A5381

Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir (TLD) for First- or Second-Line ART or with Rifampicin-Containing TB Treatment: The Hakim Study

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

NIAID CRMS # 38564

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

Sponsored by:

National Institute of Allergy and Infectious Diseases

In Collaboration with:
United States President's Emergency Plan for AIDS Relief (PEPFAR)

Non-IND Protocol

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Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir (TLD) for First- or Second-Line ART or with Rifampicin-Containing TB Treatment**: The Hakim Study**

SIGNATURE PAGE

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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A5381 will be open to ACTG clinical research sites (CRSs) in Haiti, Kenya, Malawi, South Africa, Uganda, Zimbabwe**, the Philippines, and Vietnam**.

A participating CRS must be a PEPFAR-supported site or able to collaborate with a PEPFAR supported site to implement, enroll, and monitor participants.

To participate in Group 1, sites must be able to enroll participants switching from first-line ART with HIV-1 RNA >1000 copies/mL. To participate in Group 2, sites must be able to enroll participants switching from second-line ART with HIV-1 RNA >1000 copies/mL. These restrictions may change after a review of enrollment targets.

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All general questions concerning this protocol should be sent to actg.teamA5381@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5381@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5381 e-mail group. Include the protocol number in the e-mail subject line.

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

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

- Send an e-mail message to actg.coreA5381@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
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- Send an e-mail message to actg.teamA5381@fstrf.org (ATTENTION: Urvi Parikh, Carole Wallis, Kelly Dooley, and Gary Maartens).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Kathleen Donahue and **Autumn Rolack** directly.
- For other questions, send an e-mail message to actg.teamA5381@fstrf.org (ATTENTION: Kathleen Donahue and **Autumn Rolack**).
- Include the protocol number, PID, and a detailed question.

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

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

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

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

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.
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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 Division of AIDS (DAIDS) Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

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

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Telephone Calls
Sites are responsible for documenting telephone calls made to A5381 team members.
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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

3TC	lamivudine
AE	adverse event
ART	antiretroviral therapy
ATV/r	atazanavir/ritonavir
BMI	body mass index
DBS	dried blood spot
DDIs	drug-drug interactions
DTG	dolutegravir
EFV	efavirenz
FDA	US Food and Drug Administration
GCLP	**Good Clinical Laboratory Practices**
INSTI	integrase strand transfer inhibitor
LMIC	low- and middle-income countries
LPV/r	lopinavir/ritonavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NTD	neural tube defects
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
PEPFAR	United States President's Emergency Plan for AIDS Relief
PI	protease inhibitor
PLHIV	people living with HIV
PSWP	protocol-specific web page
RIF	rifampicin
TB	tuberculosis
TFV	tenofovir
TLD	tenofovir disoproxil fumarate/lamivudine/dolutegravir
TFV-DP	tenofovir-diphosphate
WHO	World Health Organization

SCHEMA

A5381

Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir (TLD) for First- or Second-Line ART or with Rifampicin-Containing TB Treatment**: The Hakim Study**

DESIGN

This is an observational, longitudinal prospective cohort study to assess therapeutic efficacy and emergence of HIV drug resistance following initiation of tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) for first- or second-line antiretroviral therapy (ART), or start of concomitant TLD and rifampicin (RIF)-containing tuberculosis (TB) treatment. To the greatest extent possible, participants will be managed according to local standards of care, and preferably in accordance with current World Health Organization (WHO) Guidelines for HIV and TB treatment and monitoring. Participants will be divided into four study groups for enrollment:

Group 1: Participants switching to TLD from a first-line regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI). These participants will be divided into two subgroups based upon their HIV-1 RNA level in a sample obtained at entry, before starting TLD. Group 1a will include participants with viremia (HIV-1 RNA >1000 copies/mL at start of TLD) and Group 1b will include participants with suppressed viremia (HIV-1 RNA ≤1000 copies/mL at start of TLD).

Group 2: Participants switching to TLD from a second-line regimen containing a boosted protease inhibitor (PI). These participants will be divided into two subgroups based upon their HIV-1 RNA level in a sample obtained at entry, before starting TLD. Group 2a will include participants with viremia (HIV-1 RNA >1000 copies/mL at start of TLD) and Group 2b will include participants with suppressed viremia (HIV-1 RNA ≤1000 copies/mL at start of TLD).

Group 3: Participants initiating concomitant TLD and RIF-containing TB treatment, with an additional daily dose of dolutegravir (DTG) 50mg. For participants already on RIF-containing TB treatment when TLD treatment is started, TLD treatment must be started within 8 weeks (56 days) of the start of RIF-containing TB treatment. Group 1, 2, or 4 participants who start RIF-containing TB treatment after enrollment will have additional evaluations at the start and end of concomitant HIV and TB treatment but will not be co-enrolled in Group 3 (their additional evaluations will, however, be considered when analyzing data from Group 3).

Group 4: ART-naïve participants initiating therapy with TLD.

DURATION Each participant will be followed for 36 months.

SAMPLE SIZE Approximately 1350 participants: 540 in Group 1 with the goal of at least 180 in Group 1a, 540 in Group 2 with the goal of at least 180 in Group 2a, 90 in Group 3, and 180 in Group 4. Participants in Group 3 who were already taking TLD at the time of study entry and who are found to have HIV-1 RNA >1000 copies/mL from the entry HIV-1 RNA test will be discontinued from the study and will be replaced.

In each group, there is a goal of enrolling 10% of participants who are adolescents aged 10 to 19 years. In Group 1a, there is also a goal to enroll 45 participants with nevirapine (NVP)-based first-line ART exposure.

POPULATION HIV-infected adults and adolescents (>30 kg, ≥10 years of age) initiating or switching to TLD and receiving care through a President's Emergency Plan for AIDS Relief (PEPFAR)-supported treatment program.

REGIMEN Observational study, no treatments are provided through A5381.

Qualifying treatment (initiated within 7 days after study entry):

For Groups 1, 2, and 4: Co-formulated tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg/dolutegravir 50 mg (TLD) taken once daily.

For Group 3: During TB treatment and for 2 weeks following completion of rifampicin-containing TB treatment, TLD taken once daily with an additional daily dose of DTG 50 mg such that DTG is taken twice daily. TB treatment will follow WHO Guidelines.

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Among participants still on tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) at 6 months of followup, the proportion achieving virologic success (HIV-1 RNA ≤1000 copies/mL) at that time will be high, specifically:

- ≥85% among participants switching from first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing and second-line protease inhibitor (PI)-containing therapy with HIV-1 RNA >1000 copies/mL at start of TLD (Groups 1a and 2a);
- ≥90% among participants switching from first-line NNRTI-containing and second-line PI-containing therapy with HIV-1 RNA ≤1000 copies/mL at start of TLD (Groups 1b and 2b);
- ≥85% among participants who are ART-naïve when starting TLD (Group 4); and the proportion with new dolutegravir (DTG) resistance mutations will be low (<5%).

1.1.2 Among participants in Group 3, the proportion achieving virologic success (HIV-1 RNA ≤1000 copies/mL) at the end of concomitant TLD (including an additional daily dose of DTG 50 mg) and rifampicin (RIF)-containing TB treatment will be high (≥85%) and the proportion with new DTG resistance mutations will be low (<5%).

1.2 Primary Objectives

1.2.1 Among participants still on TLD at 6 months of followup, to estimate the proportion achieving virologic success (HIV-1 RNA ≤1000 copies/mL) and the proportion with new DTG resistance mutations in each of the following groups:

- Participants switching from first-line NNRTI-containing therapy with HIV-1 RNA >1000 copies/mL at start of TLD (Group 1a);
- Participants switching from second-line PI-containing therapy with HIV-1 RNA >1000 copies/mL at start of TLD (Group 2a);
- Participants switching from first-line NNRTI-containing therapy with HIV-1 RNA ≤1000 copies/mL at start of TLD (Group 1b);
- Participants switching from second-line PI-containing therapy with HIV-1 RNA ≤1000 copies/mL at start of TLD (Group 2b);
- Participants who are ART-naïve when starting TLD (Group 4).

1.2.2 Among participants taking concomitant TLD (including an additional daily dose of DTG 50 mg) and RIF-containing TB treatment (Group 3), to estimate the proportion achieving virologic success (HIV-1 RNA ≤1000 copies/mL) and the proportion with new DTG resistance mutations at the end of concomitant treatment.

1.3 Secondary Objectives

1.3.1 To describe treatment outcomes at 6 months, 12 months, 24 months, and 36 months after starting TLD according to the US Food and Drug Administration (FDA) Snapshot algorithm using a threshold of ≤1000 copies/mL for virologic suppression in each of Groups, 1a, 1b, 2a, 2b, and 4; and at the end of concomitant TLD and RIF-containing TB treatment, 12 months, 24 months**,** and 36 months after starting concomitant TLD and RIF-containing TB treatment in Group 3.

1.3.2 To assess the long-term durability of TLD (up to 36 months) in suppressing viremia in each of the study groups/subgroups.

1.3.3 To assess drug resistance and accumulation of drug resistance mutations over time (up to 36 months) in the participants experiencing virologic failure in each of the study groups/subgroups.

1.3.4 To describe the frequency of toxicities leading to discontinuation of the TLD regimen in each of the study groups/subgroups.

1.3.5 To assess change in quality of life after starting TLD in each of the study groups/subgroups.

1.3.6 To describe the frequency of clinical events relevant for TLD in each of the study groups/subgroups.

1.3.7 To assess virologic success, accumulation of drug resistance mutations, frequency of toxicities leading to discontinuation of TLD, change in quality of life, and frequency of clinical events relevant for TLD over time by gender in each of the study groups/subgroups.

1.4 Exploratory Objectives

1.4.1 To assess virologic success, accumulation of drug resistance mutations, frequency of toxicities leading to discontinuation of TLD, change in quality of life, and frequency of clinical events relevant for TLD over time, specifically among participants switching from first-line nevirapine (NVP)-containing ART.

1.4.2 To assess virologic success, accumulation of drug resistance mutations, frequency of toxicities leading to discontinuation of TLD, change in quality of life, and frequency of clinical events relevant for TLD over time, specifically in adolescents (using the World Health Organization (WHO) definition of anyone aged 10 to 19 years).

1.4.3 To assess virologic success, accumulation of drug resistance mutations, frequency of toxicities leading to discontinuation of TLD, change in quality of life,

frequency of clinical events relevant for TLD over time, and pregnancy outcomes in women who are pregnant while receiving TLD.

1.4.4 To identify baseline predictors of virologic success including CD4+ cell count, HIV-1 RNA, and drug resistance mutations.

1.4.5 To assess the relationship between tenofovir-diphosphate (TFV-DP) in dried blood spot (DBS) sampling, and months 6, 12, 24, and 36 virologic failure and development of integrase inhibitor resistance mutations on TLD.

1.4.6 To estimate the rate of successful suppression of plasma HIV-1 RNA to three thresholds: ≤1000, ≤200, and <50 copies/mL at 6, 12, 24, and 36 months after starting TLD in each of the study groups/subgroups, and to compare these rates:

(a) between participants with viremia (HIV-1 RNA >1000 copies/mL) versus suppressed viremia (HIV-1 RNA ≤1000 copies/mL) at start of TLD among those switching from first-line NNRTI-containing ART (Group 1) and among those switching from second-line PI-containing ART (Group 2); and

(b) among participants with suppressed viremia (HIV-1 RNA ≤1000 copies/mL at start of TLD) switching from first-line NNRTI-containing ART (Group 1b) and among participants with suppressed viremia switching from second-line PI-containing ART (Group 2b) to that achieved among ART-naïve participants starting TLD (Group 4).

1.4.7 To assess change in body mass index (BMI) over time (up to 36 months) after starting TLD.

1.4.8 In each study group/subgroup, to describe the proportion of females of reproductive potential starting TLD who are receiving contraceptives.

1.4.9 In each study group, to describe the reproductive potential, number of live births, and fertility desires of females starting TLD.

1.4.10 To assess the metabolic complications of DTG, including hyperglycemia and hyperlipidemia.

2.0 INTRODUCTION

2.1 Background

By mid-2017, there were 20.9 million people living with HIV (PLHIV) on antiretroviral therapy (ART) worldwide [1], the majority of these being from HIV high-burden countries. The rapid rollout of ART in these countries has been made possible through support from the United States President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund, other agencies, and from in-country resources. With an HIV population of 36.7 million [1], the 90-90-90 targets (identifying 90% of PLHIV, 90% of these on ART

and achieving a viral suppression rate of 90% of those on treatment), and the ambitious target of ending the AIDS epidemic by 2030 [2], there is urgent need to identify and promote ART regimens and strategies that include drugs that can be co-formulated and have high potency, high genetic barrier to resistance, proven safety, and no food or other restrictions. Integrase strand transfer inhibitor (INSTI)-based regimens, especially those including DTG, have emerged as highly attractive regimens for ART-naïve and ART-experienced patients. Nevertheless, the recent observation of a possible increase in the risk of neural tube defects (NTD) in children born to mothers exposed to DTG during conception underscores the need to carefully monitor DTG regimens that are rolled out, irrespective of strong attributes demonstrated in clinical trials.

Antiretroviral therapy, comprising a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a NNRTIs or boosted PI, is the recognized standard of care for treatment of HIV-1 infection. These combinations have helped extend the life expectancy of many PLHIV [3-6], and are still being used as first- and second-line regimens in many countries.

