks (1HP) in individuals living with HIV-1 and LTBI.

The majority of participants will be on study for 6 weeks (a 4-week on-study treatment period and a 2-week follow-up period). The duration may be up to 8 weeks as participants will have up to 6 weeks from enrollment to complete 4 weeks of treatment. Participants who are required to return for confirmation of virologic failure within 1 to 3 weeks after the follow-up visit may be on study for up to 11 weeks.

Initially, the study will begin enrollment with Arm 1. Once PK data are available from Arm 1 with at least 32 evaluable participants (participants with at least 6 plasma sample collections on each of the two intensive PK visits [6 of these collections must include 23- and 24-hr time points (trough levels) to ensure PK laboratory analysis can occur on at least 32 participants]), the clinical management committee (CMC) team and the SMC will review the DTG BID PK data to ensure sufficient plasma exposures of DTG (C_{trough}) are achieved with twice-daily DTG dosing. Upon review of the Arm 1 PK data, the PK data will be used to model the anticipated PK of QD DTG when co-administered with 1HP. Based on these models and simulations of QD DTG dosing with 1HP, a decision will be made on whether to open Arm 2 for enrollment. Refer to section 7.4 for details on criteria for opening of Arm 2.

Plasma PK profiles for DTG will be determined at two time points. At the first time point, plasma samples will be drawn in participants at steady state with respect to DTG when receiving once daily DTG prior to 1HP. At the second time point, DTG will be given BID in Arm 1 and QD in Arm 2 during the 1HP LTBI regimen and PK sampling for DTG will occur on Day 28 of the 1HP regimen. In addition, sparse PK sampling will be performed on days 3, 14, and 21 of the 1HP regimen. Remaining plasma from the DTG analysis will be used to determine RPT concentrations achieved from 1HP dosing to support exploratory study objectives.

The study regimen will be as follows starting on Day 1 continuing through Day 28.

Arm 1
- DTG 50 mg orally BID (~12 hours apart)
  - 1st dose: DTG 50 mg each morning from non-study ARV supply
  - 2nd dose: DTG 50 mg each evening from study supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

Arm 2 (upon opening)
- DTG 50 mg orally each morning from non-study ARV supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

All participants must also be on stable once-daily DTG-based ART with 2 nucleoside reverse transcriptase inhibitors (NRTIs) (excluding TAF) during the study.

All participants must receive pyridoxine (vitamin B6) 25 or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines. Pyridoxine is not provided by the study.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Males and females at least 18 but no more than 65 years of age at study entry.

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

4.1.3 Weight ≥40 kg and a body mass index (BMI) of greater than 18.5 kg/m^2.

4.1.4 Documentation of HIV-1 infection status, as below:

HIV-1 infection, documented by any licensed rapid HIV test or HIV-1 E/CIA test kit at any time prior to entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load. Two or more HIV-1 RNA viral loads of >1,000 copies/mL are also acceptable as documentation of HIV-1 infection.

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

Note B: WHO and Centers for Disease Control and Prevention (CDC) 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.

4.1.5 HIV-1 plasma viral load <50 copies/mL obtained within 30 days prior to study entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that is Virology Quality Assessment (VQA) certified.

4.1.6 At US sites: Evidence of LTBI by tuberculin skin test (TST) reactivity ≥5 mm, or a positive interferon gamma release assay (IGRA) at any time prior to study entry.

At non-US sites: Indication for LTBI treatment according to WHO latent TB guidelines (Note: TST/IGRA results not required).

4.1.7 On a stable once daily DTG (50 mg) based ART with once daily 2 NRTIs and

- With at least 28 total days of DTG and NRTI dosing prior to study entry
- With no gaps in self-reported DTG and NRTI adherence of more than 3 consecutive days in the 28 days prior to study entry
- With no intention to change ART for the duration of the study

NOTE A: Participants who switch from another ART regimen to DTG to meet eligibility requirements for this study will be eligible to enroll as long as the ART is switched at least 28 days prior to study entry.

4.1.8 Chest radiograph (X-ray) or chest computed tomography (CT) scan performed within 30 days prior to study entry without evidence of active TB.

NOTE: An existing chest X-ray or CT scan from within 30 days prior to entry can be used as qualifying chest imaging. If chest imaging will be performed for study evaluation (i.e., Screening), then chest X-ray should be performed. A CT scan will be used only if an existing scan is already available and will not be performed as part of study.

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

- Absolute neutrophil count (ANC) >750 cells/mm^3
- Hemoglobin ≥7.4 g/dL
- Platelet count ≥50,000/mm^3
- Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) **<2.5 X the upper limit of normal (**ULN**)**
- Alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) **<2.5 X** ULN
- Total bilirubin ≤1.5 x ULN
- **Creatinine <1.3 X ULN**

4.1.10 For females of reproductive potential, negative serum or urine pregnancy test at Screening within 30 days prior to entry and within 48 hours prior to entry by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test, or at any network-approved non-US laboratory or clinic that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

NOTE A: If screening visit occurs within 48 hours prior to entry, only one test will occur prior to entry.

NOTE B: Urine test must have a sensitivity of 15-25 mIU/mL.

4.1.11 Female participants of reproductive potential must agree not to participate in the conception process (i.e., active attempt to become pregnant, in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, must agree to use one reliable nonhormonal method of contraception, as listed below, while on study treatment and through study completion.

Acceptable forms of contraception include:

- Intrauterine device (IUD) or intrauterine system
- Cervical cap with spermicide
- Diaphragm with spermicide
- **Condoms (male or female)**

NOTE A: **Hormonal methods may be used, however, one of the other acceptable forms of contraception listed above must also be used through the duration of the study because of potential interactions with RPT.**

NOTE B: Participant-reported history is acceptable documentation of menopause (i.e., at least 1 year amenorrheic), hysterectomy, or bilateral oophorectomy or bilateral tubal ligation; these candidates are considered not of reproductive potential and are eligible without the required use of contraception.

4.2 Exclusion Criteria

4.2.1 Breastfeeding, pregnancy, or plans to become pregnant.

4.2.2 Known allergy/sensitivity or any hypersensitivity to components of the study drugs, or their formulations.

4.2.3 Presence of any confirmed or probable active TB based on criteria listed in the current ACTG Diagnosis Appendix at screening.

4.2.4 History of rifamycin-monoresistant, INH-monoresistant, multi-drug resistant (MDR), or extensively-drug resistant (XDR) TB at any time prior to study entry.

4.2.5 Known exposure to rifamycin-monoresistant, INH-monoresistant, MDR- or XDR-TB (e.g., household member of a person with rifamycin-monoresistant, INH-monoresistant, MDR- or XDR-TB) at any time prior to study entry by participant self report or medical records.

4.2.6 **History** of peripheral neuropathy Grade ≥2 according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

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

4.2.8 Acute or serious illness requiring systemic treatment and/or hospitalization within 7 days prior to study entry.

4.2.9 Known cirrhosis, a history of decompensated liver disease (ascites, hepatic encephalopathy, or esophageal varices) or current Child Pugh Class B or C hepatic impairment.

NOTE: Refer to section 6.3.10 for Child Pugh scoring and classification table.

4.2.10 Initiated, discontinued, or changed doses of drugs that are P-glycoprotein (PGP) inducers, that are P-glycoprotein (PGP) inhibitors, or that are known to have drug interactions with DTG, within 30 days prior to study entry.

NOTE: Refer to the list of prohibited and precautionary medications in Appendix I.

4.2.11 Known porphyria at any time prior to study entry.

4.2.12 Receipt of any other antiretroviral therapy other than DTG and 2 NRTI within 28 days prior to study entry.

4.2.13 Receipt of TAF within 28 days prior to study entry.

4.2.14 Documented resistance that may confer reduced susceptibility to DTG, at any time prior to study entry. This includes the following integrase strand transfer inhibitor (INSTI) mutations: Q148 substitutions, T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, G193E/R, or N155H.

4.2.15 Clinically suspected INSTI resistance, at any time prior to study entry, as evidenced by prior receipt of INSTI-containing ART, during which time two or more HIV-1 RNA levels of >200 copies/mL were observed after having attained virologic suppression to <200 copies/mL and without known interruption.

4.2.16 Consumption of more than 3 alcohol beverages on any day within 30 days prior to entry.

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 required documents have been received. Site-specific ICF(s) WILL NOT be reviewed or approved by the DAIDS PRO. 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.

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

4.3.2 Protocol Activation

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

4.3.3 Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure 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 Co-enrollment Guidelines

- US sites are encouraged to co-enroll participants in A5128, "Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses." Co-enrollment in A5128 does not require permission from the A5372 protocol chairs.
- Non-US sites are encouraged to co-enroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses." Co-enrollment in A5243 does not require permission from the A5372 protocol chairs.
- For specific questions and approval for co-enrollment in other studies, sites should contact the team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as dolutegravir (DTG), rifapentine (RPT), and isoniazid (INH).

