**The Steady-State Pharmacokinetics of Dolutegravir/Rilpivirine Fixed Dose Combination (FDC) in Patients with End Stage Renal Disease (ESRD) Requiring Hemodialysis**

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SCHEMA

DESIGN

The objectives of this study will be met by performing a single-center, prospective, two-group comparative study of the 24-hour steady-state pharmacokinetics (PK) of fixed dose combination (FDC) Dolutegravir(DTG)+Rilpivirine(RPV), or JULUCA. We will enroll a total of 20 HIV-negative participants, 10 of whom require hemodialysis (HD) for end stage renal disease (ESRD) and the other 10 who have normal renal function [Creatinine Clearance (CrCl) ≥75 mL/min]. Up to 40 participants may be screened to identify the 20 who will be enrolled. All participants will receive DTG+RPV for 10-14 days and will undergo intensive 24-hour PK evaluations in the Indiana Clinical Research Center (ICRC) between days 11-14.

OBJECTIVES

The primary objective of this study is to compare the steady-state PK of FDC DTG+RPV in HIV-negative ESRD patients requiring HD to those with normal renal function. The key secondary objective is to assess the short-term safety and tolerability of FDC DTG+RPV in HIV-negative patients requiring HD.

DURATION

Each individual participant will be followed no more than 60 days from their Screening Visit. We expect to enroll the 20 required participants over a 10 month period.

POPULATION

All participants will be HIV-negative, be of age 18-65 years, and either require HD for ESRD (HD Group) or have normal renal function (Healthy Group). The Healthy Group participants will be matched 1:1 to the HD study group by age (±5 years), sex, and BMI (±5 $kg/m^2$). We will enroll the Healthy Group after the HD study group participants have completed their study procedures. HD participants will be recruited from the HD clinics staffed by the faculty of the Division of Nephrology of the Indiana University School of Medicine or from self-referrals in response to recruitment advertisements. The Healthy Group participants will be recruited from the community using an advertisement on CTSI All In for Health website along with the CTSI All IN for Health voluntary registry IU IRB Protocol Number 1105005444 to identify and contact potential subjects.

SAMPLE SIZE

The total sample size for this study will consist of 20 enrolled participants. Up to 40 participants may be screened to identify the 20 eligible for enrollment. If a consented and otherwise eligible participant withdraws prior to the PK study visit, this participant will be replaced.

## 1.0 STUDY OBJECTIVES

### 1.1 Primary Objective

1.1.1 Compare steady-state pharmacokinetics (with a focus on Ctau) of FDC DTG+RPV in HIV-negative ESRD patients requiring HD to those with normal renal function.

### 1.2 Secondary Objective

1.2.1 Assess the short-term safety and tolerability of FDC DTG+RPV in HIV-negative persons requiring HD.

## 2.0 HYPOTHESES, BACKGROUND, AND RATIONALE

### 2.1 Hypotheses

2.1.1 Ctau for DTG will be lower in the HD group compared to the Healthy group.

2.1.2 Ctau for RPV will not be different in the HD group compared to the Healthy group.

2.1.3 Treatment with DTG+RPV will be safely tolerated in the HD group.

### 2.2 Background

There is a growing population of HIV-positive patients with end stage renal disease (ESRD) who require hemodialysis (HD) (1-4). Providing effective and well-tolerated antiretroviral therapy (ART) with low pill-burden is a priority in this population, especially as large numbers of medications and supplements are needed for managing their renal failure. Current ART with nucleoside inhibitors typically require lower dosages in renal failure that preempt usage of most currently available fixed dose combinations (FDC). As such, many HIV-positive patients requiring HD use multicomponent ART with its inherently increased pill burden.

One possible strategy to lower this pill burden while minimizing potential renal, bone, and cardiovascular complications from existing therapies (e.g. TDF, ABC) is to switch these patients' current treatments to an NRTI-sparing FDC. In addition, the use of a 'booster' agent for integrase inhibitors (e.g. GENVOYA) or protease inhibitors (e.g. PREZCOBIX) would lead to possible drug-drug interactions that would lead to increased safety concerns. One possible solution is to use JULUCA, or the FDC dolutegravir+rilpivirine (DTG 50 mg+RPV 25 mg). With the results of the recently presented SWORD 1 and 2 trials (5), this strategy appears safe and effective.