In clinical trials, DTG-containing first-line ART has been better tolerated, has higher virologic efficacy, fewer drug-drug interactions (DDIs), and less frequent emergence of HIV drug resistance than efavirenz (EFV)-containing ART [7]. In August 2017, the decision was made to support rapid adoption of the single-tablet regimen of TLD as first-line and second-line ART for adults and adolescents in PEPFAR programs, with rollout starting in 2018. Countries are encouraged to include HIV-1 positive pregnant women, breastfeeding women, adolescents (from age 10 years and body weight >30 kg), and patients requiring treatment for TB (for whom an additional DTG 50 mg dose is used with RIF-based treatment) in their TLD transition planning.

In the Tsepamo study, an ongoing birth outcome surveillance study conducted in Botswana, 4 cases of NTD have been reported in 426 infants born to women who took DTG as part of combined ART at the time of conception. This represents an incidence of about 0.9% compared with an expected background rate of about 0.1% in infants born to women taking other ART at the time of conception [8].

Non-communicable diseases are becoming a significant concern in individuals living with HIV including in resource-limited settings. Obesity, especially visceral fat, is emerging as a key risk factor for several non-infectious comorbidities such as cardiovascular disease, diabetes, certain cancers, and neurocognitive disorders. There is growing recognition that obesity is prevalent in sub-Saharan Africa, with southern Africa having the highest prevalence of overweight individuals, women being more affected than men [9, 10]. Obesity is emerging as a problem for HIV-infected individuals in both resource rich and resource poor environments [11, 12]. There is a growing body of data suggesting that the use of INSTIs may have a negative impact on BMI [13-15]. There is little prospective data on the effects of INSTIs in diverse settings among diverse populations. **It is unknown whether obesity in the setting of the use of these drugs is associated with metabolic consequences. Emerging evidence suggests that the presentation of metabolic complications may be different in sub-Saharan Africa.**

2.2 Rationale

TLD Rollout

There is limited data on the performance and emergence of resistance to TLD in diverse settings. Understanding the risks and benefits of TLD rollout is a priority research question, as many programs in low- and middle-income countries (LMIC) may not use viral load testing in the transition to DTG-based, first-line ART and will not have the benefit of individual resistance testing to guide ART optimization. It is critical to monitor programmatic and clinical outcomes for patients initiating or transitioning to TLD. Consequently, to better inform policy and clinical practice moving forward, we propose to enroll a cohort study at AIDS Clinical Trial Group (ACTG) sites coincident with TLD rollout to systematically track clinical and virologic outcomes, HIV drug resistance, adverse events (AEs), and drug toxicities among diverse participant groups. The study will also actively and closely monitor birth outcomes, particularly amongst women who conceive while receiving TLD to confirm safety in pregnancy as part of the TLD rollout, as well as TB outcomes for TB patients treated with TLD while on TB therapy.

Neuropsychiatric symptoms are common with EFV. It is postulated that switching to a DTG-containing regimen will result in improved quality of life, adherence, and retention in care in support of viral suppression.

TLD as first-line ART

TLD is being recommended by PEPFAR for all first-line ART initiations. In randomized clinical trials, DTG has shown higher efficacy and lower overall risks of AEs than the NNRTI EFV (in the SINGLE trial [7]), and the protease inhibitors darunavir/ritonavir (DRV/r; in the FLAMINGO study [16]), atazanavir/ritonavir (ATV/r; in the ARIA trial [17]) and lopinavir/ritonavir (LPV/r; in the DAWNING trial [18]). Furthermore, the ARIA trial was composed entirely of women, and it confirmed that AE profiles were similar in men and women. DTG has shown similar rates of AEs to the integrase inhibitors raltegravir (in the SPRING-2 trial [19]) and bictegravir (in the Gilead 1489 and 1490 trials [20, 21]).

TLD as second-line ART

The current WHO guidelines for second-line treatment recommend two NRTIs and LPV/r, ATV/r, or DTG after failure of an NNRTI-based first-line regimen [22]. The most significant challenges with this current WHO recommendation are side effects and DDIs. In an effort to simplify treatment and minimize or avoid long term toxicities, various studies have been performed or are currently underway to determine alternatives to the currently recommended second-line regimens [23]. The search continues for durable regimens that are simple, safe and tolerable, provide superior virologic efficacy, and have less frequent emergence of resistance. Initial data from the ViiV-sponsored DAWNING study of best available NRTIs plus DTG in participants on failing first-line, NNRTI-containing ART showed excellent virologic efficacy, tolerability, and superiority to 2 NRTI + LPV/r, although at least one active NRTI by genotype analysis was required for study entry [18]. TLD is likely to be used as a second-line regimen in most PEPFAR-supported countries regardless of resistance to NRTIs. However, current WHO guidelines [22] recommend that patients who received TDF/emtricitabine (XTC) in first-line ART should switch to azidothymidine (AZT)/XTC for second-line treatment; if the

recycled TDF/3TC backbone is found to be virologically effective, TLD would be preferable to AZT/3TC/DTG, due to lower toxicity and single tablet formulations. A switch to TLD is also being considered for individuals on second-line ART with 2 NRTI + LPV/r or ATV/r. Use of TLD in both treatment-naïve and treatment-experienced PLHIV is programmatically very attractive because it facilitates distribution of drug, thus minimizing supply chain interruptions and lowering cost compared to current first- or second-line regimens.

HIV Resistance to Dolutegravir

HIV drug resistance is an important consideration when contemplating DTG for treatment. Use of DTG for second-line treatment when extensive NRTI resistance is present may increase the risk of development of HIV drug resistance. DTG without an effective NRTI agent has been recently reported to incompletely suppress viremia and select for DTG resistance in at least 10% of individuals [24, 25]. Many studies in LMIC have shown that prolonged failure of first-line NNRTI-containing ART can cause extensive NRTI resistance, including tenofovir (TFV) and lamivudine (3TC) resistance, which could increase the risk of both TLD failure and the emergence and spread of DTG resistance. The ACTG A5288 study of people failing second-line ART showed triple class mutations in 27% of participants, and 22% of participants had three or more thymidine analog mutations (TAMS). This level of resistance could increase the risk of TLD failure. Importantly, the effect of some common drug-resistance mutations (K65R, M184 I/V, TAMs) in combination is unknown, and must be evaluated for their impact on response to TLD, although recent subanalyses [26] from the DAWNING study are reassuring that DTG-containing regimens perform well regardless of prior NRTI exposure when WHO recommended NRTIs were used in combination. Furthermore, some of these mutations (K65R, M184I/V) reduce viral fitness; this may result in high DTG efficacy, even if both NRTIs are compromised. Nevertheless, TLD for second-line ART requires additional study of outcomes among groups at higher potential risk of TLD failure in LMIC.

In addition, RIF-containing therapy for TB co-infection complicates the use of TLD because of DDIs potentially affecting TFV and DTG pharmacokinetics, drug exposure, and efficacy.

Cohort Rationale

This cohort study will provide critical information on the frequency of treatment failure and new drug resistance rates after initiation of TLD in higher-risk groups (Groups 1, 2, and 3). The study could identify patient groups with suboptimal responses to TLD, which could be studied in a subsequent randomized comparison of alternative ART regimens.

Adolescents on ART pose a special concern because of issues related to adherence, use of substances, and mental health. These issues impact viral suppression rates and treatment outcomes. This study is not more than minimal risk, as enrolled adolescents must be receiving a DTG-containing regimen as part of their medical care, and a small volume of blood will be collected per the Schedule of Evaluations (SOE) to assess primary endpoints. There are no additional procedures.

Group 1: Individuals switching to TLD from a first-line regimen containing an NNRTI
Among individuals taking NNRTI-based first-line ART, some will be suppressed and others will be viremic. Patients who are viremic may have NRTI resistance and be at risk of functional DTG monotherapy after switching to TLD with the potential to fail on TLD with emergence of DTG resistance. Studies in LMIC have shown that prolonged failure of first-line, NNRTI-containing ART can cause extensive NRTI resistance, including TFV and 3TC resistance [26-29]. DTG monotherapy has been reported to incompletely suppress viremia and select for DTG resistance in at least 10% of individuals [24, 25]. However, it is not known if DTG monotherapy carries the same resistance risk as DTG plus 2 NRTIs with genotypic evidence of resistance to those NRTIs, as this has never been investigated prospectively. High quality evidence demonstrating the long-term efficacy of DTG alongside a compromised NRTI backbone is also lacking. There is evidence from A5353 that dual therapy with DTG and emtricitabine is efficacious in individuals with VL < 100000 c/ml. This provides some reassurance that even in the setting of some resistance a TLD combination will be effective. Group 1 will include individuals who are viremic or have unknown plasma HIV-1 RNA status as well as those who are known to have suppressed plasma HIV-1 RNA to facilitate comparison of outcomes between these subgroups.

Group 2: Individuals switching to TLD from a second-line regimen containing a boosted PI
Individuals on a second-line regimen containing a boosted PI may have viremia, HIV-1 RNA suppression, or unknown HIV-1 RNA status. It is unknown if patients with prior first-line regimen failure but current suppression on a second-line boosted PI regimen will maintain virologic suppression if they are switched to DTG with the same or different NRTI. In addition, there is currently no data on DTG use for patients not suppressed on a second-line, PI-containing regimen. This group will provide longitudinal data and critical information about the frequency of treatment failure and drug resistance after switching to TLD, comparing the subgroup that is suppressed to the subgroup that is not virologically suppressed on a second-line boosted PI regimen.

Group 3: Participants initiating concomitant TLD (including an additional daily dose of DTG 50 mg) and RIF-containing TB treatment
RIF is a critical component of first-line TB treatment. RIF induces hepatic drug metabolizing enzymes and drug transport proteins. It increases clearance of many drugs, including DTG. In healthy volunteers, RIF reduced DTG levels by about 30%. This reduction can be overcome by giving DTG 50 mg twice a day. In the INSPIRING trial, Dooley et al. demonstrated that DTG 50 mg twice a day, given during concomitant RIF-based therapy achieved target trough concentrations, was safe, and demonstrated high HIV treatment efficacy and a good immunologic response through week 48 [30-32]. The study provides evidence that DTG is effective and well tolerated in adults with HIV/TB coinfection who are receiving RIF-based TB treatment. WHO currently recommends that the dose of DTG be increased to 50 mg BID for patients who are on concurrent RIF-based TB regimen. As TLD is widely rolled out and DTG is administered with RIF-based TB regimens, there is need for data on effectiveness of TLD with an additional dose of DTG 50 mg with RIF in patients with TB/HIV co-infection in different clinical settings, including among individuals with low CD4 count.

Perinatal outcomes are negatively affected by concomitant TB and HIV infections. Moreover, there is growing evidence that RIF affects the exposure of several commonly used contraceptive agents potentially making them less effective. Sites should follow local guidelines with respect to contraceptive counseling.

Group 4: Treatment-naïve individuals initiating therapy with TLD
Treatment-naïve individuals initiating therapy with TLD will serve as a parallel comparator group for treatment-experienced individuals who switch to TLD, and for individuals who switch to or start TLD and require RIF-based treatment for TB.

3.0 STUDY DESIGN

A5381 is an observational, longitudinal prospective cohort study to assess therapeutic efficacy and emergence of HIV drug resistance following initiation of TLD for first- or second-line ART provided through PEPFAR-supported sites. Participants will be managed according to local standards of care, and preferably in accordance with current WHO Guidelines for HIV and TB treatment and monitoring. Participants will be divided into four study groups for enrollment and analysis:

Group 1: Participants switching to TLD from a first-line regimen containing an NNRTI. These participants will be divided into two subgroups based upon their HIV-1 RNA level in a sample obtained at entry, before starting TLD: Group 1a will include participants with viremia (HIV-1 RNA >1000 copies/mL at start of TLD), and Group 1b will include participants with suppressed viremia (HIV-1 RNA ≤1000 copies/mL at start of TLD).

Group 2: Participants switching to TLD from a second-line regimen containing a boosted PI. These participants will be divided into two subgroups based upon their HIV-1 RNA level in a sample obtained at entry, before starting TLD: Group 2a will include participants with viremia (HIV-1 RNA >1000 copies/mL at start of TLD), and Group 2b will include participants with suppressed viremia (HIV-1 RNA ≤1000 copies/mL at start of TLD).

Group 3: Participants who are initiating concomitant TLD and RIF-containing TB treatment with an additional daily dose of DTG 50 mg within 7 days after entry. This includes:

- Participants on TLD at screening, and initiating RIF-containing TB treatment within 7 days after entry. For these participants to be eligible, TLD treatment must have been taken for at least 6 consecutive calendar months before initiation of RIF-containing TB treatment.
- Participants on RIF-containing TB treatment at screening, and initiating TLD within 7 days after entry. These participants may be ART-naïve, or may be switching from a first- or second-line ART regimen. TLD treatment must be started within 8 weeks (56 days) of the start of RIF-containing TB treatment.
- Participants who are initiating both TLD and RIF-containing TB treatment within 7 days after entry. These participants may be ART-naïve, or may be switching from a first- or second-line ART regimen.

NOTE: Participants who are enrolled in Groups 1, 2, or 4 and start RIF-containing TB treatment while on study will have additional evaluations at the start and end of concomitant treatment. These participants will not be co-enrolled in Group 3 (their additional evaluations will however be considered when analyzing data from Group 3).

Group 4: ART-naïve participants initiating therapy with TLD.

The study will enroll approximately 1350 participants: 540 in Group 1 with the goal of at least 180 in Group 1a, 540 in Group 2 with the goal of at least 180 in Group 2a, 90 in Group 3, and 180 in Group 4.

The 90 participants in Group 3 do not include those already enrolled in Group 1, 2, or 4. Participants in Groups 1, 2, and 4 who start RIF-containing treatment during followup will have additional samples obtained at the start and end of concomitant treatment and will also be included in the Group 3 analysis.