5.1 Regimens and Duration

Arm 1
- DTG 50 mg orally BID (~12 hours apart)
  - 1st dose: DTG 50 mg each morning from non-study ARV supply
  - 2nd dose: DTG 50 mg each evening from study supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

Arm 2 (upon opening)
- DTG 50 mg orally each morning from non-study ARV supply
- 1HP: INH 300 mg + RPT 600 mg orally each morning for 4 weeks

All participants must be on stable once-daily DTG-based ART with 2 nucleoside reverse **transcriptase** inhibitors (NRTI).

All participants must receive pyridoxine (vitamin B6) 25 or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines. Pyridoxine is not provided by the study.

5.2 Administration and Dispensing

Dolutegravir (DTG) will be administered orally as 50 mg either QD or BID. As RPT and INH will be given with food, the DTG dose when aligned with 1HP administration will be given with food as well. DTG doses not aligned with 1HP doses may be given with or without food with exception of DTG doses taken on Day 0 and Day 28, which should be taken with food. Separate each DTG 50 mg dose by 12 hours when giving BID. In Arm 1, 1HP should be taken with the first daily dose of DTG.

Isoniazid (INH) will be administered orally as 300 mg QD. INH may be taken with food and at the same time as rifapentine. The 300 mg tablets must not be divided or crushed.

Rifapentine (RPT) will be a administered orally as 600 mg QD with food.

To align with the PK sample collections, participants should be on morning dosing regimen for the duration of the study (except the 2nd dose DTG in Arm 1), including at least 3 days prior to Day 0 intensive PK. The dose on the morning of PK sampling day will be an observed dose. Thus, participants will need to hold the dose until the clinic visit.

1HP medications will be provided for Day 1 to Day 28. DTG 50 mg tablets will be dispensed to participants in Arm 1 of the study for the second daily dose of DTG. Participants will continue 2 NRTI plus one dose DTG 50 mg daily from their own supply while on the study treatment regimen in both Arm 1 and Arm 2 (Day 1 to Day 28). Participants will have up to 6 weeks from enrollment to complete 4 weeks of 1HP treatment. Following 1HP, participants will continue antiretroviral therapy prescribed by their routine HIV care provider.

The 1HP treatment is ideally taken once daily for 28 consecutive days. If doses are interrupted, participants are allowed up to 42 days to complete the 1HP therapy. For Arm 1 participants, BID dosing of DTG should continue for the entire 1HP treatment, up to 42 days. Additional doses of DTG for Arm 1 may be dispensed as required, either in intact bottles or dispensed into prescription bottles. For Arm 2 participants, daily DTG and NRTIs should continue from their own supply for the entire 1HP treatment.

5.3 Study Product Formulation

Dolutegravir (DTG): 50 mg tablets. Store at 25°C (77°F) with excursions between 15° and 30°C (59°-86°F) permitted (see USP Controlled Room Temperature).

Isoniazid (INH): 300 mg tablets. Store below 30°C (86°F) and in the original container.

Rifapentine (RPT): 150 mg tablets. Store at 25°C (77°F) with excursions between 15° and 30°C (59°-86°F) permitted (see USP Controlled Room Temperature).

5.4 Pharmacy: Product Supply, Distribution, and Accountability

5.4.1 Study Product Acquisition/Distribution

DTG 50 mg (Tivicay) is supplied by ViiV Healthcare Ltd.

INH is purchased from Macleods Pharmaceuticals Ltd.

Rifapentine (Priftin®) will be manufactured by Sanofi and supplied through the study with funding support from the ACTG.

DTG (where applicable), INH, and RPT will be made available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

Pyridoxine (vitamin B6) will not be provided through the study and should be obtained locally by the site.

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or –sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at: https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf.

5.4.2 Study Product Accountability

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

5.5 Concomitant Medications

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

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

5.5.1 Required Medications (not provided by the study)

Refer to Section 5.1 for the list of required medications.

5.5.2 Prohibited Medications

Prohibited medications are listed in Appendix I.

5.5.3 Precautionary Medications

Precautionary medications are listed in Appendix I.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Arms 1 and 2

Evaluation	Screening	Entry		On-Study Treatment				Follow Up	Confirmation of Suspected Virologic Failure	Premature Treatment/Study Discontinuation [c]
	-30 to -1 days	Day 0	Day 1	Day 3	Day 14	Day 21	Day 28	Day 42	Day 49	
(Visit Window)				(+2 Days)	(±2 Day)	(±2 Day)	(-2/+14 Days)	(-2/+14 days)	(+28 days)	
Documentation of HIV	X									
Medical History	X	X								
Medication History	X	X								
Clinical Assessments	X	X		X	X	X	X	X	X	X
Contraception Counseling	X				X		X			
Chest X-Ray or Chest CT	X									
Hematology	X	X		X			X			X
Liver Function Tests	X	X		X	**X**	**X**	X			X
Blood Chemistries	X	X		X			X			X
Pregnancy Testing	X [a]	X	X (if indicated)				X			
Plasma HIV-1 Viral Load	X						X	X	X	
TST or IGRA	X									
Child Pugh Score for Hepatic Impairment	X									

Evaluation	Screening	Entry		On-Study Treatment				Follow Up	Confirmation of Suspected Virologic Failure	Premature Treatment/Study Discontinuation [c]
	-30 to -1 days	Day 0	Day 1	Day 3	Day 14	Day 21	Day 28	Day 42	Day 49	
(Visit Window)				(+2 Days)	(±2 Day)	(±2 Day)	(-2/+14 Days)	(-2/+14 days)	(+28 days)	
PK Sampling (Intensive) [b]		X					X			
Dispensation of Study Medications		X								
Start of Study Regimen			X							
PK Sampling (Sparse) [b]				X	X	X				
Whole Blood for Pharmacogenetic Testing (optional)		X								
Stored Plasma for HIV Resistance Testing									X	

[a] Pregnancy test will be performed **with a negative result available** prior to Chest X-ray at Screening visit.

[b] PK sampling will occur after ensuring 3 **days** consecutive dosing of ART and/or RPT/INH prior to study visit. **Day 3 sparse PK may have only 2 prior doses of 1HP.** Detailed information about last three doses will be collected per participant self report. See sections 6.2.2 and 6.2.3.

[c] These evaluations should be performed at the time of study treatment discontinuation and/or at the time of study discontinuation, as applicable. No further evaluations can be performed on a participant after study discontinuation.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

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

Screening evaluations to determine eligibility must be completed within 30 days prior to entry, unless otherwise specified.

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

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluations unless otherwise specified.

On the day of registration, Entry/Day 0 evaluations must be completed after eligibility is determined from the screening evaluations. All Entry/Day 0 evaluations must be completed prior to treatment administration.

Participant must begin treatment (study provided DTG and 1HP) following completion of Entry/Day 0 intensive PK evaluations.

Participants will be admitted to the Clinical Research Unit (CRU) or equivalent at Entry/Day 0 for intensive PK sampling. Hospitalization is recommended but is not mandatory and is at the discretion of the participant and/or investigator to allow for flexibility and feasibility. PK sampling may only occur after ensuring 3 days of consecutive dosing of ART prior to entry (participant self-report is sufficient).

Study treatment will begin on what will be termed ‘Day 1’ following completion of Day 0 PK sampling. However, no additional Day 1 evaluations will occur.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations

Day 3
A study visit including sparse PK sampling will occur on Day 3 with a window of +2 days.

Day 14
A study visit including sparse plasma PK sampling will occur on Day 14, with a window of ±2 days.

Day 21
A study visit including sparse plasma PK sampling will occur on Day 21, with a window of ±2 days.

PK sampling at Day 3, Day 14, and Day 21 may only occur after ensuring 3 days of consecutive dosing of ART and/or RPT/INH prior to study visit. This will be recorded per participant self report.

Day 28
A study visit including intensive PK sampling will occur on Day 28 (window -2/+14 days).

PK sampling at Day 28 may only occur after ensuring 3 days of consecutive dosing of ART and RPT/INH prior to study visit (participant self report is sufficient).

NOTE: Participants will have 6 weeks to complete 4 weeks of on-study treatment.

Day 42
A follow up study visit should occur approximately 14 days following the completion of study treatment. The window for the day 42 follow-up visit is -2/+14 days.

NOTE: The timing of the day 42 visit may vary for some participants as participants will have up to 6 weeks from enrollment to complete 4 weeks of treatment.

Event-Driven Evaluations

Day 49 Confirmation of Suspected Virologic Failure
Participants with plasma HIV RNA > 50 copies/mL at the Day 42 follow-up visit will return for a confirmatory plasma HIV RNA measurement approximately 7 days after the original sample collection or as soon as testing results are available.