However, without adequate pharmacokinetic data justifying the use of this FDC in ESRD patients requiring HD, it would be unwise to make such a change in treatment. DTG has been studied in HIV-negative persons with creatinine clearance (CrCl) <30mL/min, but not yet requiring HD, and was found to have 23-40% modestly lower Cmax and $AUC_{0-\infty}$ and a 50% reduction in unbound DTG Ctau (C24) after a single dose of 50 mg when compared to those receiving DTG with normal renal function (6). In a case report of DTG 50 mg used daily in an HIV-positive ESRD patient requiring HD, the trough concentration was 85% lower than that found in patients with normal renal function, although there was no appreciable extraction of DTG during dialysis (7). A separate study of five HIV-positive ESRD patients requiring HD receiving DTG 50 mg daily also demonstrated minimal DTG extraction during dialysis (8), although the study did not perform comprehensive PK analysis to assess Ctau and AUC parameters which may affect DTG virologic efficacy. To our knowledge, the steady-state PK of RPV in ESRD requiring HD has not been studied.

## 2.3 Study Rationale

The above-mentioned results with DTG are in line with other ART drugs that are similarly highly protein-bound, not water-soluble, and not renally cleared. For example, we have previously found that lopinavir circulating steady-state concentrations were surprisingly lower than expected when formally studied in HIV-positive ESRD patients requiring HD, although protein-binding was not affected (9). Thus, it would be important not to assume there would be no effects of ESRD on the circulating concentrations of either DTG or RPV. Therefore, formal assessment of the steady-state concentrations of FDC DTG+RPV in ESRD patients requiring HD is required to optimize dose selection for both treatment and prevention in this population. In addition, the ensuing data will help inform the need for additional PK studies with other integrase inhibitors.

# 3.0 STUDY DESIGN

## 3.1 Overview

The objectives of this study will be met by performing a single-center, prospective, two-group comparative study of the 24-hour steady-state PK of FDC DTG+RPV. Twenty participants will be enrolled; there will be 10 in each of two study groups. The HD group will consist of 10 participants who require HD for ESRD. The Healthy Group will consist of 10 participants who have normal renal function (CrCl ≥75mL/min) and matched 1:1 to the HD group by age (±5 years), sex, and BMI (±5 kg/$m^2$). We will enroll each Healthy Group control participant after their matched HD participant has completed his/her study procedures. All 20 participants will be 18-65 years old, be HIV-negative, and do not have contraindications to taking DTG-+RPV for up to 14 days. The intensive PK visit in the Indiana CRC (ICRC) will occur preferably on Day 11 or 12 of the study period but can occur up to Day 14.

We will enroll HIV-negative, instead of HIV-positive, participants for several reasons. First, although HIV-positive ESRD patients would be most clinically relevant for treatment of HIV, from our experience performing similar studies, recruitment at a single site would be challenging and likely unachievable. Performing a multicenter study would involve unacceptably high costs and prolonged study completion timeframes. Second, to our knowledge, the effects of ESRD requiring HD on percentage change in PK parameters in HIV-negative patients should be readily extrapolated to HIV-positive patients. Third, use of an HIV-negative study group would provide relevant data if either DTG or RPV was to be used as an HIV pre-exposure prophylaxis agent in an ESRD population.

We have chosen to perform a steady-state PK study (as opposed to a single dose PK study) as DTG+RPV FDC is given chronically, and thus the data derived from steady-state would reflect actual clinical conditions. Although predicting steady-state conditions may be inferred from a single dose administration, there are a number of assumptions that would need to be made, including linear pharmacokinetics, which are not guaranteed.

## 3.2 Screening Visit (Visit 1)

If deemed eligible for screening, the participant will be approached (with permission/referral of the potential participant's primary dialysis/renal provider) by a study team member to enter the screening phase of the study. After written, informed consent is provided by the participant, a random study code number will be assigned to the participant to ensure confidentiality. This study code number will be used for laboratory transport and processing, result reporting, and data recording.

The study participant does ***not*** need to be fasting for the Screening Visit. At this Screening Visit, the participant's medical, psychiatric, and medication history will be reviewed. A brief physical examination

including vital signs will be performed. The PHQ-9 questionnaire will be administered to assess for ongoing depressive symptoms that could be worsened by DTG+RPV. A resting ECG will be obtained to determine QT interval. If the potential participant is eligible based on these initial assessments, and if a complete blood count and comprehensive metabolic panel is not available within the past 30 days through routine clinical care, then blood will be drawn to determine if the participant meets the safety laboratory eligibility criteria (see Section 4.0) and for archiving samples for studies of future interest related to changes that may occur during study drug administration. Serum pregnancy testing for female study volunteers of reproductive potential will also be performed. All screening tests will be performed at the Indiana Clinical Research Center (ICRC). If the eligibility criteria are met, then the participants will enter the study.