There are additional enrollment goals to provide information about outcomes on TLD in adolescents and individuals with NVP-based first-line ART exposure. In each group, there is a goal of enrolling 10% of participants who are adolescents aged 10 to 19 years. In Group 1a, there is also a goal to enroll 45 participants with NVP-based first-line ART exposure.

Visits will include collection of plasma and DBS samples, and collection of medical history, safety (including pregnancy outcomes) and tolerability data. Plasma HIV-1 RNA will be batch tested regularly (e.g., monthly) in samples obtained per the SOE, and will be collected for retrospective testing per the SOE. Given reports of incomplete CD4+T-cell recovery on DTG-containing regimens [33], CD4+/CD8+ testing will be done per the SOE in section 6.1.

Confirmed virologic failure is defined as HIV-1 RNA >1000 copies/mL based on two consecutive plasma HIV-1 RNA viral load measurements at or after 6 months from starting TLD. If virologic failure occurs, on-treatment samples will be analyzed for evidence of immunologic failure, for TFV-DP levels in DBS, and genotypic and phenotypic analysis will be performed retrospectively on paired samples (entry and virologic failure) to assess the emergence of new drug resistance including to DTG.

To support generalizability of results, to the extent practically possible, sites will approach all individuals starting TLD within the PEPFAR program for screening to determine eligibility and study participation. However, recognizing that testing of samples to determine HIV-1 RNA at start of TLD will be done after enrollment, enrollment may be restricted to selected sites as the study proceeds to achieve the targeted sample sizes of all Groups and subgroups. Specifically, a review of the relative enrollment into Group 1a versus 1b, and into Group 2a versus 2b, will be undertaken when 25% and 50% of the planned enrollment has been reached in Group 1 and Group 2. After these reviews, enrollment may be restricted to selected sites if this might help achieve the targeted

sample sizes. For example, enrollment to Group 1 (or to Group 2) may need to be restricted to sites with higher proportions of participants with elevated HIV-1 RNA levels identified in samples obtained at the start of TLD. In addition, enrollment may be increased over the targets to facilitate reaching the enrollment goals for adolescents and participants switching from NVP-based first-line ART. **To participate in Group 1, sites must be able to enroll participants switching from first-line ART with HIV-1 RNA >1000 copies/mL. To participate in Group 2, sites must be able to enroll participants switching from second-line ART with HIV-1 RNA >1000 copies/mL. These restrictions may change after a review of enrollment targets.**

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Receiving care at a PEPFAR-supported site.

4.1.2 Documentation of HIV-1 infection acceptable to the local PEPFAR-supported program to allow antiretroviral (ARV) treatment to be initiated or continued.

4.1.3 Age ≥10 years.

4.1.4 Ability and willingness of participant or legal guardian/representative to provide informed consent to participate in the study.

4.1.5 Expectation that the participant will receive care within the local PEPFAR-supported program and will be able to be followed for study evaluations for at least 6 months and ideally for 36 months.

4.1.6 Group 1 participants:
Receipt of an NNRTI-containing first-line ARV regimen from a clinic in a PEPFAR-supported country for at least 6 consecutive calendar months prior to study entry.

NOTE: ARV treatment gaps are allowed, but treatment gaps should not exceed 14 consecutive days in the 6 calendar months prior to study entry.

Group 2 participants:
Receipt of a boosted PI-containing second-line ARV regimen from a clinic in a PEPFAR-supported country for at least 6 consecutive calendar months prior to study entry.

NOTE: ARV treatment gaps are allowed, but treatment gaps should not exceed 14 consecutive days in the 6 calendar months prior to study entry.

Group 4 participants:
No current or prior ARV treatment.

NOTE: Women who received ARV regimens only during pregnancy and/or breastfeeding for prevention of mother-to-child transmission but who have not taken any ARV drugs for at least 6 calendar months immediately prior to study entry will be allowed.

4.1.7 For Group 1, 2, and 4 participants, expected initiation of TLD taken once daily within 7 days after study entry.

NOTE: Group 1, 2, and 4 participants may not be on, or expected to start, RIF-containing TB treatment at the time of study entry.

4.1.8 For Group 3 participants already on RIF-containing TB treatment but not on TLD at study entry, expected initiation of TLD taken once daily with an additional daily dose of DTG 50 mg. This must be started within 7 days after study entry AND within 56 days after the start of RIF-containing TB treatment. These participants may be ART-naïve, or may be switching from a first- or second-line ART regimen.

NOTE: For ART-naïve participants who start RIF-containing TB treatment first and then start TLD at a later date, screening **must** occur within 14 days before the intended TLD start date.

4.1.9 For Group 3 participants not already on RIF-containing TB treatment but already on TLD at study entry, receipt of TLD for at least 6 consecutive calendar months prior to study entry AND expected initiation of RIF-containing TB treatment within 7 days after study entry.

4.1.10 For Group 3 participants not already on RIF-containing TB treatment or TLD at study entry, expected initiation of TLD and RIF-containing TB treatment within 7 days after study entry. These participants may be ART-naïve, or may be switching from a first- or second-line ART regimen.

4.1.11 For Group 1 participants, HIV-1 RNA >1000 copies/mL obtained as part of standard of care or with a real-time test within 12 weeks prior to study entry at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

4.1.12 For Group 2 participants, HIV-1 RNA obtained as part of standard of care or with a real-time test within 12 weeks prior to study entry at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

a. If Group 2b reaches its enrollment target of 360 participants, the protocol team will notify sites that the following criteria will be implemented: For Group 2 participants, an HIV-1 RNA >1000 copies/mL

will need to be obtained as part of standard of care or with a real-time test within 12 weeks prior to study entry.

b. If Group 2a reaches its enrollment target of 180 participants, the protocol team will notify sites that the following criteria will be implemented: For Group 2 participants, an HIV-1 RNA ≤1000 copies/mL will need to be obtained as part of standard of care or with a real-time test within 12 weeks prior to study entry.

4.2 Exclusion Criteria

4.2.1 Weight ≤30 kg.

4.2.2 For participants already on ART in Groups 1, 2, and 3, known to have had an ART interruption encompassing the entire 14 day window (≥14 consecutive days) immediately prior to study entry.

4.2.3 For Group 3, if a participant is already taking TLD at the time of study entry, HIV-1 RNA >1000 copies/mL within the past 9 months while taking TLD with no subsequent HIV-1 RNA ≤1000 copies/mL.

4.2.4 Prior enrollment in any group in this study.

4.2.5 For Group 3 participants, already on concomitant TLD and RIF-containing TB treatment prior to study entry.

4.2.6 For Group 2 participants with HIV-1 RNA >1000 copies/mL from a host country in which treatment guidelines require a genotypic test prior to switching patients on a boosted PI-containing second-line ARV regimen to TLD, 65R RT mutation within 12 weeks prior to study 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 Division of AIDS (DAIDS) Protocol Registration Office (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 NOT* be reviewed or approved by the DAIDS PRO. Sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the

DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in 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 parent or legal representative if the participant is younger than 18 years of age or under guardianship) will be asked to read and sign the approved protocol consent form. For those under the age of consent, assent will also be obtained according to the local IRB requirements and regulations.

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 **Study** 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 protocol, 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

- 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 A5381 protocol chairs.

- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

This is an observational study; no treatment is provided.

Qualifying treatment (initiated within 7 days after study entry):

For Groups 1, 2, and 4: Co-formulated tenofovir disoproxil fumarate 300 mg/Lamivudine 300 mg/Dolutegravir 50 mg (TLD) taken once daily.

For Group 3: During TB treatment and for 2 weeks following completion of rifampicin-containing TB treatment, TLD taken once daily with an additional daily dose of DTG 50 mg such that DTG is taken twice daily. TB treatment will follow WHO Guidelines.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: Schedule of Evaluations for Participants Who Enter the Study in Group 1, 2, or 4

Evaluation	Screening	Entry	Post Entry Evaluations (Months)							Virologic Failure Confirmation	Initiating Concomitant TLD/RIF-Based Treatment	Ending Concomitant TLD/RIF-Based Treatment	Premature TLD Disc. Evals	Premature Study Disc. Evals
	- 2 Weeks	Day 0	3	6	12	18	24	30	36	≤ 6 Months After Initial Failing Viral Load	- 1 Week Prior to Starting RIF	+ 4 Weeks	+ 4 Weeks	
			± 2 Weeks		± 4 Weeks									
Documentation of HIV	X	**X**												
Medical History	X	X												
ART, TB, & Contraception Medication History	X	X												
Adherence Assessment	X	X												
Clinical Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X			X	X		X		X					X
Quality of Life Questionnaire		X		X										
Fertility Desires Questionnaire		**X**	**See section 6.3.8**											
CD4+/CD8+		X							X	X			X	X
HIV-1 RNA, Real-Time For Groups 1 and 2 Only	**X See section 6.3.10**													

Evaluation	Screening	Entry	Post Entry Evaluations (Months)							Virologic Failure Confirmation	Initiating Concomitant TLD/RIF-Based Treatment	Ending Concomitant TLD/RIF-Based Treatment	Premature TLD Disc. Evals	Premature Study Disc. Evals
	- 2 Weeks	Day 0	3	6	12	18	24	30	36	≤ 6 Months After Initial Failing Viral Load	- 1 Week Prior to Starting RIF	+ 4 Weeks	+ 4 Weeks	
			± 2 Weeks		± 4 Weeks									
HIV-1 RNA, Batch Test Monthly		X		X	X		X		X	X	X	X	X	X
HIV-1 RNA, Retrospective			X			X		X						
Plasma Resistance Testing - Standard Genotype	**Group 2 Only; See section 6.3.10**	X								X	X		X	
Plasma Resistance Testing - Next Generation Sequencing Genotype		X								X	X		X	
Plasma Resistance Testing - Phenotype		X								X	X		X	
DBS for TFV-DP				X	X		X		X	X			X	X
Stored Plasma		X	X	X	X	X	X	X	X	X	X	X	X	X
Stored Whole Blood		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Stored Serum		**X**		**X**	**X**		**X**		**X**					
Remote data collection			**When necessary; see section 6.2.2**											

Table 6.1-2: Schedule of Evaluations for Participants Who Enter the Study in Group 3

Evaluation	Screening	Entry	Ending Concomitant TLD/RIF Treatment	Post Entry Evaluations (Months)					Virologic Failure Confirmation	Premature TLD Disc. Evals	Premature Study Disc. Evals
	- 2 Weeks	Day 0	+ 4 Weeks	12	18	24	30	36	≤ 6 Months After Initial Failing Viral Load	+ 4 Weeks	
				± 4 Weeks							
Documentation of HIV	X	**X**									
Medical History	X	X									
ART, TB, & Contraception Medication History	X	X									
Adherence Assessment	X	X									
Clinical Assessments		X	X	X	X	X	X	X	X	X	X
BMI	X		X	X		X		X			X
Quality of Life Questionnaire		X	X								
Fertility Desires Questionnaire		**X**	**See section 6.3.8**								
CD4+/CD8+		X						X	X	X	X
HIV-1 RNA, Batch Test Monthly		X	X	X		X		X	X	X	X
HIV-1 RNA, Retrospective					X		X				
Plasma Resistance Testing - Standard Genotype		X							X	X	
Plasma Resistance Testing - Next Generation Sequencing Genotype		X							X	X	
Plasma Resistance Testing - Phenotype		X							X	X	
DBS for TFV-DP			X	X		X		X	X	X	X
Stored Plasma		X	X	X	X	X	X	X	X	X	X
Stored Whole Blood		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Stored Serum		**X**	**X**	**X**		**X**		**X**			
Remote data collection			**When necessary; see section 6.2.2**								

Table 6.1-3: Schedule of Site Evaluations

Evaluation	Timepoint
Documentation of PEPFAR Site SOC	Annually at each site, beginning with enrollment of its first participant

6.2 Timing of Evaluations

6.2.1 Screening and Entry Evaluations

Screening evaluations must be completed within 14 days prior to study entry unless otherwise specified **(see sections 4.1 and 4.2)**. Screening and entry evaluations can be done on the same day or on different days.

NOTE: For ART-naïve participants who start RIF-containing TB treatment first and then start TLD at a later date, screening should be delayed until within 14 days before the intended TLD start date.

In addition to data being collected on participants who enroll into the study, demographic and clinical data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

For participants who are starting TLD:

- Screening and entry evaluations must occur before the participant starts TLD.
- Participants must begin TLD treatment within 7 days after entry.
- If, immediately prior to starting TLD, the participant is known to have missed ≥14 consecutive days of the prescribed first- or second-line ART, any remaining entry evaluations should not be performed and the participant should be discontinued from the study (refer to sections 6.2.3 and 9.2).

For Group 3 participants already on TLD and are starting RIF-containing TB treatment:

- Screening and entry evaluations must occur before the participant starts RIF-containing TB treatment.
- Participants must begin RIF-containing TB treatment within 7 days after entry.

6.2.2 Post Entry Evaluations

Post Entry Evaluations
All participants will be followed for 36 months, with evaluations per the SOE irrespective of changes in ART.

Post entry evaluations are calculated from the date of study entry and are targeted to be scheduled per the SOE. Data and samples that cannot be collected during the appropriate visit window, as specified in the SOE, can be collected outside of the window during an unscheduled visit.

Virologic Failure Confirmation
If a failing HIV-1 RNA sample is collected as part of standard of care 6 or more months after TLD initiation (or, in Group 3, after the end of concomitant TLD and RIF-containing TB treatment), then virologic failure confirmation evaluations should occur within 6 months or earlier, to be consistent with country guidelines, after the collection of that initial failing HIV-1 RNA sample. Adherence counseling may occur as part of standard of care between the visit at which the initial failing HIV-1 RNA sample was drawn and the confirmatory virologic failure visit.