At non-US sites, an additional plasma sample will also be collected for possible resistance testing, if viremia is confirmed. At US sites, the confirmatory sample should be sent to reflex for resistance testing if HIV viremia is confirmed, where feasible. If not feasible, an additional plasma sample for resistance testing should be collected at time of confirmation of viremia. Resistance testing should include integrase and reverse transcriptase resistance.

The window for the day 49 confirmation of suspected virologic failure visit is +28 days.

NOTE: The timing of the day 49 visit may vary for some participants as participants have up to 6 weeks from the time of enrollment to complete 4 weeks of treatment.

6.2.4 Discontinuation Evaluations

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

Discontinuation Evaluations
If a confirmation of suspected virologic failure visit is not necessary (i.e., plasma HIV RNA is determined to be <50 copies/mL at Day 42), participants should discontinue study once they complete their Day 42 follow-up visit. Refer to the Discontinuation Log in the A5372 eCRF completion guideline.

If a confirmation of suspected virologic failure visit is necessary based on the Day 42 follow-up visit plasma HIV RNA, participants should discontinue study after they complete their Day 49 Confirmation of Suspected Virologic Failure visit. Refer to the Discontinuation Log in the A5372 eCRF completion guideline.

Premature Discontinuation Evaluations
Participants who prematurely discontinue the study will have evaluations performed as indicated in the schedule of evaluations and then be taken off study.

Participants who discontinue study participation due to Grade 3 or 4 toxicity attributed to study drug should have premature study discontinuation evaluations completed per the SOE when the toxicity has decreased to Grade ≤2 and then be taken off study. No further evaluations can be performed on a participant after study discontinuation. Refer to the Discontinuation Log in the A5372 eCRF completion guideline.

6.3 Instructions for Evaluations

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

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

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the DAIDS AE Grading Table and AE reporting of adverse events requirements.

6.3.1 Documentation of HIV-1

Sections 4.1.4 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Medical History

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

- AIDS-defining conditions
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Prior Tuberculosis
- Chronic obstructive pulmonary disease (COPD)
- Chronic hepatitis C
- Chronic hepatitis B

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

6.3.3 Medication History

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

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Prescription drugs	30 days prior to study entry
Sex-hormone medications or sex-hormone analogues or antagonists*	12 months prior to study entry

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.4 Clinical Assessments

Complete Physical Exam
A complete physical examination will be performed at Screening only and is to include, at a minimum:

- examination of the skin, head, mouth, and neck
- auscultation of the chest
- cardiac exam; abdominal exam
- examination of the lower extremities for edema
- signs and symptoms
- diagnoses
- height **(in cm)**
- weight **(in kg)**; **calculated** body mass index
- vital signs (temperature, pulse, respiration rate, and blood pressure)

Targeted Physical Exam
Targeted physical examination will be performed at all visits after Screening (except for on Day 1) and is to be driven by any previously identified or new signs or symptoms including diagnoses or adverse events that the participant has experienced since the last visit.

The exam must include:
- vital signs (temperature, pulse, respiration rate, and blood pressure)
- weight **(in kg)**

Refer to section 7.2 for AE collection requirements.

Concomitant Medications
After entry, any new and discontinued concomitant medications must be recorded on the eCRFs.

Study Treatment Modifications
After entry, record all study drug modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, **and** inadvertent and deliberate interruptions since the last visit. **All interruptions of study-supplied drugs, regardless of duration, must be recorded.** Record any permanent discontinuation of treatment. **Interruptions to non-study ART will be recorded on the concomitant medications log.**

6.3.5 Contraception Counseling

Due to the potential risk from neural tube defect associated with DTG treatment during the first trimester of pregnancy (see section 2.1.1), study staff must review the following information with all female participants of reproductive potential:
- Importance of pregnancy avoidance and of adherence to contraception requirements;
- Safer sexual practices and the proper use of their chosen contraceptive methods in accordance with the applicable contraceptive product label;
- The importance of informing the core team immediately if they become pregnant or plan to become pregnant, as they must be withdrawn from the study.

In addition, at the Screening visit, study staff must review the following information with all female participants of reproductive potential:

- In an early analysis of one observational study, women who were taking DTG when they became pregnant had an increased risk of having babies with serious brain and spine defects. These defects happen early in pregnancy, before many women even know they are pregnant.

Documentation of contraception counseling is not recorded on the eCRF.

6.3.6 Chest X-Ray or Chest CT

Chest X-ray or chest CT is required within 30 days prior to entry and must not show evidence of active TB.

An existing chest X-ray or CT scan from within 30 days prior to entry can be used as qualifying chest imaging. If chest imaging will be performed for study evaluation (i.e., Screening), then chest X-ray should be performed. A CT scan will be used only if an existing scan is already available and will not be performed as part of study.

6.3.7 Laboratory Evaluations

At screening and entry all laboratory values must be recorded on the eCRF. For post-entry assessments, record abnormal laboratory findings as per section 7.2.

Hematology
Hemoglobin, hematocrit, red blood cells, white blood cell count, absolute neutrophil count (ANC), and platelets.

Liver Function Tests (LFTs)
Total bilirubin, AST (SGOT), ALT (SGPT).

Blood Chemistries
Sodium, potassium, creatinine, and albumin.

Pregnancy Testing
For women with reproductive potential: Serum or urine β-HCG. Urine test must have a sensitivity of 15-25 mIU/mL.

In addition to a pregnancy test at the Screening visit within 30 days prior to entry, negative pregnancy will be confirmed within 48 hours prior to Entry. **A** pregnancy test **will be** perform**ed and a negative result available** prior to Screening X-ray.

NOTE: If screening visit occurs within 48 hours prior to entry, only one test will occur.

Record pregnancy and pregnancy outcome per section 8.5.

6.3.8 Virologic Studies

Plasma HIV-1 Viral Load
Obtain HIV-1 viral load per the SOE at a laboratory that possesses a CLIA certification or equivalent (US sites) or VQA certification (non-US sites). Screening HIV-1 RNA must be performed within 30 days prior to study entry. Eligibility will be determined based on the screening value.

6.3.9 Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA)

For participants at US sites, a TST or a licensed IGRA assay will be performed at screening if prior positive test results are not already available.

For participants outside of the US, a TST or IGRA is not required, per the site investigator's discretion and WHO latent TB guidelines.

NOTE: TST and IGRA results will not be recorded on an eCRF.

6.3.10 Child Pugh Score for Hepatic Impairment

Child Pugh Score, if necessary, will be assessed at screening to determine eligibility. The scoring and classification table is provided below.

Child Pugh Score will not be recorded on an eCRF.

Parameter	Numerical score		
	1	2	3
Ascites	None	Slight	Moderate to severe
Encephalopathy	None	Slight to moderate	Moderate to severe
Bilirubin (mg/dL)	< 2.0	2-3	> 3.0
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (prolonged in seconds)	1-3 s	4-6 s	> 6.0

Child's Pugh Class A = 5-6 points; Child's Pugh Class B = 7-9 points; Child's Pugh Class C = 10-15 points.

Figure 6.3.10-1: Child Pugh Score for Hepatic Impairment

6.3.11 Pharmacokinetic Sampling

Intensive PK
A 24 hour intensive PK sampling will occur per the SOE.

Arm 1
The intensive plasma PK samples will be collected at hours 0 (pre-dose), 1, 2, 4, 8, 12, 13, 14, 23, and 24 hours post-DTG dose at Entry/Day 0 and on Day 28 (-2/+14 days).

Arm 2
The intensive plasma PK samples will be collected at hours 0 (pre-dose), 1, 2, 4, 8, 12, 23 and 24 hours post-DTG dose at Entry/Day 0 and on Day 28 (-2/+14 days).

NOTE: For Arms 1 and 2, a minimum of 6 samples must be collected, including the 23- and 24-hour collections.

All intensive samples should be collected within a 15 minutes window of the designated sampling time. The following should be recorded:

- Date and time of sampling
- Time of dosing of three prior days of ART and/or 1HP per participant self report
- Time of dosing of ART and/or 1HP taken during the PK sampling
- Whether DTG, RPT, INH, NRTI doses were taken with food

NOTE: The Entry/Day 0 DTG dose is from participant's existing ART regimen and should be taken with food. Entry/Day 0 PK sampling may only occur after ensuring 3 days of consecutive dosing of ART prior to entry. Day 28 visit may occur up to 2 weeks later as participants will have 6 weeks to complete 4 weeks of on-study treatment. However, PK sampling at Day 28 may only occur after ensuring 3 days of consecutive dosing of ART and RPT/INH prior to study visit. Day 28 DTG dose should be taken with food.

Sparse PK
The sparse plasma PK samples will be collected per the SOE at 20 minutes (±15 minutes) (trough) before the dose.

All sparse samples should be collected within the designated window above. The following should be recorded:

- Date and time of sampling
- Time of dosing of three prior days of ART and 1HP per participant self report. **Of note, Day 3 sparse PK may have only two prior days of 1HP.**
- Time of dosing of ART and 1HP taken during the PK sampling
- Whether DTG, RPT, INH, NRTI doses were taken with food

6.3.12 Whole Blood for Pharmacogenetic Testing (Optional)

A whole blood sample will be obtained for genotyping of polymorphisms in human genes that may affect metabolism, disposition, and toxicity of the study drugs, as well as concomitant medications.