If possible, the virologic failure confirmation evaluations should coincide with the next scheduled study visit. If these do coincide, required evaluations should be conducted only once, even when evaluations are listed for both time points. For example, if the participant has a viral load result indicating viremia (HIV-1 RNA >1000 copies/mL) from the 12 month visit, then the virologic failure confirmation evaluations and the 18 month evaluations should be done once at the 18 month visit.

If the participant has been switched to a new therapy prior to the virologic failure confirmation visit, then record the medication modifications per section 6.3.5, and continue the virologic failure confirmation visit per the SOE.

Initiating Concomitant TLD/RIF-Containing TB Treatment, for Participants Who Enter the Study in Group 1, 2, or 4
Evaluations for initiating concomitant TLD/RIF-containing TB treatment are performed only for participants who initiated concomitant TLD/RIF-containing TB treatment after study entry. These evaluations must be performed within one week prior to the participant starting RIF-containing TB treatment.

Ending Concomitant TLD/RIF-Containing TB Treatment
Evaluations for ending concomitant TLD/RIF-containing TB treatment must be performed within 4 weeks after the end of concomitant treatment.

NOTE: For Group 3 participants, the Ending Concomitant TLD/RIF-Containing TB Treatment visit is expected to occur within the first year on study.

Premature TLD Discontinuation Evaluations
Participants who permanently discontinue TLD while on the study will have the TLD discontinuation evaluations performed within 4 weeks after TLD discontinuation. Participants who discontinue TLD will continue to be followed on study.

Remote Data Collection
Study visits may be conducted remotely (e.g., telephone, telehealth) in the following situations:

- **A participant is unable to attend a visit because of personal illness, illness among others in his or her home, or local conditions or guidelines restricting travel to the clinic.**

- **The site is temporarily unable to conduct non-essential visits in the clinic; the site must inform the core team (actg.corea5381@fstrf.org) once when it has to stop non-essential visits.**

Regardless of the situation, sites should document which visits were conducted remotely, attempt to obtain as much of the visit-specific required information, based on the SOE, as possible, and record it. The impacted visits and rationale must be reported and documented, following instructions provided by the team or network leadership.

The need for remote data collection, whether by site or across the network, is expected to be time-limited in relation to the COVID-19 pandemic. Each site should inform the core team when it is able to return to the conduct of non-essential visits. In consultation with ACTG Network leadership and the study sponsor, the protocol team may determine when remote data collection across the network is no longer required. When such a determination is made, study sites will be formally notified. In all cases, it is the sites' responsibility to inform their IRBs/ECs as needed.

6.2.3 Premature Study Discontinuation Evaluations

Premature Study Discontinuation Evaluations for Registered Participants Who Do NOT Start TLD (Groups 1, 2, and 4) or Who Do NOT Start Concomitant TLD and RIF-Containing Treatment (Group 3)
All eCRFs must be keyed for the period up to and including the entry visit, but further followup is not required for these participants.

Premature Study Discontinuation Evaluations for Participants Who Started TLD (Groups 1, 2, and 4) or Who Started Concomitant TLD and RIF-Containing Treatment (Group 3)
Participants will have the premature study discontinuation evaluations performed prior to being taken off the study.

6.3 Instructions for Evaluations

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

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

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of

Adult and Pediatric Adverse Events (DAIDS AE Grading Table), and AE and toxicity reporting requirements.

6.3.1 Documentation of HIV-1

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

For participants who are <25 years of age at the time of study entry, document if the participant acquired HIV-1 infection perinatally.

6.3.2 Medical History

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

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

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

6.3.3 ART, TB, **and Contraception** Medication History

ART and TB Medication History is performed per the SOE. A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Contraceptive Medication History is performed at entry for females of reproductive potential only.

NOTE: Start and stop dates are not recorded for Contraceptive Medication History.

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Complete History
TB treatment	For Group 3 Participants, History of the Current Period of TB Treatment
Contraceptives expected to be effective at the present time	**Last 6 Months**

6.3.4 Adherence Assessment

At screening, entry, and within 24 hours prior to TLD initiation (If TLD is initiated >24 hours after entry), assess adherence to prescribed ART medications over the prior 14 days. The adherence assessment evaluation should be conducted just once if screening, entry, and TLD initiation occur on the same day.

Document if an adherence assessment was performed post-entry as part of the participant's clinical care.

Detailed adherence assessments are not recorded on the eCRF.

See sections 4.2.2 and 9.2 for adherence requirements.

6.3.5 Clinical Assessments

Documentation of Clinical Events
See section 8.2 for collection requirements for pregnancy.

Breastfeeding is not recorded on the eCRF.

Post-entry, record the following targeted events regardless of grade:
- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Death
- Depression
- Diabetes
- Immune Reconstitution Inflammatory Syndrome (IRIS) conditions
- Suicidal ideation
- Suicide attempt
- Tuberculosis
- HIV-associated nephropathy

All clinical events that are recorded must have their severity graded. To grade clinical events, site must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Refer to section 7.1 for AE collection requirements.

Gynecological History
At entry, all female participants will be asked about reproductive potential, including history of bilateral oophorectomy and hysterectomy, and postmenopausal status. Female participants of reproductive potential will be asked about their last menstrual period, history of intermenstrual bleeding, number of live births, and year of births.

NOTE: "Postmenopausal" is defined as amenorrhea for at least 12 consecutive months prior to study entry (in the absence of medications known to induce amenorrhea), and have a documented follicle-stimulating hormone (FSH) release factor measurement >40 mIU/mL or a result in the testing laboratory's menopausal range. If an FSH level is not available, "postmenopausal" is defined as 24 consecutive months of amenorrhea prior to study entry (in the absence of medications known to induce amenorrhea). Follicle-stimulating hormone documentation is not reported on an eCRF.

Documentation of Creatinine Results
At entry and post-entry, record serum creatinine test results from any testing performed as part of the participant's clinical care or as part of another ACTG or non-ACTG study.

ART Treatment Modifications
At entry and post-entry, record all ART medication modifications, including initial doses, participant-initiated modifications, and inadvertent and deliberate interruptions of more than 14 consecutive days since the last visit. Record any permanent discontinuation of treatment.

TB Medication Modifications
At entry and post-entry, record all TB medication modifications, including initial doses, participant-initiated modifications, and inadvertent and deliberate interruptions of more than 14 consecutive days since the last visit. Record any permanent discontinuation of treatment.

6.3.6 BMI

At screening, record height and weight for all participants.

NOTE: Only weight is an exclusionary criterion (see section 4.2.1).

Post entry, record weight for all participants. Record height only for participants who were age 10-19 years at study entry.

6.3.7 Quality of Life Questionnaire

The quality of life questionnaire will be administered per the SOE. The questionnaire is administered by the site staff, and requires an additional 10 minutes of the participant's time.

The quality of life questionnaire includes the ACTG SF-21 questionnaire and additional questions. The questionnaire is posted on the DMC Portal in the Forms Management Utility.

6.3.8 Fertility Desires Questionnaire

The fertility desires questionnaire will be administered for female participants of reproductive potential who are ≥18 years of age. The questionnaire will be administered at entry. If a participant is already enrolled by the time the questionnaire is added to the SOE, then the questionnaire will be administered at the next scheduled study visit. The questionnaire is posted on the DMC Portal in the Forms Management Utility.

6.3.9 Immunologic Studies

CD4+/CD8+
Record absolute CD4+/CD8+ counts per the SOE. If available, also record CD4+/CD8+ percentages per the SOE. For entry and post-entry evaluations, all laboratories must possess DAIDS Immunology Quality Assessment (IQA) **certification**. CD4+/CD8+ results will only be shared with the treatment site if the evaluation at the time point is part of standard of care, as described in the national guidelines followed by the treatment site. Refer to the Manual of Procedures (MOPS) for additional instructions for sharing CD4+/CD8+ results.

6.3.10 Virologic Studies

HIV-1 RNA
Plasma HIV-1 RNA must be obtained by a laboratory that possesses DAIDS Virology Quality Assurance (VQA) **certification**.

Batch test and retrospective HIV-1 RNA results will only be shared with the treatment site if the evaluation at the time point is part of standard of care, as described in the national guidelines followed by the treatment site. HIV-1 RNA results will be shared with the treatment site and participant if the participant is prematurely discontinued from the study as a direct consequence of the HIV-1

RNA test result, as described in section 9.2. Refer to the MOPS for additional instructions for sharing HIV-1 RNA results.

HIV-1 RNA, Real-Time For Groups 1 and 2 Only
Plasma HIV-1 RNA may be performed in real-time at screening within 12 weeks prior to study entry for participants who are being screened for Groups 1 or 2. The real-time screening plasma HIV-1 RNA must be performed after confirmation that the participant meets all other eligibility criteria for Group 1 or 2 (see sections 4.1 and 4.2, and the MOPS). Screening plasma HIV-1 RNA testing must be done at a network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

Plasma HIV-1 RNA, Batch Test Monthly
Plasma HIV-1 RNA for monthly batch testing is collected per the SOE.

Plasma HIV-1 RNA, Retrospective
Plasma HIV-1 RNA will be collected per the SOE, and tested retrospectively.

Plasma Resistance Testing – Standard Genotype, Next Generation Sequencing Genotype (NGS), and Phenotype
Standard genotype, NGS genotype, and phenotype plasma resistance samples will be collected for all participants per the SOE.

For participants in screening for Group 2a in countries that require exclusion of the 65R RT mutation before switching to TLD, standard genotype testing will be performed in real-time after confirmation of eligibility for Group 2 and HIV-1 RNA >1000 copies/mL within 12 weeks prior to study entry (see sections 4.1 and 4.2, and the MOPS).

For participants with viremia (HIV-1 RNA >1000 copies/mL) at the 6 month visit (for Groups 1, 2, and 4) or at the Ending Concomitant TLD/RIF Treatment (for Group 3), standard genotype testing will be performed near-time using a stored plasma sample.

For participants with confirmed viremia (HIV-1 RNA >1000 copies/mL at the virologic failure confirmation visit), the following standard genotype samples that were drawn per the SOE will be batch tested near-time, and the NGS genotype and phenotype samples that were drawn per the SOE will be batch tested retrospectively:

- The virologic failure plasma resistance sample
- The entry plasma resistance samples will be tested at the same time as the virologic failure sample only if the participant had HIV-1 RNA >1000 copies/mL at entry
- The Premature TLD Discontinuation visit plasma resistance sample (for participants who have this visit)

- The Initiating Concomitant TLD/RIF-Based Treatment plasma resistance sample (for participants who have this visit)

Standard genotype and NGS genotype testing results will be shared with the treatment site in aggregate, if requested, 6 months after the end of the study.

Phenotype testing will not be shared with the treatment site or the participant.

Standard genotype, NGS genotype, and phenotype resistance testing results will be submitted to the DMC by the testing lab and will not be collected on an eCRF.

DBS for TFV-DP
Two dried blood spot samples for TFV-DP will be collected at the virologic failure confirmation timepoint. One DBS sample will be collected at all other timepoints indicated in the SOE. Dried blood spot samples for TFV-DP will be used to perform intracellular TFV-DP concentration measurements as a quantitative assessment of adherence in patients who fail therapy, for use as matched controls in the pharmacology nested case-control study (refer to section 11.3), and for future tests.

Dried blood spot for TFV-DP results will not be shared with the treatment site or the participant. Dried blood spot for TFV-DP results will not be recorded on an eCRF. Refer to section 11.0 for additional pharmacology plan details.

Stored Plasma
Stored plasma will be collected per the SOE, and stored for future protocol-required tests.

6.3.11 Stored Whole Blood

Whole blood will be collected per the SOE, and stored for retrospective hemoglobin A1c testing.

6.3.12 Stored Serum

Serum will be collected per the SOE, and stored for retrospective lipid and chemistry testing.

6.3.13 Documentation of PEPFAR Site SOC

Each site will record a description of SOC at the PEPFAR site and submit relevant country guidelines per the Schedule of Site Evaluations (Table 6.1-3). **Refer to the MOPS for additional instructions.**

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Adverse Event Collection Requirements for this protocol

A5381 is an observational study and does not require Expedited Adverse Event (EAE) reporting to DAIDS via the DAIDS Adverse Experience Reporting System (DAERS).

All **AEs** must be recorded on the eCRFs if the following criteria has been met.

- **All events, regardless of grade, that caused a change in TLD or TB medications, and that are considered to be related to TLD or TB medications.**

All **AEs** must have their severity graded. To grade **AEs**, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

For reporting purposes, a voluntary MedWatch form may be submitted to the FDA by the site investigator for all TLD or TB related side effects that are "unexpected" per the latest version of the package insert. This protocol will use form FDA 3500 for voluntary reporting of adverse events. Instructions for completing MedWatch Form 3500 are found at https://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm. Sites are requested to forward the MedWatch report to the RSC. A copy of the MedWatch report should be sent to the DAIDS clinical representative via the RSC Safety Office. Upon submission of such a report to the regulatory authority, a copy of the report should be provided to the Protocol Team and DAIDS RSC via email.

Site investigators are required to report to the site IRB as per the IRB requirements. Site investigators are responsible for following the in-country regulatory authority's reporting requirements for observational studies.

7.2 Study Monitoring

The Protocol Core Team will monitor the conduct of the study via regular summaries of accrual, study discontinuation, and data completeness, as appropriate.

The study will undergo interim review as described in section 10.5.

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

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Toxicity will be managed by the primary care provider per standard of care.

8.2 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.

Pregnancy Outcomes and Reporting
If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Pregnant women will continue on study and will follow the schedule outlined in section 6.0. Pregnancy outcome will be submitted on an eCRF at the end of the pregnancy.

8.3 Breastfeeding

Sites should follow local guidelines to prevent mother-to-child transmission during breastfeeding.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

This study is observational. All decisions about TLD discontinuation will be made by the participant's primary care provider.

9.2 Premature Study Discontinuation

The intent of the study is to follow all participants for 36 months irrespective of changes in ART. The following are therefore reasons for participant discontinuation from the study:

- For Groups 1 and 2, and Group 3 if the participant is on ART prior to entry, participant is known to have had an ART interruption encompassing the entire 14 day window (≥14 consecutive days**)** of prescribed first- or second-line ART immediately prior to initiating TLD.
- Participant does not start taking TLD or RIF (if already taking TLD at study entry) within 7 days after the entry visit.

- For Group 3 participants who were already taking TLD at the time of study entry, HIV-1 RNA >1000 copies/mL from the entry HIV-1 RNA test. These participants will be replaced.
- Request by the participant to withdraw.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, National Institute of Allergy and Infectious Diseases (NIAID), Office for Human Research Protections (OHRP), PEPFAR, other government agencies as part of their duties, or investigator.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is an observational, longitudinal prospective cohort study to assess therapeutic efficacy and emergence of HIV drug resistance following initiation of TLD for first- or second-line ART, or start of concomitant TLD and RIF-containing TB treatment. Participants will be enrolled into Groups 1, 2, 3, or 4 (see section 3.0 for definitions). However, for analysis purposes, Groups 1 and 2 will each be subdivided into two subgroups according to the results of HIV-1 RNA testing on samples obtained at the time of start of TLD: Groups 1a and 2a will include participants with viremia (HIV-1 RNA >1000 copies/mL) and Groups 1b and 2b will include participants with suppressed viremia (HIV-1 RNA ≤1000 copies/mL).

The design of this study is driven by a desire to estimate the virologic success rate at 6 months after starting TLD (Groups 1a, 1b, 2a, 2b, and 4), and at the end of concomitant TLD and RIF-containing TB treatment (Group 3), with good precision and to identify high rates of virologic failure with new drug resistance mutations in each of the group/subgroups as quickly as possible. Therefore, enrollment will proceed as quickly as possible, regardless of site distribution. As such, it is recognized that the study population will be a convenience sample of people starting TLD.

However, recognizing that testing of samples to determine HIV-1 RNA at start of TLD will be done after enrollment, enrollment may be restricted to selected sites as the study proceeds in order to achieve the targeted sample sizes (refer to section 3.0).

10.2 Outcome Measures

The following outcome measures will be evaluated for the purposes of characterizing outcomes in each of the study groups.

10.2.1 Primary Outcome Measures

10.2.1.1 For Groups 1, 2, and 4:

Virologic success, defined as suppression of plasma HIV-1 RNA to ≤1000 copies/mL, at 6 months after starting TLD. This will be based on the measurement closest to exactly 6 months (i.e., 183 days) after the date of start of TLD, within the window of 6 months ±3 months (specifically 92 to 274 days, inclusive).

For participants experiencing virologic failure (HIV-1 RNA >1000 copies/mL) at 6 months after starting TLD, new DTG resistance mutations defined as those present at **the time of the failing measurement** that were not present at the time of starting TLD.

10.2.1.2 For Group 3:

Virologic success, defined as suppression of plasma HIV-1 RNA to ≤1000 copies/mL, at the end of concomitant TLD (including an additional daily dose of DTG 50 mg such that DTG is taken twice daily) and RIF-containing TB treatment. This will be the measurement closest to the end of concomitant treatment within the window of 4 weeks (28 days) before the end to 6 months (183 days) after the end, inclusive.

For participants experiencing virologic failure (HIV-1 RNA >1000 copies/mL) at the end of concomitant TLD (including an additional daily dose of DTG 50 mg such that DTG is taken twice daily) and RIF-containing TB treatment, new DTG resistance mutations defined as those present at **the time of the failing measurement** that were not present at the time of starting TLD.

10.2.2 Secondary Outcome Measures

10.2.2.1 Treatment outcome measure based on the FDA Snapshot algorithm at 6 months, 12 months, 24 months, and 36 months after starting TLD in each of Groups, 1a, 1b, 2a, 2b, and 4; and at the end of concomitant TLD and RIF-containing TB treatment, 12 months, 24 months, and 36 months after starting concomitant TLD and RIF-containing TB treatment in Group 3.

Based on the FDA Snapshot algorithm, participants' outcomes will be grouped into the following three categories:

- HIV-1 RNA ≤1000 copies/mL
- HIV-1 RNA >1000 copies/mL (also includes participants who discontinued study/TLD for Other Reasons [e.g., withdrew

consent, loss to followup, moved, etc.] while >1000 copies/mL; and participants who changed ART)
- No Virologic Data (participants will be grouped by the following reasons: on study but missing data in window; discontinued study/TLD due to AE or death; discontinued study/TLD for other reasons [e.g., withdrew consent, loss-to-followup])

10.2.2.2 Suppression of plasma HIV-1 RNA to ≤1000 copies/mL at months 12, 24, and 36.

10.2.2.3 Time to confirmed virologic failure (VF), defined as the time from start of TLD to the first HIV-1 RNA >1000 copies/mL at or after 6 months which is confirmed by the next HIV-1 RNA measurement also being >1000 copies/mL (irrespective of the time between the initial and confirmatory measurements provided that they are obtained on different days, and irrespective of ART being received at the times of these measurements).

10.2.2.4 Time to confirmed virologic failure (as defined above) with a new DTG resistance-associated mutation detected in population-based sequencing (i.e., one not present in the last population-based sequence obtained prior to initiating TLD).

10.2.2.5 Time from start of TLD to TLD discontinuation.

10.2.2.6 Time from start of TLD to TLD discontinuation due to toxicity.

10.2.2.7 Summary score of quality of life measure.

10.2.2.8 Time from start of TLD to first occurrence of a targeted clinical event (a list of targeted clinical events to be considered is provided in section 6.3.5).

10.2.3 Exploratory Outcome Measures

10.2.3.1 Suppression of plasma HIV-1 RNA to three thresholds: ≤1000, ≤200, and <50 copies/mL at months 6, 12, 24, and 36

10.2.3.2 Change in CD4+ cell count from entry to 36 months.

10.2.3.3 TFV-DP levels in DBS.

10.2.3.4 BMI. For adolescents, WHO BMI z-score will be used.

10.2.3.5 Change in HbA1C from study entry at each measurement time during follow-up.

10.2.3.6 Change in lipid measurements from study entry at each measurement time during follow-up.

10.3 Randomization and Stratification

There is no randomization in this study.

10.4 Sample Size and Accrual

A sample size of 180 participants each in Groups 1a, 2a, and 4; 360 participants each in Groups 1b and 2b; and 90 participants in Group 3 has been chosen to address the primary objectives. It is expected that accrual will take approximately 18 months after the first participant enrolls into the study.

NOTE: The 90 participants in Group 3 does not include those already enrolled in Groups 1, 2, or 4. Participants in Groups 1, 2, and 4 who start RIF-containing treatment during followup will have additional samples obtained at start and end of concomitant treatment and will be included also in the Group 3 analysis. In addition, Group 3 participants who were already taking TLD at the time of study entry and who were found to have HIV-1 RNA >1000 copies/mL from the entry HIV-1 RNA test will be discontinued from the study and replaced.

The larger sample sizes of 360 participants (with HIV-1 RNA ≤1000 copies/mL at start of TLD) in each of Groups 1b and 2b reflect the overall goal of enrolling 180 participants in each of Groups 1a and 2a (with HIV-1 RNA >1000 copies/mL at start of TLD), recognizing that testing of samples to determine HIV-1 RNA at start of TLD will be done after enrollment. The sample size of 360 participants is therefore an estimate which assumes that about one-third of participants in each of Groups 1 and 2 have HIV-1 RNA >1000 copies/mL at the start of TLD. Enrollment may be restricted to selected sites as the study proceeds in order to achieve the targeted sample sizes. The study design includes a review after 25% and 50% of the targeted sample size has been achieved in Group 1b and Group 2b to allow for the possibility that enrollment will need to be restricted to sites which enable the relative numbers in Groups 1a versus 1b, or 2a versus 2b, to be achieved.

The sample size goals are driven by a desire to estimate the virologic success rate at 6 months after starting TLD among those still on TLD at 6 months in each of Groups 1a, 1b, 2a, 2b and 4 or at the end of concomitant TLD and RIF-containing TB treatment in Group 3 with good precision. Table 10.4-1 shows two-sided 95% confidence intervals (CI) and precision for selected observed virologic success rates and sample sizes.

For Groups 1a, 2a, and 4, with the planned sample size of 180 participants in each, the width of a 95% CI will be approximately ±5.2% if the success rate is 85% as hypothesized (maximally, the width would be ±7.3% if the success rate was 50%). Even if as many as 20% of participants are lost to followup or discontinue TLD before 6 months, the precision of the estimated success rate among those remaining on TLD at

that time will still be good: 95% CI width of ±5.9% for success rate of 85% based on 144 participants on TLD (maximally ±8.2% if the success rate is 50%).

For Groups 1b and 2b, with the planned sample size of 360 participants in each, the width of a 95% CI will be approximately ±3.1% if the success rate is 90% as hypothesized (maximally, the width would be ±5.2% if the success rate was 50%). Even if as many as 20% of participants are lost to followup or discontinue TLD before 6 months, the precision of the estimated success rate among those remaining on TLD at that time will still be good: 95% CI width of ±3.5% if the success rate is 90% based on 288 participants on TLD (maximally ±5.8% if the success rate is 50%).

For Group 3, with the planned sample size of 90 participants, the width of a 95% CI will be approximately ±7.4% if the success rate is 85% as hypothesized (maximally, the width would be ±10.4% if the success rate was 50%). Even if as many as 20% of participants are lost to followup or discontinue TLD before the end of concomitant TLD and RIF-containing TB treatment in Group 3, the precision of the estimated success rate among those remaining on TLD at that time will still be good: 95% CI width of ±8.3% if the success rate is 85% based on 72 participants on TLD (maximally ±11.6% if the success rate is 50%).

As a point of reference, the following are results based on the FDA Snapshot algorithm in DTG-containing arms from previous clinical trials:

- STRIIVING: Among participants who were virally suppressed (HIV-1 RNA <50 copies/mL) on first-line ART, 85% of the participants on DTG-containing ART achieved HIV-1 RNA <50 copies/mL at 24 weeks.
- DAWNING: Among participants failing (HIV-1 RNA ≥400 copies/mL) first-line NNRTI-containing ART, 82% of participants on DTG-containing ART achieved HIV-1 RNA <50 copies/mL at 24 weeks.
- INSPIRING: Among HIV/TB coinfected ART-naïve participants, 81% of the participants on DTG-containing ART achieved HIV-1 RNA <50 copies/mL at 24 weeks.
- SINGLE: Among ART-naïve participants, 92% of the participants on DTG-containing ART achieved HIV-1 RNA <50 copies/mL at 24 weeks.

NOTE: Instead of using the FDA Snapshot approach, our target for the primary outcome of the proportion with virologic success (HIV-1 RNA ≤1000 copies/mL) in each group/subgroup are restricted to those on TLD at 6 months.

Table 10.4-1: Two-Sided 95% Confidence Interval (CI) and Precision for Selected Observed Virologic Success Rates and Sample Sizes

Number of Participants in Group	Observed Virologic Success Rate	Two-Sided 95% CI*	Precision
90	50%	[39.7%, 60.3%]	±10.4%
	70%	[60.5%, 79.5%]	±9.5%
	75%	[66.1%, 83.9%]	±9.0%
	80%	[71.7%, 88.3%]	±8.3%
	85%	[77.6%, 92.4%]	±7.4%
	90%	[83.8%, 96.2%]	±6.2%
180	50%	[42.7%, 57.3%]	±7.3%
	70%	[63.3%, 76.7%]	±6.7%
	75%	[68.7%, 81.3%]	±6.4%
	80%	[74.2%, 85.8%]	±5.9%
	85%	[79.8%, 90.2%]	±5.2%
	90%	[85.6%, 94.4%]	±4.4%
360	50%	[44.8%, 55.2%]	±5.2%
	70%	[65.3%, 74.7%]	±4.8%
	75%	[70.5%, 79.5%]	±4.5%
	80%	[75.9%, 84.1%]	±4.2%
	85%	[81.3%, 88.7%]	±3.7%
	90%	[86.9%, 93.1%]	±3.1%

*Confidence Interval based on Wald (normal approximation to the binomial) Method

We expect the proportion of participants experiencing virologic failure (HIV-1 RNA >1000 copies/mL) with new DTG resistance mutations to be low at 6 months after starting TLD. As a point of reference, no participants in the DTG-containing arms of the above clinical trials had detectable treatment-emergent resistance-associated mutations at week 24. Table 10.4-2 shows 95% two-sided CIs and precision for selected sample sizes and observed cumulative proportions with virologic failure and new drug resistance mutations.

NOTE: Many of the participants in the aforementioned clinical trials had screening resistance testing and were susceptible to at least one NRTI. Individuals eligible for this study may be failing for a longer time without regular virologic monitoring and have more accumulated resistance.