6.3.13 Stored Plasma for HIV Resistance Testing

For resistance testing, plasma may be collected and stored at the Confirmation of Suspected Virologic Failure visit.

At non-US sites, an additional plasma sample will also be collected for possible HIV resistance testing for integrase and reverse transcriptase resistance, if viremia is confirmed.

At US sites, the confirmatory sample should be sent to reflex for HIV resistance testing for integrase and reverse transcriptase resistance if HIV viremia is confirmed, where feasible. If not feasible, an additional plasma sample for resistance testing should be collected at time of confirmation of viremia

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Event

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

7.2 Adverse Event Collection Requirements for this Protocol

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

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

<u>Serious Adverse Events (SAEs)</u>
An SAE is defined as any untoward medical occurrence that:
- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

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

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

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

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

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

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

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are:
  - Dolutegravir (DTG)
  - Rifapentine (RPT)
  - Isoniazid (INH)

7.3.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

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

7.4 Study Monitoring

The core team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation (to ensure the total target number of evaluable participants is met), stored sample completeness (to ensure that samples for primary and secondary outcome measures are collected as expected), and adverse events. An evaluable participant will be considered any participant who has completed the 28 daily doses of RPT/INH within the 6 week time period from study entry and has additionally completed both intensive PK visits with a minimum of 6 samples collected at each PK visit. The 23- and 24-hour (trough) time points must be part of the 6 collected samples.

The site should notify the core team within 72 hours (preferably within 48 hours) by email if a participant has not completed each of the two intensive PK visits with at least 6 plasma sample collections including the 23- and 24-hr PK draws, or if a participant has not completed 28 daily doses of RPT/INH within the 6-week time period from study entry.

During the study, the safety and tolerability of the study medication will be monitored by toxicity reports presenting laboratory and clinical data. The core team will discuss these reports on regularly-scheduled conference calls or by e-mail. It is the responsibility of the core team to interpret the toxicity data and make any decisions needed to protect participants from undue risk. Any concerns will be presented to the DAIDS Clinical Representative.

The DAIDS clinical representative will review and assess EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs, as applicable. Additionally, the DAIDS clinical representative will review aggregated adverse event summaries by arm prepared quarterly by the SDAC.

The study will undergo interim feasibility and safety review approximately every 6 months after the enrollment of the first participant by an ACTG-appointed Study Monitoring Committee (SMC). The first interim review will occur no more than 6 months after the enrollment of the first study participant.

An SMC interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the CMC team. See section 10.0 for statistical and other considerations related to interim monitoring.

For all SMC reviews, the SMC will be provided detailed information on safety (including treatment tolerability and mortality), and administrative aspects (including accrual, retention, compliance with study requirements).

An interim review of DTG PK data will be conducted by the CMC team and the SMC once DTG PK data from participants in Arm 1 (n=32 evaluable) are available prior to opening Arm 2.

A 10 mg daily dose of DTG was associated with virologic suppression in the SPRING-1 study [18] and the pharmacokinetic parameters reached following this dose in SPRING-1 are adequate to be considered as DTG C_{trough} PK targets (5^{th}, 50^{th}, and 95^{th} percentile of 158, 316, and 555 ng/mL, respectively). These PK data form the basis for opening rules for Arm 2. Once DTG C_{trough} PK data are available from 36 participants in Arm 1, an evaluation of DTG PK in these participants will occur.

Arm 2 will open to enrollment if simulation of Arm 1 PK data suggest that 50 mg DTG dosed QD in combination with 1HP will result in DTG trough concentrations that mimic reported plasma concentrations following a 10 mg DTG QD dose. Based on the population pharmacokinetic model built and adequately evaluated based on the data from Arm 1, we will simulate the clinical trial population of Arm 2 (QD dosing) 1000 times, and generate troughs for each of these simulated participants. These trough values will be summarized in terms of reported statistics from the SPRING Study (5^{th}, 50^{th}, and 95^{th} percentile for each repetition). The median value (from 1000 repetitions) of the 5^{th} percentile of DTG trough concentrations (C_{tau}) assessed via simulations should not fall below the reported 5^{th} percentile of 158 ng/mL which was observed in the 10 mg DTG dose from the SPRING-1 study. If this criterion is met, A5372 will open Arm 2 for enrollment for evaluation of QD DTG 50 mg given with 1HP. The estimation of expected lower boundary with QD dosing (derived from simulations) will be done using model-based analysis with the models derived from PK data collected data in Arm 1 receiving 50 mg BID + 1HP.

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

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

General instructions for management of Grades 1-4 AEs is provided in section 8.1. Refer to sections 8.2, 8.3, and 8.4 for information on the following specific toxicities:

- **Rifamycin Hypersensitivity Syndrome (RHS)**
- **Suspected allergic reactions to dolutegravir**

- **Cutaneous**
- **Drug-associated fever**
- **Elevated liver-associated enzymes**
- **Peripheral neuropathy**
- **Suicidal ideation**

8.1.1 Grade 1 or 2

Participants who develop a Grade 1 or 2 AE or toxicity may continue all study-supplied drugs (INH, RPT and DTG if receiving through the study) at the discretion of the site investigator, and will be followed carefully.

If the site investigator or participant chooses to discontinue any study-supplied drug, the site should notify the A5372 core team within 72 hours (preferably within 48 hours). The premature treatment/study discontinuation evaluations must be completed, and then the participant will be taken off study.

8.1.2 Grade 3 or 4

For Grade 3 or 4 AE or toxicity that is definitely, probably, or possibly related to study-supplied drugs, study-supplied drugs **as well as any other drugs suspected in the site investigator's causality assessment** must be permanently discontinued and participants followed carefully. Premature treatment discontinuation evaluations should be performed. In the event of Grade 3 or 4 toxicities, the A5372 core team should be notified within 72 hours (preferably within 48 hours).

The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, the premature study discontinuation evaluations must be completed, and then the participant will be taken off study.

8.2 Rifamycin Hypersensitivity Syndrome (RHS)

Participants who develop signs or symptoms suggestive of RHS (i.e., fever, myalgia, rash, hypotension, clinical hepatitis) should undergo clinical evaluation and laboratory testing including comprehensive metabolic panel, CBC with manual differential, and other tests that, at the discretion of the site investigator, are necessary to exclude likely alternative diagnoses (e.g., if symptoms suggest influenza, a nasopharyngeal aspirate for viral testing could be sent). Any participant in whom the investigator suspects RHS and no alternative etiology is identified must permanently discontinue INH, RPT, and other study-provided medications. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study.

8.3 Suspected Allergic Reactions to Dolutegravir

Participants with Grade ≥3 allergic reactions, which are considered possibly or probably

related to DTG should be evaluated by the investigator and must discontinue study-provided DTG and other study-provided medications. Locally provided DTG must be stopped as well. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study. ART management will be at the discretion of the site investigator.

8.4 Other Toxicities

Cutaneous

Participants with an isolated Grade 1 or Grade 2 rash may continue study-supplied drugs at the study investigator's discretion. Participants should be advised to contact the site staff immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

If Grade ≥3, all study-provided drugs must be discontinued**, as well as any other drugs suspected in the site investigator's causality assessment**. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study. ART management will be at the discretion of the site investigator.

Drug-Associated Fever

If Grade ≥3, all study-supplied drugs must be discontinued**, as well as any other drugs suspected in the site investigator's causality assessment**. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study.

Elevated Liver-Associated Enzymes

Sites must notify the core team within 72 hours and hold study-supplied drugs (INH, RPT, and DTG if applicable) if any of the following criteria are met.

a) Grade 3 or 4 AST, ALT or total bilirubin values are recorded;
b) ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin);
c) ALT ≥3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

For any Grade 1 AST (SGOT), ALT (SGPT) (1.25 to <2.5 x ULN) or total bilirubin (1.1 to <1.6 x ULN) elevation, repeat liver chemistries (ALT, AST, total bilirubin) should be conducted at regular intervals at the investigator's discretion until resolution to ≤ULN **or to baseline if abnormal at entry**.

For Grade 2 AST (SGOT), ALT (SGPT) (2.5 to 5 x ULN), or total bilirubin (1.6 to <2.6 x ULN) increase, study-supplied drugs will be held until the levels return to Grade ≤1, and then liver

chemistries repeated until resolution to <ULN **or to baseline if abnormal at entry**, as above. Reintroduce the study-supplied drug(s) with caution. **Locally provided DTG should be discontinued if suspected in the site investigator's causality assessment.**

INH, RPT, and study-supplied DTG will be permanently discontinued in the event of Grade 3 to 4 AST (SGOT), ALT (SGPT) (≥5 ULN) or total bilirubin (≥2.6 x ULN) toxicity that is definitely, probably, or possibly related to study-supplied drugs. Locally provided DTG **should be discontinued if suspected in the site investigator's causality assessment**. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study. ART management will be at the discretion of the site investigator.

In consultation with the team, 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 for any liver toxicity that warrants permanent study drug discontinuation based on the liver stopping criteria specified above. Specific tests that may be considered are listed on the PSWP.

Peripheral Neuropathy

Peripheral neuropathy associated with INH is usually avoided by the concurrent administration of pyridoxine (vitamin B6). In this study, all participants will take vitamin B6 concomitantly with INH. If peripheral neuropathy develops, every effort should be made to determine the etiology (i.e., whether the neuropathy is due to INH toxicity, alcohol, or other factors). Participants with peripheral neuropathy Grade ≤2 may be entered into the study, but should be monitored carefully for any progression of peripheral neuropathy.

For Grade 1 or 2, continue study-supplied drugs and follow the participant more frequently for progression of peripheral neuropathy. Consider increase in vitamin B6 dose.

For Grade 3 or 4, study-supplied drugs must be permanently discontinued**, as well as any other drugs suspected in the site investigator's causality assessment**. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study.

Suicidal Ideation

Participants will be monitored appropriately and observed 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. For Grade 3 or 4 suicidal ideation, study-supplied drugs must be permanently discontinued**, as well as any other drugs suspected in the site investigator's causality assessment**. Locally provided DTG

must be stopped as well. Premature treatment discontinuation evaluations should be completed. The participant should be followed until the AE has decreased to Grade ≤2. After the AE has decreased to Grade ≤2, premature study discontinuation evaluations should be completed, and then the participant will be taken off study**.**

Other toxicity
Toxicity management will be performed per the standard clinical practice.

8.5 Pregnancy Outcomes and Reporting

Pregnant women must discontinue study medication and study evaluations, but will be encouraged to remain on study to collect pregnancy outcome data. The outcome and the adverse events for the participant and infant will be recorded on an outcome eCRF.

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

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Pregnancy
- Drug-related toxicity (see sections 8.1, 8.2, 8.3, and 8.4)
- At the discretion of the ACTG, IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter

9.2 Premature Study Discontinuation

- Request by the participant to withdraw
- Requirement for prohibited concomitant medications (see section 5.5)
- Clinical reasons believed life-threatening by the physician, even if not addressed in the toxicity section of the protocol
- Failure by the participant to complete either of the intensive PK visits
- Participant repeatedly noncompliant (per investigator’s discretion) with study medications as prescribed
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant
- At the discretion of the ACTG, IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is an open-label, two-arm, multicenter PK study to examine drug-drug interactions between RPT and DTG in HIV-1 and LTBI co-infected participants.

Participants in Arm 1 will receive DTG 50 mg BID in combination with 1HP for 4 weeks. After 36 participants from Arm 1 are enrolled and PK data are available, a review of DTG trough concentrations by the team and the SMC will take place to determine whether Arm 2 should open based on an analysis of DTG trough concentrations. There will be a pause in study enrollment between the completion of Arm 1 and the start of Arm 2.

If the team decides to open Arm 2, participants in Arm 2 will receive DTG 50 mg QD in combination with 1HP for 4 weeks.

Participants will serve as their own controls and PK parameters of DTG will be compared in the presence or absence of 1HP. The maximum sample size is 72 participants.

10.2 Outcome Measures

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

10.2.1 Primary Outcome Measures

Evaluation of effect of 1HP on the PK of DTG in plasma

10.2.1.1 Plasma DTG PK parameters (C_{max}, area-under-the-curve (AUC_{0-12} for BID & AUC_{0-24} for QD dosing), C_{min}) at Day 0 and Day 28 (-2/+14 days), by arm.

10.2.1.2 Plasma DTG PK parameter (C_{trough}) at Day 28 (-2/+14 days), by arm.

10.2.2 Secondary Outcome Measures

10.2.2.1 Proportion of participants with all adverse events meeting the reporting criteria in Section 7.2 during administration of DTG with 1HP, by arm.

10.2.2.2 Proportion of participants who discontinue study or study drugs during DTG and 1HP dosing, by arm.

10.2.2.3 Proportion of participants with HIV-1 RNA levels >50 copies/mL at Day 28 (-2/+14 days) and/or at the Follow Up visit.

10.2.3 Other Outcome Measures

Model predicted dosing of DTG during concomitant 1HP

10.2.3.1 Dosing algorithm for DTG in the presence of RPT/INH dosing derived by simulation using nonlinear mixed effects models.

Evaluation of the role of pharmacogenomics on DTG and RPT PK

10.2.3.2 PK parameters of DTG in the presence or absence of 1HP, taking into account relevant pharmacogenetics (SNPs TBD).

10.2.3.3 PK parameters of RPT after 1HP dosing taking into account relevant pharmacogenetics (SNPs TBD).

Combined evaluation of DTG and RPT PK models

10.2.3.4 Joint pharmacokinetic model of RPT and DTG PK and its DDI where relationship and interaction between dynamic RPT and DTG concentrations is modelled, quantified and described.

10.3 Randomization and Stratification

Participants will be enrolled into the study without randomization since the accrual for Arm 1 will be completed when the decision to open Arm 2 will be made.

10.4 Sample Size and Accrual

Sample size estimates are aimed to provide data to support precise estimation of the pharmacokinetic model parameters for DTG in the presence and absence of 1HP. These models, once validated, will further be used to deliver dosing algorithms for DTG to be recommended for treatment of patients living with HIV and co-infected with LTBI, pending appropriate safety assessment.

The sample size assessment was done by evaluating different study designs (varying number of participants and time points) using clinical trial simulations. The stochastic simulation-estimation (SSE) methodology for clinical trial simulation and re-estimation was employed to evaluate sample sizes required to evaluate key pharmacokinetic parameters with precision adequate for decision making on use of RPT + DTG at the proposed doses. This methodology simulates the data from the planned trial with proposed design (number of samples, participants) followed by the estimation of the parameters under the true and alternative models. This is repeated at least 1000 times and parameter estimates relative standard errors and between subject variability (BSV) estimates are assessed. This methodology was used to assess sample size calculations and probability of opening Arm 2. The effect of RPT on DTG PK parameters

(bioavailability) was assumed to be 30%-50% decrease based on a previously developed model of DTG + 3HP [16]. The range of inter-participant variability in PK parameters (CL and F) was assumed to be 25-40%. The team has assumed design where each participant is its own control and time course of RPT induction is considered. Under these assumptions, data from ≥32 participants will provide >80% power to detect the DDI effect on bioavailability and to unbiasedly (relative bias <5%) and precisely (RSE<25%) estimate PK parameters and inter-participant variability. These unbiased parameters will be then used for simulations of Arm 2 and derivation of the median 5th percentile of DTG troughs by simulations. Probability of opening Arm 2 will be dependent on magnitude of both, decrease in bioavailability due to DDI and between participant variability. Decrease in bioavailability of up to 35% coupled with acceptable inter-participant variability (up to 30%) will provide 90% chance of satisfying criteria for opening Arm 2.

The proposed design for DTG requires 32 evaluable participants with at least 6 plasma sample collections which must include the 23- and 24-hr samples on each of the two intensive PK visits in order to estimate pharmacokinetic parameters with required the precision defined as relative standard errors <10% for typical values and RSE <25% for random effects (between subject variability).

To protect against loss of the primary outcomes (e.g., unevaluable PK measurements) after study accrual is closed, the study will enroll 36 participants in each arm. This is an increase of ~12% from the required sample size of 32 evaluable participants.

Data from participants who drop out between sampling times or participants who do not have at least 6 sample collections on each of the two intensive PK visits will be utilized in the analysis, however, those participants will not be counted towards full sample size requirement (i.e., 36 participants in each arm) and will be replaced.

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

The core team will monitor adverse events (AEs) on a regular basis. Should 3 or more participants experience Grade 3 or higher AEs deemed to be definitely, probably, or possibly related to DTG or RPT or INH, the study will be halted while a safety review is conducted by the ACTG's Tuberculosis Transformative Science Group (TB TSG) SMC. **The core team will also monitor viral loads on Days 28, 42, and 49 on a regular basis. Specifically, at the time of the interim review for Arm 1, the proportion of participants with HIV-1 viral load above 50 c/mL will be reported.**

10.5.2 Analysis Plan

For the interim PK assessment in Arm 1 participants, PK data from the SPRING-1 study [15] will form the basis of the opening rule for Arm 2. Refer to section 7.4 for criteria and considerations for opening Arm 2.

10.6 Analyses

Primary outcome plasma PK parameters **(C_{min}, AUC_{0-24h}, and C_{max})** will be determined using **nonlinear mixed-effects population pharmacokinetic modeling**. PK parameters will be log-transformed as needed.