Table 10.4-2: Two-Sided 95% Confidence Interval (CI) and Precision for Selected Sample Sizes and Observed Cumulative Proportions with Virologic Failure and New DTG Resistance Mutations

Number of Participants in Group	Observed Cumulative Proportion with Virologic Failure and New DTG Resistance Mutations	Two-Sided 95% CI*	Precision
90	1%	[0.0%, 5.8%]	±2.9%
	5%	[1.5%, 11.7%]	±5.1%
	10%	[4.7%, 18.1%]	±6.8%
	15%	[8.3%, 24.1%]	±7.9%
	20%	[12.3%, 29.8%]	±8.7%
	25%	[16.5%, 35.2%]	±9.4%
180	1%	[0.1%, 3.8%]	±1.9%
	5%	[2.3%, 9.3%]	±3.5%
	10%	[6.0%, 15.3%]	±4.7%
	15%	[10.1%, 21.1%]	±5.5%
	20%	[14.4%, 26.6%]	±6.1%
	25%	[18.9%, 32.0%]	±6.6%
360	1%	[0.2%, 2.7%]	±1.2%
	5%	[3.0%, 7.8%]	±2.4%
	10%	[7.1%, 13.6%]	±3.3%
	15%	[11.5%, 19.1%]	±3.8%
	20%	[16.0%, 24.5%]	±4.3%
	25%	[20.6%, 29.8%]	±4.6%

*Confidence Interval based on Exact (Clopper-Pearson) Method

10.5 Data and Safety Monitoring

This study will be reviewed by the ACTG ARTS TSG Study Monitoring Committee (SMC). The first review of virologic and safety outcomes will occur approximately 12 months after the enrollment of the first participant. Thereafter, reviews will be completed every 6 months until all participants should have completed the 6 month visit (Groups 1, 2, and 4) or the “ending concomitant TLD/RIF-based treatment” visit (Group 3). Thereafter, reviews will be completed every 12 months. Throughout, the SMC may request additional reviews but the study will be reviewed by the SMC at least annually. A review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team.

At each interim review, safety outcomes in all groups/subgroups will be reviewed, and virologic outcomes in groups/subgroups with at least 25% of the planned enrollment having HIV-1 RNA results at 6 months of followup (Groups 1a, 1b, 2a, 2b, and 4) or at the end of concomitant TLD/RIF-based treatment (Group 3) will be reviewed to ensure participants' safety.

Efficacy outcome data will only be provided to the SMC while the study is ongoing (unless otherwise recommended by the SMC) except **that** results **may** be made available for public dissemination when **50% of the targeted accrual in a particular group/subgroup have completed the 6 month time point (for Groups 1, 2, and 4) or the Ending Concomitant TLD/RIF Treatment (for Group 3) (including from standard resistance testing), and when** follow up is complete for all participants in a particular group/subgroup through to key time points, specifically 6, 12, 24, and 36 months **(including from standard resistance testing)**. **Group 1a results may also be made available for public dissemination when 50% of the targeted accrual to Group 1b have completed the 6 month time point. Similarly, Group 2a results may also be made available for public dissemination when 50% of the targeted accrual to Group 2b have completed the 6 month time point.**
The primary role of the interim reviews is to evaluate whether there are any unexpectedly high failure or HIV resistance rates, or safety concerns. In addition, the reviews will evaluate whether there are any issues with study conduct (e.g., low data completeness or unexpectedly high rate of loss to followup).

Interim results provided at each SMC review will include: accrual, loss to followup, data completeness for primary outcomes, mortality, TLD discontinuations, AEs associated with TLD discontinuation, birth outcomes, primary virologic outcome measure, HIV resistance, the secondary treatment outcome measure based on the FDA Snapshot algorithm, and confirmed virologic failure. Results will be provided by group/subgroup.

The study team will monitor the conduct of the study via regular summaries of accrual, study discontinuation, and data completeness. In the event that the study team becomes aware of a possible safety issue during the study, the study team including the DAIDS clinical representative may refer the issue to the SMC for review.

10.5.1 Guideline for Monitoring Virologic Outcomes

As a guideline for monitoring the primary outcome of virologic suppression at 6 months after starting TLD (Groups 1a, 1b, 2a, 2b, and 4), and at the end of concomitant TLD and RIF-containing TB treatment (Group 3), a possible efficacy concern will be triggered if the upper bound of the two-sided 95% repeated CI for the proportion suppressed among those still on TLD at the measurement time is below the targeted proportion for the relevant group/subgroup as specified in the study hypotheses (see section 1.0). The repeated CI takes account of the multiple interim analyses that may be undertaken and will be calculated using the Lan and DeMets method with an O'Brien and Fleming spending function. Since early interim analyses (i.e., based on <50% information) can be extremely conservative, the nominal confidence level used at any interim analysis will be

capped at 99.9%. If there is a possible efficacy concern, the SMC may make a recommendation to release the interim information for the affected group/subgroup to the study team and sponsors. In making a recommendation, the SMC may consider findings for other outcome measures and in specific subpopulations (e.g., the type of NNRTI-containing therapy in Groups 1a and 1b). Table 10.5-1 illustrates potential observed proportions with virologic success at 6 months after starting TLD (Groups 1a, 1b, 2a, 2b, and 4) or at the end of concomitant TLD and RIF-containing TB treatment (Group 3), where the upper bound of the two-sided 95% repeated CI is below the pre-specified hypothesized proportion for the relevant group/subgroup at interim analyses with 25% and 50% information on the primary outcomes.

Table 10.5-1: Observed Proportions with Virologic Success at 6 Months After Starting TLD (Groups 1a, 1b, 2a, 2b and 4) or at the End of Concomitant TLD and RIF-containing TB Treatment (Group 3) with the Upper Bound of the Two-Sided 95% Repeated CI Is Below the Pre-Specified Hypothesized Proportion for the Relevant Group/Subgroup at an Interim Analyses with 25% or 50% Information on the Primary Outcomes.

Percentage of Participants Evaluated at 6 Months	Group / Subgroup	Number Evaluated	Observed Proportion with Virologic Success	95% Repeated CI*
25%	1a	45	61%	[37.1%, 84.9%]
	1b	90	74%	[58.8%, 89.2%]
	2a	45	61%	[37.1%, 84.9%]
	2b	90	74%	[58.8%, 89.2%]
	3	23	50%	[15.7%, 84.3%]
	4	45	61%	[37.1%, 84.9%]
50%	1a	90	71%	[57.2%, 84.8%]
	1b	180	81%	[72.6%, 89.4%]
	2a	90	71%	[57.2%, 84.8%]
	2b	180	81%	[72.6%, 89.4%]
	3	45	64%	[43.3%, 84.7%]
	4	90	71%	[57.2%, 84.8%]

*Based on the O'Brien and Fleming stopping guideline assuming four equally spaced analyses, 99.9% (using a standard cap 99.9%) and 99.61% nominal confidence levels are used at interim analyses where 25% and 50%, respectively, of the planned enrollment have completed the 6 month visit (Groups 1a, 1b, 2a, 2b, 4) or ending concomitant TLD/RIF-based treatment visit (Group 3).

10.6 Analyses

A detailed Statistical Analysis Plan for addressing the primary and secondary outcomes will be developed prior to enrollment of participants. The following provides a brief overview of the general approach.

As noted above, efficacy outcome data will only be provided to the SMC while the study is ongoing (unless otherwise recommended by the SMC) except **that** results **may** be made available for public dissemination when **50% of the targeted accrual in a particular group/subgroup have completed the 6 month time point (for Groups 1, 2, and 4) or the Ending Concomitant TLD/RIF Treatment (for Group 3) (including from standard resistance testing), and when** follow up is complete for all participants in a particular group/subgroup through to key time points, specifically 6, 12, 24, and 36 months **(including from standard resistance testing)**. **Group 1a results may also be made available for public dissemination when 50% of the targeted accrual to Group 1b have completed the 6 month time point. Similarly, Group 2a results may also be made available for public dissemination when 50% of the targeted accrual to Group 2b have completed the 6 month time point.**

10.6.1 Primary Analyses

The primary objectives regarding virologic success rates will be addressed by computing the proportion of participants in each study group/subgroup for whom virologic success has been achieved (based on the primary outcome measure) together with the associated two-sided 95% Wald CI. To account for multiple interim analyses that may be undertaken, a 95% repeated CI will be calculated using the Lan and DeMets method with an O'Brien and Fleming spending function.

The primary objective regarding drug resistance will be addressed by computing the cumulative proportion of participants in each study group with virologic failure and new DTG drug resistance mutations together with the associated two-sided 95% CI. The two-sided 95% CI will be calculated using the Exact method since the proportion experiencing VF with new drug resistance mutations is expected to be low.

The primary analysis will be restricted to participants who have not permanently discontinued TLD prior to the time of the qualifying HIV-1 RNA measurement, but the reasons for discontinuation of TLD beforehand will also be documented (including the possibility that discontinuation was motivated by efficacy failure though this is considered unlikely during the first 6 months of TLD as HIV-1 RNA and CD4 count monitoring is not generally conducted with such frequency in programs with PEPFAR-supported treatment). Although this is a reasonable presumption, if it is not the case, a sensitivity analysis will be undertaken to take account of such discontinuations in calculating the proportion.

10.6.2 Secondary Analyses

Virologic success at scheduled visit weeks will be analyzed using the same approach for the primary analysis and summaries of plasma HIV-1 RNA results will be provided.

The proportion of participants in each of the treatment outcome categories as defined by FDA Snapshot algorithm will be calculated together with the associated two-sided 95% Wald CI.

Patterns of drug resistance mutations at study entry and failure will be summarized for participants who experienced virologic failure.

Reported toxicities will be tabulated. Premature treatment discontinuation will be summarized with detailed reasons provided.

For time to event outcome measures, Kaplan-Meier estimates will be used to characterize the distribution of time to the event; the Kaplan-Meier estimate with the event will be obtained together with the associated 95% CI calculated using the Greenwood variance. For analyses of time to VF, the analysis will be based on the discrete scheduled measurement times and will be censored after the last scheduled HIV-1 RNA measurement; for other “time to event” analyses, time will be considered as continuous and censoring will be at the time of the last time of contact with the participant that provides the necessary evaluations to define the outcome measure. Sensitivity analyses will be undertaken to evaluate whether censoring due to participant loss to followup affects the conclusions that might be drawn from the analysis.

Comparisons between groups with respect to the primary outcome measure will be based on estimating the difference in proportions with the associated 95% CI. Comparisons adjusted for baseline characteristics will also be undertaken. However, it is a recognized limitation of the study that enrollment to different groups may be differential among sites, and there may be unmeasured confounding variables that might influence the interpretation of the differences between groups.

Comparisons by gender for primary and secondary outcome measures will also be undertaken within each group/subgroup. Details will be described in the Statistical Analysis Plan. It is recognized that this comparison may have limited precision and that it will be important to consider differential representation of males versus females among sites.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

Refer to section 1.4.5.

11.2 Pharmacology Study Design

Dried blood spot samples will be collected for all study participants per the SOE (section 6.1) and Instructions for Evaluations (section 6.3.9). Dried blood spot samples will be collected, stored, and shipped as per the LPC.

11.2.1 Methods and Timing for Assessing, Recording, and Analyzing PK Outcome Measures

Sparse sampling will be performed as per the SOE in section 6.1. A single pre-dose PK sample will be collected at each visit, approximately 24 hours following the preceding day's dose. The time of the sample collection as well as the last dose time will be strictly recorded.

11.2.2 Pharmacokinetics: Blood Collection, Processing, and Storage

The blood sample for measurement of TFV-DP concentrations will be collected by direct venipuncture. Whole blood will be spotted from the tube onto a Whatman 903 DBS card. Detailed blood processing, handling, and storage procedures can be found in the A5381 Laboratory Processing Chart (LPC).

11.2.3 Laboratory Performing the Assays

Intracellular TFV-DP concentrations from whole blood DBS samples will be determined by a validated high-performance liquid chromatography procedure performed according to written standard operating procedures. The intraday accuracy and intraday precision will be obtained with quality control samples, which will be analyzed concurrently with each set of volunteer samples. Quality control procedures will be in place to ensure stability of sample materials.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

To assess the relationship between TFV-DP in DBS and virologic failure at month 6, 12, 24, and 36 on TLD, a nested case control study will be done by randomly selecting one control for each case of virologic failure on TLD (defined as HIV-1 RNA >1000 copies/mL). Controls (defined as HIV-1 RNA ≤1000 copies/mL) will be matched for group, site, and duration on TLD. TFV-DP concentrations will be analyzed as continuous variables and as one of five categories developed from a healthy volunteer study [34]. For continuous variable analyses TFV-DP concentrations below the limit of quantification of the assay will be assigned a value of 0.5 × lower limit of quantification. Distribution of TFV-DP concentrations will be compared for cases and controls. C-statistic will be calculated to assess discrimination. Thresholds will be determined using the five categories of TFV-DP and from continuous variable analyses. Multivariable models will be developed to adjust for other factors predictive of virologic failure (age, sex, duration on ART, nadir CD4 count, group).

An exploratory analysis will be done to assess the relationship between TFV-DP in DBS and emergence of integrase inhibitor resistance mutations in cases with virologic failure at month 6, 12, 24, and 36 on TLD who have had resistance testing done.

11.4 Anticipated Outcomes

An overall virologic failure rate of 10% is expected. DBS samples from these participants will be used to estimate adherence, and the quantitative relationship between TLD adherence and virologic failure will be explored.

There will be no overall correlation between DBS TFV-DP concentrations and virologic outcomes; however, at any given visit, absence of drug at one or more of the participant's preceding visits will be associated with HIV-1 RNA >1000 copies/mL.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form 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 Clinical Research Site 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.

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, the site monitors, the NIAID, the OHRP, PEPFAR, 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 documents (Appendices I, II, and III) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). 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, parent, 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, NIAID, OHRP, PEPFAR, and other local, US, and international regulatory entities as part of their duties, or designee.