Primary PK analysis:
The bootstrap method with replacement will be applied on the observed C_{trough} values from Arm 1, and the mean and 95% CI of the 5th percentile C_{trough} will be calculated. The lower **bound of a** 95% CI **around** the 5th percentile **of** C_{min} from Arm 1 will be compared with the 5th percentile of C_{tau} in the DTG 10 mg dosing arm (i.e., 158 ng/mL) from the SPRING-1 study, which has been demonstrated to be sufficient in maintaining viral suppression. If the lower **bound of the** 95% CI **around** the 5th percentile C_{min} is greater than 158 ng/mL, the dosing is considered acceptable. The same analysis will be conducted for Arm 2 if it opens.

Geometric mean ratios and associated 90% confidence intervals within arm will be calculated to assess the overall effect of 1HP on DTG PK.

For all PK parameters (including both primary and other outcome PK measures), descriptive statistics including mean, standard deviation, median, interquartile range, minimum, and maximum will be presented. All statistical tests will be performed without adjustment for multiple comparisons unless otherwise stated.

Detailed analysis methods will be put in a Statistical Analysis Plan.

Because PK variability has been associated with differences in drug response, understanding whether differences in DTG and RPT concentrations observed in A5372 have a genetic basis will be explored as an exploratory objective. Polymorphisms in host genes involved in both DTG and RPT metabolism or transport will be explored. The primary genes of interest will include: CYP3A4/5, UGT1A1, PXR (pregnane x receptor), CAR (constitutive androstane receptor), as well as other metabolic enzymes and transporters that may play a role in either DTG or RPT disposition (TBD).

11.0 PHARMACOLOGY PLAN

See section 6.3.11 for details on PK sampling **and section 10.6 for details of population PK modeling**.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC.

Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

12.2 Role of Data Management

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

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

12.3 Clinical Site Monitoring and Record Availability

12.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, 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.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity [23]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

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

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix II) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight

of the study. A signed consent form will be obtained from the participant (or legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

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

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, or other local, US, and international regulatory entities as part of their duties to ensure that research participants are protected.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies.

15.0 BIOHAZARD CONTAINMENT

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

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

16.0 REFERENCES

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APPENDIX I: PROHIBITED AND PRECAUTIONARY MEDICATIONS

Division of AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For Protocol A5372

The prohibited and precautionary medications with dolutegravir (DTG), rifapentine (RPT), and isoniazid (INH) are listed below.

I. Prohibited Medications

- Phenytoin
- Phosphenytoin
- Lamotrigine
- Perampanel
- Phenobarbital
- Primidone
- Carbemezepine
- Oxcarbazepine
- Eslicarbazepine
- Felbamate
- St. John's wort
- Dofetilide
- Azole antifungals including fluconazole, itraonazole, ketoconazole and posaconazole (topical formulations are acceptable as they do not achieve systemic concentration)
- Enzalutamide
- Mitotane
- Other rifamycin antibiotics including rifabutin and rifampicin
- Tenofovir alafenamide (TAF)
- Other antiretroviral drugs except DTG and 2 NRTI
- Protease inhibitors (HIV or HCV)

II. Precautionary Medications

- Antacids – follow product labeling for instructions on separation with DTG
- Buffered Medications – follow product labeling for instructions on separation with DTG
- Divalent cations (e.g., calcium or iron supplements) – follow product labeling for instructions on separation with DTG
- Ethinyl estradiol/norgestimate
- Metformin
- Methadone
- Multivitamin – follow product labeling for instructions on separation with DTG
- Omeprazole
- Prucalopride
- Sucralfate
- Topiramate

APPENDIX II: SAMPLE INFORMED CONSENT

Division of AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

Industry Support Provided by:
Viiv Healthcare, Ltd.

For protocol: A5372, "Drug-Drug Interactions Between Rifapentine and Dolutegravir in HIV/LTBI Co-Infected Individuals," Final Version 2.0, dated 11Jun2021

SHORT TITLE FOR THE STUDY: RPT-DTG DDI Study

PURPOSE

This is a research study and your participation in this study is voluntary. The purpose of this study is to see if taking a medicine to treat tuberculosis (TB) called rifapentine (RPT), affects the levels of dolutegravir (DTG) (an HIV medicine) in the blood or not.

NUMBER OF PARTICIPANTS

There will be up to 2 treatment groups of people, for a total of up to 72 participants. The study will open with one treatment group only. Based on the results from the first group in the study, the study team will decide if the second group will open.

LENGTH OF STUDY

Most people will be on this study for six weeks (4 weeks on study treatment and 2 weeks of follow-up). You may be on study up to 11 weeks if you have to have additional follow-up visits to check your viral load.

REQUIRED ACTIVITIES

Blood collections
At all visits, some blood will be collected from a vein in your arm. Over the duration of the study, approximately 13 to 15 tablespoons of blood will be collected.

Special procedures
Chest X-ray/scan

RISKS

Possible risks related to the study drugs DTG, RPT, and isoniazid (INH) are listed later in this informed consent.

There are also risks related to blood draws, TB skin test, chest X-ray, and social harm. All of these risks are explained in later in this informed consent.

BENEFITS As part of this drug interaction study, you will receive short-course therapy for latent TB (known as 1HP), which may benefit you.

OTHER CHOICES You may choose to not participate in the study. This is a pharmacokinetic (PK) study to study interaction between a proven latent TB treatment (what is referred to as 1HP) and a DTG-2NRTIs regimen for HIV treatment. Instead of being in this study, you have the option of continuing with your current treatment or starting a new one under the care of your regular doctor or other health care provider. You may also check with your doctor about your options for treatment of latent TB under clinical care or other research studies.

INTRODUCTION

You are being asked to take part in this research study because the medicines you take to treat HIV include dolutegravir (DTG), and you have either tested positive for the bacteria that causes tuberculosis (TB) or you live in a place where TB infection occurs frequently.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

This research study is being done to help us figure if taking medications to prevent TB affect the drug levels in blood of a commonly used HIV medication called dolutegravir (DTG) and if an extra dose of DTG is needed during this TB preventive treatment. The other medicines, rifapentine (RPT) and isoniazid (INH), are drugs used to prevent active TB in people who have been exposed to TB. This study will also help us make sure that people tolerate the medicines and that they are safe when given together.

Some people are infected with the bacteria that cause TB, but their immune systems (the system in a person's body that helps fight infections) prevent the bacteria from multiplying, and they do not have any symptoms from the infection. These people have latent TB infection (LTBI). Latent TB can develop into active disease and cause sickness, especially in people with weakened immune systems, such as those with HIV. One treatment to prevent latent TB from becoming active is to take RPT and INH daily for 4 weeks. This therapy is referred to as 1HP, **and is an alternative recommendation by the World Health Organization (WHO) but not currently approved by the US FDA or recommended by the Centers for Disease Control and Prevention (CDC)**. **In the BRIEF TB study, a large multicenter study, 1HP was compared to standard therapy with 9 months of INH; both regimens had similar low rates of TB and a similar rate of side effects. This study suggested that 1HP worked similarly to 9 months of**

INH to prevent TB. However, it is still possible that 1HP is less effective than the currently approved regimens in preventing TB. A5372 is not intended to evaluate the ability of the 1HP regimen to prevent TB.

In many countries, DTG is the recommended first-line treatment for HIV. DTG, RPT, and INH are proven beneficial treatments for people living with HIV and latent TB, but it is unclear whether these treatments work differently when taken together. Understanding how DTG interacts with the short-term treatment for latent TB (1HP) is very important for delivering both treatments effectively.

The study will have two (2) arms. Arm 2 will only open after the results from Arm 1 are reviewed.

Below are the medicines that you may take during the study depending on which Group you are in:

Arm 1
- DTG 50 mg orally twice daily – about 12 hours apart
  - 1st dose will be taken in the morning; this will not be supplied by the study
  - 2nd dose will be taken in the evening; this will be supplied by the study for 4 weeks
- 1HP: INH 300 mg + RPT 600 mg orally once daily (in the morning) for 4 weeks (supplied by the study)

Arm 2 (upon opening)
- DTG 50 mg orally once daily (in the morning) (not supplied by the study)
- 1HP: INH 300 mg + RPT 600 mg orally once daily (in the morning) for 4 weeks (supplied by the study)

You will continue taking your existing ART drugs while on the study – your ART must include two NRTIs (excluding TAF) during the study. Your ART will not be provided by the study.

You will also receive pyridoxine (vitamin B6) 25 mg or 50 mg with each dose of INH based on the current local, national, or international dosing guidelines.

Because the blood draws on study visits will be dependent on the time you take the drugs, you will need to take your HIV drugs and drugs provided by the study (except second dose of DTG if you are in Arm 1) in the morning during the duration of the study. If you generally take your HIV drugs in the evening, you will need to switch to taking them in the morning for this study, including at least 3 days before the Day 0 visit. On the study visit days, you will hold off on taking the drugs until you arrive at the clinic.

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

Information Collected at Screening
There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for

example, disease condition, diagnosis), and laboratory (for example, viral load) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

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

If you agree to join this study, you will be asked to sign this consent form. After you have signed the form, the research staff will determine if you are eligible to join the study.

Screening

If you would like to be in this study, after you have read and signed this consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. This will take about 1 hour. At this visit:

- You will have a physical exam and answer questions about your medical history and any medications you are taking or have taken in the past.
- If your HIV status is unknown or not documented, blood will be drawn to confirm your HIV status. You may have to sign a separate consent form for this test.
- You will have approximately 2 tablespoons of blood drawn. This blood will be used for the following tests:
  - For routine lab tests for safety
  - To measure the amount of HIV in your blood
- You will be asked to give blood or a urine sample for a pregnancy test (applicable to individuals who can become pregnant).
- You may have a skin test or a blood draw to check if you have latent TB unless you have had a positive test in the past, or site investigator determines a need for LTBI treatment.
- After confirming a negative pregnancy test, **if you have not had a chest X-ray or CT scan within the last month,** you will have a chest X-ray to check you do not have active TB.
- A member of the staff at your site will talk to you about the contraception requirements for the study and the information that is known about DTG and pregnancy.

If you enter the study

If the tests at screening show that you are eligible for the study, you will be assigned to Arm 1 at the study entry visit. If and when Arm 2 opens for enrollment, you will be assigned to Arm 2. For both Arm 1 and Arm 2, the study visit schedule will be the same. The difference will be the regimen for DTG – twice daily in Arm 1 and once daily in Arm 2. Treatment will be taken for 28 days.

Entry / Day 0

After your screening visit, you will come in for an entry visit. Because this visit will take about 24 hours, you may be able to stay overnight at the clinic or hospital for this visit. If you are not able to stay overnight, this visit will take about 14 hours on Day 0 and you will return to the clinic the next day for another 2-3 hour visit.

At this visit:

- You will have a physical exam and answer questions about your medical history and any medications you are taking or have taken in the past.

- You will answer questions about the specific times of your HIV medicine doses on the last 3 days.
- You will have approximately 4 tablespoons of blood drawn. This blood will be used for the following tests:
  - For pharmacokinetic (PK) testing (to see how the levels of the study drugs rise and fall in your blood over time). You will not receive the results of this testing. The PK sample collection time points will be at hour 0 (before you take your anti-HIV medicine), and at 1, 2, 4, 8, 12, 13, 14, 23, and 24 hours after taking the anti-HIV medicine in Arm 1. Arm 2 will follow the same schedule, but will not have the 13 and 14 hour time points.
  - For routine lab tests for safety.
  - With your permission, some of the blood will be stored for future protocol-required pharmacogenetic testing. You will not receive the results of this testing.
- You will be asked to give blood or a urine sample for a pregnancy test (applicable to individuals who can become pregnant).

For pharmacogenetic testing, some of your blood will be tested for the human genes that affect how drugs are broken down, interact with other drugs, and potentially lead to side effects in the body. This testing may include whole genome sequencing (WGS). In WGS, researchers look at all of your genes and at almost all of your DNA. In "standard" genetic testing, researchers look at specific genes or subsets of genes, but not at all genes.

Day 1
You will start taking the study-provided drugs on Day 1 (following completion of the Day 0 visit evaluations).

Day 3
At this visit:
- You will have a physical exam.
- You will answer questions about the times when you took medicines in the last 3 days.
- You will have approximately 1 tablespoon of blood drawn for routine lab tests for safety.
- You will have blood drawn about 20 minutes before you take your study medicine to check the levels of study drugs in your blood (you will not receive the results of this testing).
- A pregnancy test may occur if indicated.

Day 14
At this visit:
- You will have a physical exam.
- A member of the staff at your site will remind you about the contraception requirements for the study.
- You will answer questions about the times when you took medicines in the last 3 days.
- **You will have approximately 1 tablespoon of blood drawn for routine lab tests for safety.**
- You will have blood drawn about 20 minutes before you take your study medicines to check the levels of study drugs in your blood (you will not receive the results of this testing).
- A pregnancy test may occur if indicated.

Day 21
At this visit:
- You will have a physical exam.
- You will answer questions about the times when you took medicines in the last 3 days.
- **You will have approximately 1 tablespoon of blood drawn for routine lab tests for safety.**
- You will have blood drawn about 20 minutes before you take your study medicines to check the levels of study drugs in your blood (you will not receive the results of this testing).
- A pregnancy test may occur if indicated.

Day 28
This visit will be similar to your Day 0 visit:
- You will have a physical exam.
- You will be asked to give blood or a urine sample for a pregnancy test (applicable to individuals who can become pregnant).
- A member of the staff at your site will remind you about the contraception requirements for the study.
- You will answer questions about the times when you took medicines in the last 3 days.
- You will have approximately 4 tablespoons of blood drawn. This blood will be used for the following tests:
  - For pharmacokinetic (PK) testing (to see how the levels of the study drugs rise and fall in your blood over time). You will not receive the results of this testing. The PK sample collection time points will be at hour 0 (before you take your anti-HIV medicine), and at 1, 2, 4, 8, 12, 13, 14, 23, and 24 hours after taking the anti-HIV medicine in Arm 1. Arm 2 will follow the same schedule, but will not have the 13 and 14 hour time points.
  - For routine lab tests for safety.
- You will have approximately 1 tablespoon of blood drawn. This blood will be used to measure the HIV levels in your blood and to store some blood for additional testing, if needed.

Day 42 Follow-up
At this visit:
- You will have a physical exam.
- You will have approximately 1 tablespoon of blood drawn. This blood will be used to measure the HIV levels in your blood and to store some blood for additional testing, if needed.

Day 49 Additional Visit
If your blood work at Day 42 shows that your anti-HIV drugs are not fighting your HIV infection well, you will come to the clinic for an additional visit within 1 to 4 weeks. This visit will take about 1 hour. At this visit, you will have a physical exam and blood drawn for additional HIV level test and possible HIV resistance testing.

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

Some of your blood will be stored and used for study-required (pharmacokinetic, virologic) testing.

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

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

Research for Pharmacogenetics – OPTIONAL **(for this study)**
If you agree, some of your blood will be tested for the human genes that affect how drugs are broken down, interact with other drugs, and potentially lead to side effects in the body. This is called pharmacogenetics.

____ (initials) I understand and I agree to this storage and use of my blood for pharmacogenetic testing.
OR
____ (initials) I understand but I do not agree to this storage or use of my blood for pharmacogenetic testing.

Please refer to Attachment I to consent for use of your samples in other studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 72 people will take part in this study—36 per arm.

HOW LONG WILL I BE IN THIS STUDY?

Most people will be on this study for six weeks (4 weeks on study treatment and two weeks of follow-up). You may be on study up to 11 weeks if you have to have additional follow-up visits to check your viral load.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- The study is stopped or cancelled
- You become pregnant
- You are not able to attend the study visits as required by the study

- You are not able to take the study drugs as required by the study
- You need a treatment that you may not take while on the study
- Your primary care provider requests it if she or he thinks the study is no longer in your best interest
- You are not able to complete the intensive PK study visits.

If you have to stop taking the study drugs before you complete the study or you are taken off the study early, you will have the following evaluations as deemed appropriate by the study doctor:
- You will have a physical exam.
- You will have approximately 1 tablespoon of blood drawn for routine lab tests for safety.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED DRUGS OR ONCE I LEAVE THE STUDY, HOW WOULD DRUGS BE PROVIDED?

The study will only provide study drugs for 28 days of the study.

If you must permanently stop taking study-provided drugs before your study participation is over, you will just continue taking your regularly prescribed anti-HIV medicines. The study staff will discuss other options that may be of benefit to you.

<u>After the study</u>
After you have completed your study participation, the study will not be able to continue to provide you with drugs you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The study will assess interaction of DTG with RPT and INH. As you may have discussed with your treating clinician, the benefits of DTG and RPT/INH, when taken in isolation, are considered to outweigh the risks. It is still important for you to be aware of the side effects of these treatments, so you and the study team can manage the risks.

One risk of this study is that taking the study drugs together might cause the level of DTG in your blood to drop too low to fight your HIV. **If DTG levels become too low, it is possible that HIV virus may start reproducing again in the body and that the current HIV medications could stop working to control the HIV virus due to development of drug resistance.** The study plans to minimize this risk in the following ways:
- Starting with a double dose of DTG in Arm 1 which, based on published data, is itself not known to carry risks
- Moving to a single dose of DTG in Arm 2 only when the initial results of Arm 1 are encouraging
- Testing your HIV viral load during the study

For Arm 1, the study requires participants to receive double the recommended dose of DTG for treatment-experienced individuals. However, there are no known risks of taking 50 mg of DTG twice a day or of DTG overdosage. Furthermore, if RPT causes the level of DTG to drop, additional dosing of DTG may compensate for this interaction.