13.3 Study Discontinuation

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

14.0 PUBLICATION OF RESEARCH FINDINGS

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

15.0 BIOHAZARD CONTAINMENT

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

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APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol: A5381

Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir (TLD) for First- or Second-Line ART or with Rifampicin-Containing TB Treatment**: The Hakim Study**

FINAL Version 2.0, 03/05/21

SHORT TITLE FOR THE STUDY: Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of TLD

SUMMARY

This study is research. Your participation is voluntary. If you choose not to participate, it will not change your medical care or your access to antiretroviral (ARV) HIV medication.

PURPOSE: The purpose of this observational study is to see how successful the ARV drug combination called Tenofovir-Lamivudine-Dolutegravir (TLD) is at treating HIV.

NUMBER OF PARTICIPANTS: About 1350 people will take part in this study

LENGTH OF STUDY: You will be in this study for about 3 years.

REQUIRED ACTIVITIES: At every visit, you will have blood collected from a vein in your arm. You will also be asked questions about your current anti-HIV and anti-tuberculosis (TB) medications, and about any new HIV or TB diagnoses.

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

This is an observational study of the antiretroviral HIV medication that you are receiving locally. So, the risks of taking those medications are not part of this study. Your medical provider should give you that information.

BENEFITS: There will be no direct benefit to you if you take part in this study.

INTRODUCTION

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

1. You are living with human immunodeficiency virus (HIV-1), and you will soon start taking the antiretroviral (ARV) drug combination called Tenofovir-Lamivudine-Dolutegravir (TLD).

   OR

2. You are living with HIV-1 and tuberculosis (TB), you have started or will soon start taking the ARV drug combination TLD, and you have started or will soon start taking the TB medication that includes the drug rifampicin.

You are encouraged to discuss the risks and benefits of TLD with your clinician.

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?

TLD is being used more widely across the world to treat HIV. This is an observational study (a type of study in which participants are observed and certain outcomes are measured). The aim of this study is to observe how successful TLD is at treating HIV, in the following groups of people:

- People switching to TLD, after taking anti-HIV medication that contains a NNRTI drug (non-nucleoside reverse transcriptase inhibitor, such as Efavirenz or Nevirapine) (Group 1).
- People switching to TLD, after taking anti-HIV medication that contains a PI drug (protease inhibitor, such as Lopinavir or Atazanavir) (Group 2).
- People taking TLD and receiving medication for TB that includes the drug rifampicin (Group 3). These people must be starting one or both of these medications when they enter the study.
- People starting TLD who have not taken anti-HIV medication before (Group 4).

Another goal of this study is to use genetic testing of the virus (HIV) to see how often HIV is resistant to TLD. Genetic testing of the virus is one way to see if the TLD medication is not working to treat your HIV infection.

The United States Food and Drug Administration (US FDA) has approved Tenofovir, Lamivudine, and Dolutegravir for treatment of HIV.

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

If you enter the study
If you decide to take part in this research study, after you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. If you are eligible for the study and you choose to enroll, you will have the entry evaluations done. You have to start taking TLD or rifampicin (if you are already taking TLD) within 7 days after this entry visit to remain on the study. You will have up to 7 scheduled visits on this study. Your last visit will be about 3 years after you enter the study.

- You will be seen at the clinic 3 months and 6 months after your screening and entry visit.
- Or, if you are receiving treatment for TB when you start the study, you will have one visit within 4 weeks after you finish taking your TB treatment. This visit will be in the first year after your screening and entry visit.
- You will then be seen at the clinic about once every 6 months.

Study visits may be conducted remotely (like over the telephone) if you are unable to attend a visit for any of the following reasons:

- **You are sick.**
- **Someone in your home is sick.**
- **Local conditions or guidelines restrict travel to the clinic.**
- **The site is temporarily unable to have these visits in the clinic.**

If any of the following events occur, you may have to come back to the clinic for an additional visit. If possible, these visits will coincide with your next scheduled visit.

- Virologic failure confirmation: If a test to see how much HIV is in your blood shows that your anti-HIV medication might not be helping you, you will have a visit about 6 months later.
- Starting rifampicin-Based TB treatment: If you start taking TB medicine that includes rifampicin while also taking TLD for HIV, you will have a study visit.
- Ending rifampicin-Based TB Treatment: If you finish taking TB medicine that includes rifampicin while also taking TLD for HIV, you will have a study visit.
- TLD Discontinuation: If you stop taking TLD while on the study, you will have a study visit, and then continue on study.
- Early Study Discontinuation (Leaving the Study Early): If you leave the study early, you will be asked to return to the clinic for one final visit.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information is being collected from you so that AIDS Clinical Trial Group (ACTG) researchers may help determine whether there are patterns or common reasons why people do not join a 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, CD4 cell count, viral load) information will be collected from you.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns and/or common reasons why people do not join a study.
CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used to check the level of anti-HIV medications in your blood, and for immunologic and viral testing that is required for this study.

Samples collected from you will be stored in the **United States**. **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.**

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

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

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

<u>A5381 Study Visits</u>
The study staff can answer any questions you have about individual study visits, and how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

Appendix I Table 1: Study Schedule for Groups 1, 2, and 4. You will follow this study schedule if you are <u>not</u> receiving treatment for TB when you start the study.

Evaluation	Screening Visit	Entry Visit	Post Entry Visits (Months)							Unscheduled Visits				
			3	6	12	18	24	30	36	Virologic Failure Confirmation	Starting Rifampicin-Based TB Treatment	Ending Rifampicin-Based TB Treatment	TLD Discontinuation	Early Study Discontinuation
Documentation of HIV Status	√	√												
Medical & Medication History	√	√												
Adherence Assessment	√	√												
Clinical Evaluations		√	√	√	√	√	√	√	√	√	√	√	√	√
Height & Weight	√			√	√		√		√					√
Quality of Life Questionnaire		√		√										
Fertility Desires Questionnaire		√	**At one visit if you did not have the questionnaire at Entry**											
Blood Collection	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Appendix I Table 2: Study Schedule for Group 3. You will follow this study schedule if you <u>are</u> receiving treatment for TB when you start the study.

Evaluation	Screening Visit	Entry Visit	Post Entry Visit	Post Entry Visits (Months)					Unscheduled Visits		
			Ending Rifampicin-Based TB Treatment	12	18	24	30	36	Virologic Failure Confirmation	TLD Discontinuation	Early Study Discontinuation
Documentation of HIV Status	√	√									
Medical & Medication History	√	√									
Adherence Assessment	√	√									
Clinical Evaluations		√	√	√	√	√	√	√	√	√	√
Height & Weight	√		√	√		√		√			√
Quality of Life Questionnaire		√	√								
Fertility Desires Questionnaire		√	**At one visit if you did not have the questionnaire at Entry**								
Blood Collection		√	√	√	√	√	√	√	√	√	√

Description of Study Procedures
Documentation of HIV Status: Your HIV infection status will be documented.

Medical & Medication History: You will be asked questions about your medical and medication history, and you will be asked about past and current anti-HIV and anti-TB medications that you have taken or are taking.

Adherence Assessment: You will be asked about adherence to your anti-HIV or anti-TB medications (how you are currently taking your medications).

Clinical Evaluations: You will be asked questions about any new HIV and TB diagnoses, and you will be asked about any changes in the anti-HIV and anti-TB medications that you are taking. Other health events will be reviewed. This information will be shared with you, if applicable.

Height & Weight: Your height and weight will be measured. If you are over 19 years old when you enter the study, your height will only be measured at screening.

Quality of Life Questionnaire: You will be asked questions about how you feel and how you have been sleeping.

Fertility Desires Questionnaire: If you can become pregnant, you will be asked at entry about your plans for having children. If you are already in the study when this questionnaire is added, then at your next scheduled study visit, you will be asked about your plans for having children.

Blood Collection: You will have between **about 10 mL** (**1 tablespoon**) and **about 52** mL (**3.5 tablespoons**) of blood drawn **at each visit** for some or all of the following tests:

- To test how much HIV is in your blood (viral load).
- To test how many CD4/CD8 cells (infection-fighting cells) are in your blood.
- For genetic testing of the virus (HIV). This testing is done to see if the TLD medication is a good choice of medication to treat your HIV infection.
- For a dried blood spot. The dried blood spot test will be used to test how much anti-HIV medication is in your blood, or will be stored for future tests.
- To be stored for future tests.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 1350 people will take part in this study

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 3 years.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- The study is stopped or cancelled.
- You are not able to attend the study visits as required by the study.
- You are taking HIV medications before switching to TLD, and you missed 14 or more days in a row of those medications immediately before switching to TLD.
- You do not start taking TLD or rifampicin (if you are already taking TLD when you enter the study) within 7 days after the entry visit.
- If all three of these things are true: You have a viral load (how much HIV is in your blood) that is more than 1000 copies/mL at your study entry visit, and you are receiving medication for TB that includes the drug rifampicin, and you started taking TLD before entering the study.
- Your primary care doctor requests that you be taken off the study.

WHAT ARE THE RISKS OF THE STUDY?

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

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV or TB status secret from people close to you. This may include your parent or guardian if you are under 18 years old. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

Risks of ARV Medications
This is an observational study of the ARV treatment that you are receiving locally. So, the risks of taking those medications are not included in this study. Your medical provider should give you that information.

WHAT HAPPENS IF I BECOME PREGNANT WHILE TAKING PART IN THIS STUDY?

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). You will continue on the study. 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?

If you take part in this study, there will be no direct benefit to you. Information learned from this study may help others who have HIV.

You may receive ancillary benefit from taking part in this study, such as receiving test results as described in the next section.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the result of tests that are performed as part of the recommended medical care for HIV or TB in your country (for example, some viral load and CD4 count tests). *(Site to insert site-specific information about CD4 count and viral load test results participants will receive as part of standard of care;* ***if the site is in a country in which treatment guidelines require a genotypic test prior to switching patients on a boosted PI-containing second-line ARV regimen to TLD, include: "If genetic testing of the virus (HIV) is done at your screening visit, you will receive the result of that test.")***

Some tests are done only for research purposes, to improve the care of people living with HIV/AIDS. This includes tests done with dried blood spots and genetic testing of the virus (HIV). This also includes some of the tests in this study that are not part of recommended medical care for HIV or TB in your country. You and your treatment provider will not receive the result of these tests. *(Site to insert site-specific information about CD4 and viral load test results that are not part of standard of care, which participants will not receive.)*

WHAT ABOUT CONFIDENTIALITY?

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

Your records may be reviewed by the ACTG, United States President's Emergency Plan for AIDS Relief (PEPFAR), the US 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), the NIH, study staff, study monitors, 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.

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. *(If applicable to your site. Delete if this does not apply.)*

Anti-HIV and anti-TB medicines will not be provided by the study.

WILL I RECEIVE ANY PAYMENT?

You may be reimbursed for your time and travel expenses as part of your participation in this study. *(Site to insert site-specific information about payment.)*

WHAT HAPPENS IF I AM INJURED?

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

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

- *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. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

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

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

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

SIGNATURE PAGE

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)	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-A: 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.

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.

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

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

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

OR

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

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

The ACTG has a different study that collects samples for genetic testing. This study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

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

APPENDIX II: SAMPLE PARENTAL INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol: A5381

Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir (TLD) for First- or Second-Line ART or with Rifampicin-Containing TB Treatment**: The Hakim Study**

FINAL Version 2.0, 03/05/21

SHORT TITLE FOR THE STUDY: Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of TLD

SUMMARY

This study is research. Your child's participation is voluntary. If you choose not to let your child participate, it will not change your child's medical care or his/her access to antiretroviral (ARV) HIV medication.

PURPOSE: The purpose of this observational study is to see how successful the antiretroviral (ARV) drug combination called Tenofovir-Lamivudine-Dolutegravir (TLD) is at treating HIV.

NUMBER OF PARTICIPANTS: About 1350 people will take part in this study

LENGTH OF STUDY: Your child will be in this study for about 3 years.

REQUIRED ACTIVITIES: At every visit, your child will have blood collected from a vein in his or her arm. You or your child will also be asked questions about his or her current anti-HIV and anti-tuberculosis (TB) medications, and about any new HIV or TB diagnoses.

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

This is an observational study of the HIV medication that your child is receiving locally. So, the risks of taking those medications are not included in this study. Your child's medical provider should give you that information.

BENEFITS: There will be no direct benefit to your child if he or she takes part in this study.

INTRODUCTION

You are being asked to let your child take part in this research study because your child is at least 10 years old and:

1. Your child is living with human immunodeficiency virus (HIV-1), and your child will soon start taking the antiretroviral (ARV) drug combination called Tenofovir-Lamivudine-Dolutegravir (TLD).

   OR

2. Your child is living with HIV-1 and tuberculosis (TB), your child has started or will soon start taking the ARV drug combination TLD, and your child has started or will soon start taking the TB medication that includes the drug rifampicin.

You are encouraged to discuss the risks and benefits of TLD with your child's clinician.

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 let your child be a part of this study, we want you to know about the study.

This is a consent form for your child to participate in this study. 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 let your child take part in this study, you will be asked to sign this consent form. You will get a copy to keep. We will also talk to your child about the study and ask him/her if he/she agrees to participate in the study.

WHY IS THIS STUDY BEING DONE?

TLD is being used more widely across the world to treat HIV. This is an observational study (a type of study in which participants are observed and certain outcomes are measured). The aim of this study is to observe how successful TLD is at treating HIV, in the following groups of people:

- People switching to TLD, after taking anti-HIV medication that contains a NNRTI drug (non-nucleoside reverse transcriptase inhibitor, such as Efavirenz or Nevirapine) (Group 1).
- People switching to TLD, after taking anti-HIV medication that contains a PI drug (protease inhibitor, such as Lopinavir or Atazanavir) (Group 2).
- People taking TLD and receiving medication for TB that includes the drug rifampicin (Group 3). These people must be starting one or both of these medications when they enter the study.
- People starting TLD who have not taken anti-HIV medication before (Group 4).

Another goal of this study is to use genetic testing of the virus (HIV) to see how often HIV is resistant to TLD. Genetic testing of the virus is one way to see if the TLD medication is not working to treat your child's HIV infection.

The United States Food and Drug Administration (US FDA) has approved Tenofovir, Lamivudine, and Dolutegravir for treatment of HIV.

WHAT DOES MY CHILD HAVE TO DO IF MY CHILD IS IN THIS STUDY?

If your child enters the study
If you decide to let your child take part in this research study, after you have read and signed this informed consent form, a screening visit will be done to make sure your child meets the requirements for joining the study. If your child is eligible for the study and you choose to let your child enroll, your child will have the entry evaluations done. Your child has to start taking TLD or rifampicin (if your child is already taking TLD) within 7 days after this entry visit to remain on the study. Your child will have up to 7 scheduled visits on this study. Your child's last visit will be about 3 years after your child enters the study.

- Your child will be seen at the clinic 3 months and 6 months after the screening and entry visit.
- Or, if your child is receiving treatment for TB when he or she starts the study, your child will have one visit within 4 weeks after he/she finishes taking TB treatment. This visit will be in the first year after the screening and entry visit.
- Your child will then be seen at the clinic about once every 6 months.

Study visits may be conducted remotely (like over the telephone) if your child is unable to attend a visit for any of the following reasons:
- **Your child is sick.**
- **Someone in your child's home is sick.**
- **Local conditions or guidelines restrict travel to the clinic.**
- **The site is temporarily unable to have these visits in the clinic.**

If any of the following events occur, your child may have to come back to the clinic for an additional visit. If possible, these visits will coincide with your child's next scheduled visit.

- Virologic failure confirmation: If a test to see how much HIV is in your child's blood shows that your child's anti-HIV medication might not be helping him or her, your child will have a visit about 6 months later.
- Starting rifampicin-Based TB treatment: If your child starts taking TB medicine that includes rifampicin while also taking TLD for HIV, your child will have a study visit.
- Ending rifampicin-Based TB Treatment: If your child finishes taking TB medicine that includes rifampicin while also taking TLD for HIV, your child will have a study visit.
- TLD Discontinuation: If your child stops taking TLD while on the study, your child will have a study visit, and then continue on study.

- Early Study Discontinuation (Leaving the Study Early): If your child leaves the study early, your child will be asked to return to the clinic for one final visit.

If your child does not enroll into the study
If you decide not to let your child take part in this study or if your child does not meet the eligibility requirements, we will still use some of your child's information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information is being collected from you**r** child so that AIDS Clinical Trial Group (ACTG) researchers may help determine whether there are patterns or common reasons why people do not join a 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 child's screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information will be collected from your child.

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

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

Some of your child's blood will be stored and used **t**o check the level of anti-HIV medications in his or her blood, and for immunologic and viral testing that is required for this study.

Samples collected from your child will be stored in the **United States**. **Identifiers will be removed from your child's samples and from any private information that has been collected about your child. 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 your child.**

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

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

Please refer to Attachment II-A to consent for use of your child's samples in other studies.

A5381 Study Visits

The study staff can answer any questions you have about individual study visits, and how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

Appendix II Table 1: Study Schedule for Groups 1, 2, and 4. Your child will follow this study schedule if your child is not receiving treatment for TB when he or she starts the study.

Evaluation	Screening Visit	Entry Visit	Post Entry Visits (Months)							Unscheduled Visits				
			3	6	12	18	24	30	36	Virologic Failure Confirmation	Starting Rifampicin-Based TB Treatment	Ending Rifampicin-Based TB Treatment	TLD Discontinuation	Early Study Discontinuation
Documentation of HIV Status	√	√												
Medical & Medication History	√	√												
Adherence Assessment	√	√												
Clinical Evaluations		√	√	√	√	√	√	√	√	√	√	√	√	√
Height & Weight	√			√	√		√		√					√
Quality of Life Questionnaire		√		√										
Blood Collection	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Appendix II Table 2: Study Schedule for Group 3. Your child will follow this study schedule if your child is receiving treatment for TB when he or she starts the study.

Evaluation	Screening Visit	Entry Visit	Post Entry Visit	Post Entry Visits (Months)					Unscheduled Visits		
			Ending Rifampicin-Based TB Treatment	12	18	24	30	36	Virologic Failure Confirmation	TLD Discontinuation	Early Study Discontinuation
Documentation of HIV Status	√	√									
Medical & Medication History	√	√									
Adherence Assessment	√	√									
Clinical Evaluations		√	√	√	√	√	√	√	√	√	√
Height & Weight	√		√	√		√		√			√
Quality of Life Questionnaire		√	√								
Blood Collection		√	√	√	√	√	√	√	√	√	√

Description of Study Evaluations
Documentation of HIV Status: Your child's HIV infection status will be documented.

Medical & Medication History: You or your child will be asked questions about his or her medical and medication history, and about past and current anti-HIV and anti-TB medications that your child has taken or is taking.

Adherence Assessment: Your child will be asked about adherence to his or her anti-HIV or anti-TB medications (how your child is currently taking his or her medications).

Clinical Evaluations: You or your child will be asked questions about any new HIV and TB diagnoses, and about any changes in the anti-HIV and anti-TB medications that your child is taking. Other health events will be reviewed. This information will be shared with you, if applicable.

Height & Weight: Your child's height and weight will be measured.

Quality of Life Questionnaire: Your child will be asked questions about how he or she feels, and about how he or she has been sleeping.

Blood Collection: Your child will have between **about 10 mL** (**1 tablespoon**) and **about 52** mL (**3.5 tablespoons**) of blood drawn **at each visit** for some or all of the following tests:

- To test how much HIV is in your child's blood (viral load).
- To test how many CD4/CD8 cells (infection-fighting cells) are in your child's blood.
- For genetic testing of the virus (HIV). This testing is done to see if the TLD medication is a good choice of medication to treat your child's HIV infection).
- For a dried blood spot. The dried blood spot test will be used to test how much anti-HIV medication is in your child's blood, or will be stored for future tests.
- To be stored for future tests.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 1350 people will take part in this study

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for about 3 years.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

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

- The study is stopped or cancelled
- Your child is not able to attend the study visits as required by the study
- Your child is taking HIV medications before switching to TLD, and your child missed 14 or more days in a row of those medications immediately before switching to TLD.
- Your child does not start taking TLD or rifampicin (if your child is already taking TLD when he or she enters the study) within 7 days after the entry visit.
- If all three of these things are true: Your child has a viral load (how much HIV is in your child's blood) that is more than 1000 copies/mL at his/her study entry visit, and your child is receiving medication for TB that includes the drug rifampicin, and your child started taking TLD before entering the study.
- Your child's primary care doctor requests that your child be taken off the study

WHAT ARE THE RISKS OF THE STUDY?

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

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

Risks of ARV Medications
This is an observational study of the ARV treatment that your child is receiving locally. So, the risks of taking those medications are not included in this study. Your child's medical provider should give you that information.

WHAT HAPPENS IF MY CHILD BECOMES PREGNANT WHILE TAKING PART IN THIS STUDY?

If your child becomes pregnant while on study, the study staff would like to obtain information from your child about the outcome of the pregnancy (even if it is after your child's participation in the study ends). Your child will continue on the study. If your child is taking anti-HIV drugs when she becomes pregnant, your child's 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 child's name or other information that could be used to identify her.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your child takes part in this study, there will be no direct benefit to him or her. Information learned from this study may help others who have HIV.

Your child may receive ancillary benefit from taking part in this study, such as receiving test results as described in the next section.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the result of tests that are performed as part of the recommended medical care for HIV or TB in your country (for example, some viral load and CD4 count tests). *(Site to insert site-specific information about CD4 count and viral load test results participants will receive as part of standard of care;* ***if the site is in a country in which treatment guidelines require a genotypic test prior to switching patients on a boosted PI-containing second-line ARV regimen to TLD, include: "If genetic testing of the virus (HIV) is done at your child's screening visit, you will receive the result of that test.")***

Some tests are done only for research purposes, to improve the care of people living with HIV/AIDS. This includes tests done with dried blood spots and genetic testing of the virus (HIV). This also includes some of the tests in this study that are not part of recommended medical care for HIV or TB in your country. You and your child's treatment site will not receive the result of these tests. *(Site to insert site-specific information about CD4 and viral load test results that are not part of standard of care, which participants will <u>not</u> receive)*

WHAT ABOUT CONFIDENTIALITY?

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

Your child's records may be reviewed by the ACTG, United States President's Emergency Plan for AIDS Relief (PEPFAR), the US 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), the NIH, study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about your child and his or her participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to your child 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 your child. 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 your child is taking part in a research study. *(If applicable to your site. Delete if this does not apply.)*

Anti-HIV and anti-TB medicines will not be provided by the study.

WILL I RECEIVE ANY PAYMENT?

You may be reimbursed for your time and travel expenses as part of your child's participation in this study. *(Site to insert site-specific information about payment.)*

WHAT HAPPENS IF MY CHILD IS INJURED?

If your child is injured as a result of being in this study, your child will be given immediate treatment for his or her injuries.

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

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if your child suffers 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 CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to let your child take part in this study or to remove your **c**hild from this study at any time. Your decision will not have any impact on your child's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which your child are otherwise entitled.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- Name of the investigator or other study staff
- Telephone number of above

For questions about your child's 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 let your child to take part in this study, please sign your name below.

Child Participant's Name (print)	Child Participant's Date of Birth
Parent/Legal Guardian Name (print) (As appropriate)	Parent/Legal Guardian 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 II-A: 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 child's 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 child's samples and from any private information that has been collected about your child. This means that no one looking at the labels or at other information will know that the samples or information came from your child.

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

There is no limit on how long your child's 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 child's 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 child's samples to the researcher's location. This means that researchers who are not part of the protocol team may use your child's samples without asking you or your child again for consent.

Your child will not be paid for her samples. Also, a researcher may make a new scientific discovery or product based on the use of your child's samples. If this happens, there is no plan to share any money with your child.

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

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

<u>Research without Human Genetic Testing</u>
If you agree, your child's extra samples may be stored (with usual protection of your child's 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 child's samples

OR

____ (initials) I understand but I do not agree to this storage and possible use of my child's samples

Research with Human Genetic Testing
Your child's extra samples will not be used for human genetic testing.

The ACTG has a different study that collects samples for genetic testing. This study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

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

APPENDIX III: SAMPLE ASSENT FORM

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol: A5381

Observational Cohort to Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of Tenofovir-Lamivudine-Dolutegravir (TLD) for First- or Second-Line ART or with Rifampicin-Containing TB Treatment**: The Hakim Study**

FINAL Version 2.0, 03/05/21

SHORT TITLE FOR THE STUDY: Assess Therapeutic Efficacy and Emergence of HIV Drug Resistance Following Initiation of TLD

INTRODUCTION

We are asking you to take part in this research study. We are doing this study to find out if the human immunodeficiency virus (HIV-1) medication called Tenofovir-Lamivudine-Dolutegravir (TLD) is successful at treating HIV for you and for other people in this study.

Another goal of this study is to use genetic testing of the virus (HIV) to see how often HIV is resistant to TLD. Genetic testing of the virus is one way to see if the TLD medication is not working to treat your HIV infection.

Your parent/guardian will be informed about this study and asked to sign a separate form giving their consent for you to take part. As a participant in this study, we would like you to know about the study too, and to be given a chance to ask any questions you may have about it. You will be asked to sign this assent form. You will get a copy to keep.

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

People who take part in this study will be asked to be part of it for 3 years. You will be seen at the clinic about every 6 months (for a total of about seven study visits). You may also have extra study visits, if any of the following things happen.

- If a test to see how much HIV is in your blood shows that your HIV medicine might be failing to help you, you will have a study visit about 6 months later.
- If you start or stop taking medicine for tuberculosis (TB), you will have a study visit.
- If your HIV medicine is changed, you will have a study visit.
- If you leave the study early, you will be asked to have one last study visit.

Study visits may be conducted remotely (like over the telephone) if you are unable to attend a visit for any of the following reasons:

- **You are sick.**
- **Someone in your home is sick.**
- **Local conditions or guidelines restrict travel to the clinic.**
- **The site is temporarily unable to have these visits in the clinic.**

At these study visits, the study staff will talk with you and your parent or legal guardian about your health and the medicines you are taking. You will have blood collected for testing.

The study staff can tell you more about the study visits and what exactly will be done at the study visits.

We would also like you to know that information collected in this study will be kept confidential (private) and only those people who are doing the study and are overseeing the study will be able to see your information. *[Sites should also include a statement here describing the extent to which information reported by children/adolescents will be shared with their parents/guardians].*

WHAT ARE THE RISKS OF THE STUDY?

Risks of Blood Collection

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

Risks of Social Harm

It is possible that participating in this study will make it difficult for you to keep your HIV or TB status secret from people close to you. This may include your parent or guardian. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there will be no direct benefit to you. Information learned from this study may help others who have HIV. You may indirectly benefit from taking part in this study. For example, you may receive some test results.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is your choice. This means you can say yes or no to being part of the study. No matter what decision you make, and even if your decision changes, nothing bad will

happen to you or your family. You will not lose medical care, legal rights, or any benefits that you are otherwise entitled to.

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.

_____
Child Participant's Name and Surname (print)

_____
Child Participant's Date of Birth

_____
Child Participant's Signature and Date

_____ Study Staff Conducting Assent Discussion (print)	_____ Study Staff's Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date