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

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 before starting any new medications while on the study. You must also tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Use of Combination Antiretroviral Drugs

The side effects associated with combination of antiretroviral drugs may include immune reconstitution syndrome and abnormal placement of body fat.

- 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

Dolutegravir (DTG, Tivicay)

The side effects associated with dolutegravir include allergic (hypersensitivity) reactions and liver problems. See below:

- Allergic reaction which may cause a rash. You may develop a rash with any of the following signs or 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

If you develop a rash with DTG, stop taking DTG and notify the study doctor right away.

- Liver problems which may cause:
  - 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
  - Changes in liver test results, more common in people with hepatitis B or C

You are encouraged to abstain from alcohol while on the study to reduce any risk of experiencing liver problems.

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

Additional side effects include:
- Trouble sleeping
- Abnormal dreams
- Tiredness
- Headache
- Anxiety (fear, worry)
- Muscle and joint aches
- Dizziness
- Nausea/Vomiting
- Flatulence (gas in the abdomen)
- Increase in weight

Dolutegravir and Pregnancy:
Early results from a large study in Botswana of pregnant women showed a possible increased risk of certain types of serious birth defects involving the brain and spinal cord in babies born to women who were taking DTG for HIV treatment at the time of becoming pregnant or early in their pregnancy. **Further data from this study show that 0.19% of women who were taking DTG at the time they became pregnant had babies with defects, compared to 0.11% of women who were not taking DTG, however this difference is small and not statistically significant. These defects happen early in pregnancy, before many women even know they are pregnant, however the analysis of all data available is insufficient to confirm that these defects are caused by the use of DTG.** There is no increased risk of these types of birth defects among women who started dolutegravir later in pregnancy.

Rifapentine (RPT, Priftin)
The following side effects have been associated with the use of rifapentine:

- Reddish coloring of urine, sweat, sputum, saliva, tears, and breast milk. Contact lenses and dentures may be permanently stained.
- Liver damage that may include abnormal liver function tests. If you develop any of the following symptoms of liver damage, you should call your doctor right away:
  - Unexplained loss of appetite
  - Nausea and/or vomiting
  - Pale-colored stools
  - Yellowing of the eyes or skin
  - Pain in the upper abdomen
  - Dark urine
- Loss of appetite
- Low blood counts
- Low blood sugar
- Upset stomach or vomiting
- Decreased effectiveness of hormonal contraceptives and other medications, including some anti-HIV medications. Tell your doctor about all medications that you are taking.

Although rare, flu-like symptoms and hypersensitivity reactions have also been associated with rifapentine (or rifamycin family of drugs). This reaction should resolve when rifapentine is stopped. This reaction may include the following:

- Fever
- Rash
- Inflammation of the liver
- Low blood pressure
- Muscle aching
- Temporary decrease in white blood cells called lymphocytes
- Headache
- Nausea
- Vomiting

Risk of Nitrosamine Impurities

The US Food and Drug Administration (FDA) has been investigating the presence of impurities called nitrosamines in some types of medications, including rifapentine (RPT). Low amounts of nitrosamines are common in water and foods, including cured and grilled meats, dairy products, and vegetables. Everyone is exposed to some level of nitrosamines through their diet. Some types of nitrosamines have been shown to cause cancer in laboratory animals. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time (such as many years).

The study drug RPT contains small amounts of a nitrosamine impurity that could increase cancer risk gradually over time. At these amounts in the RPT to be taken for one month in

this study, the risk of developing cancer is very low. The FDA recently noted that, because TB is a potentially deadly disease that affects the lungs and sometimes other parts of the body, the risk of not taking the medicine outweighs any potential risk from nitrosamine.

Four weeks of daily RPT and isoniazid (1HP) has been shown to be safe and can prevent latent TB from becoming active. It is an accepted alternative regimen for LTBI treatment per the WHO. Use of the currently available RPT for treatment of latent TB for a short time has clear benefits, while the cancer risk is very low. All medications have risks and benefits. You should talk with your study doctor about any concerns.

As an alternative to 1HP provided in this trial, you could take 6-9 months of INH regimen that might be available to you outside of this study as a preventive TB therapy regimen. This regimen does not have any known nitrosamine impurities.

Risk of Antibacterials: Some medications used to treat TB may be associated with diarrhea (loose or watery bowels), including bloody diarrhea, which may be serious.

Isoniazid (INH)
The following side effects have been associated with the use of isoniazid:

Serious and sometimes life threatening liver damage may develop even after many months of treatment. Older age, already having some liver disease, drinking alcohol regularly and using injection drugs are all associated with an increased risk of developing liver damage. Women, particularly black and Hispanic women, or if they are pregnant or recently gave birth to a baby, may also be at increased risk of life threatening liver damage. If you develop any of the following symptoms, you should call your doctor right away:

- Unexplained loss of appetite
- Nausea and or vomiting
- Pale colored stools
- Yellowing of the eyes or skin
- Pain in the upper abdomen
- Dark urine

Additional side effects may include:

- Tingling and numbness in the hands and feet
- Memory loss, confusion, trouble sleeping, changes in behavior or mood
- Unsteadiness or dizziness
- Seizures
- Low blood counts
- Rash and itching
- High blood sugar
- Joint pain
- Reduced vitamin B_6 levels (a vitamin that helps with many functions in your body)

Risks of Drawing Blood
Taking blood may cause some discomfort, bleeding, bruising, and/or swelling where the needle

enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of TB Skin Test
In rare cases, a TB skin test can cause severe redness and swelling of the arm in people who had a positive TB skin test in the past. There have even been a few cases where this reaction was seen in people who had not had this test before.

Risks of Chest X-ray
The amount of high-energy radiation used in a chest X-ray is relatively small and does not pose any significant risk to you.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV status. Please talk with the study staff if you are worried about this.

ARE THERE RISKS RELATED TO PREGNANCY?

Dolutegravir may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant while you are taking dolutegravir. You must use one of the following barrier methods of birth control that you discuss with the study staff:

- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD) or intrauterine system
- **Condoms (male or female)**

A barrier method of birth control is required because rifapentine can prevent birth control pills and other hormonal birth control methods from working. **Hormonal methods of contraception may continue to be used during the study, however another method listed above must also be used through the duration of the study.**

Note that condom method may not be as effective as using diaphragm, or IUD.

There is also a further, relatively small, risk to an unborn baby due to ionising radiation exposure from the chest X-ray. Hence you will be required to have a confirmed negative pregnancy test before this procedure.

If you become pregnant while on study, you must discontinue study medication and study evaluations. You will be encouraged to remain on study (but off study medication) to collect pregnancy outcome data.

If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

The study drugs include 28 days of RPT and INH, so participants have a prospect of benefiting from being treated for their latent tuberculosis (TB). An alternative for treatment of latent TB is nine months of daily isoniazid (INH). You may find taking 28 days of RPT and INH to be easier and more convenient.

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. For example, the TB treatment you receive could help prevent you from developing TB. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and risk the possibility of having TB.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Enrollment in the study is voluntary. You may choose to not participate in the study.

This is a pharmacokinetic (PK) study to study interaction between a proven latent TB treatment (what is referred to as 1HP) and a DTG-2NRTIs regimen for HIV treatment. Instead of being in this study, you have the option of continuing with your current treatment or starting a new one under the care of your regular doctor or other health care provider. You may also check with your doctor about your options for treatment of latent TB under clinical care or other research studies.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have 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.

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

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

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

For Sites Outside the US

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG Statistical and Data Management Center in the United States. Your information will be combined with information from other study participants and will be used for statistical analysis of study results. Your name and other personal identifiers will not be sent to the ACTG Statistical and Data Management Center. Your research site will send your information in accordance with the laws, regulations, and policies of your country and research site.

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

WHAT ARE THE COSTS TO ME?

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. Costs may include but not limited to transportation costs, time away from work or home.

WILL I RECEIVE ANY PAYMENT?

[This section will include information on any planned reimbursement or payment to the participants. The site will complete this based on their guidelines.]

WHAT HAPPENS IF I AM INJURED?

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

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

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*
- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH.*

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

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

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. Your site will share a summary of the results when they are ready to be presented. Your study staff can answer any questions you may have.

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

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

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

ATTACHMENT I: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

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

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

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States. There is no limit on how long your extra samples will be stored.
[*Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.*]

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan.
[*Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.*]

IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

Your specimens will never be used for commercial profit. You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

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

For each of the questions below, please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection. If you wish to withdraw your consent at a later time, you should contact your site staff.

Research Without Human Genetic Testing

If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

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

Research with Human Genetic Testing

The ACTG has two studies that collect samples and consent for genetic testing:

- **A5128, Plan for Obtaining Informed Consent to use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses**

- **A5243, Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses**

Your site might ask you if you would like to participate in the study that is being done where you live. If you would like to participate, you will sign a separate consent form.

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