Those participants who score ≥ 10 on the PHQ-9, indicating moderate to severe depression, will not be enrolled and instead be referred back to their primary physicians for appropriate follow-up. If the participant answers positively to question #9 regarding suicidality, then Dr. Gupta or Dr. Friedman (the protocol nephrologist) will be contacted immediately for consultation if urgent, formal psychiatric assessment is required by Midtown Mental Health Center (either in person or through their phone hotline).

If the participant is found to be fully eligible for study participation, then s/he will return for drug dispensation.

### 3.3 Drug Dispensation Visit (Visit 2)

This visit will occur at the ICRC –OR- at the participant's regularly scheduled dialysis session within 30 days of the Screening Visit/Visit 1. The primary purpose of this visit is to provide one bottle (30 tablets) of study drug (FDC DTG+RPV) to each study participant. Study drug will be stored at the IUH University Investigational Drug Services Pharmacy and dispensed from that facility. The participant will be queried again for changes in concomitant medications, changes in interval medical history or symptoms, and repeat serum pregnancy testing (as appropriate) to confirm ongoing study eligibility.

If study eligibility is confirmed, then the participant will then be instructed on proper use of the study drug, which includes taking the drug at about the same time every day with a meal. The study drug preferably will be taken within 2 hours before or 2 hours after the time anticipated for the observed drug administration at the Intensive PK Study Visit (Visit 3). For example, if the anticipated dosing time at Visit 3 is 8am, then the dosing should be between 6am and 10am for the days prior to Visit 3. The participant will then be given instructions on properly completing the Medication Use Log (section 3.4). As we do not anticipate dialysis itself to have clinically relevant effects of DTG or RPV circulating concentrations, the exact timing of study drug administration in relation to dialysis will not be pre-specified except that the study drug should not be taken *during* a dialysis session (please also see section 5.1 for other dosing requirements).

The Intensive PK Study Visit at the ICRC will be preferably scheduled on either Day 11 or 12 after the Drug Dispensation Visit, but this PK study visit can be scheduled as late as Day 14 after the Drug Dispensation Visit. We believe 10 days prior to the Intensive PK Study Visit will be sufficient to achieve steady-state concentrations based on previous PK studies of both DTG and RPV (10, 11). If the participant cannot attend the Intensive PK Study Visit within this window, then s/he will be discontinued from study participation and will be replaced by another participant.

The participant will then be reminded that they will be called by phone by a member of the study team or visited in person during a regular scheduled dialysis session at both 3 days and 9 days after the Drug Dispensation Visit to assess for interval toxicity development and adherence. Phone contact information will be verified at this visit; <u>if possible, alternative contact information of a family member or friend will also be documented in case the participant cannot be contacted directly</u>.

### 3.4 Interval Assessments and Medication Use Log/Adherence Assessment

The participant will be called by phone or visited in person during a regularly scheduled dialysis session by a member of the study team both 3±1 days and 9±1 days after the Drug Dispensation Visit to assess for any changes in medications, to review any interval development of potential adverse effects, and to assess drug adherence.

Participants will receive a Medication Use Log (MUL) on which to record the dose times of the study drug prior between the Drug Dispensation Visit and the Intensive PK Study Visit. The dates and times of study drug ingestion will be reviewed at the Day 3 and Day 9 assessments and at initial evaluation on the Intensive PK Study Visit.

If concerns arise about drug adherence, potential adverse effects from the study drug, or changes in study eligibility, then Dr. Gupta will be contacted immediately to discuss if the study participant should discontinue study participation and be replaced or if changes in the study timeline are required (e.g. rescheduling the intensive PK study visit).

### 3.5 Intensive PK Study Visit (Visit 3) and Follow-up Assessment

This visit will occur preferably on either Day 11 or Day 12 after the Drug Dispensation Visit but can occur as late as Day 14 after the Drug Dispensation Visit. The 24 hour period of this study visit must not overlap the scheduled dialysis session for a participant in the HD group. The participant will be admitted to the ICRC approximately one hour prior to the scheduled time of the observed administration of the study drug on this study visit. The observed study drug administration time will vary between participants based on their typically scheduled dialysis times. The participant must be fasting for at least 4 hours prior to first blood draw. The participant will undergo once again a review of concomitant medications, interval medical history, review of any new potential adverse effects, and review of the Medication Use Log and pill counts. The MUL should document that the dose taken prior to the observed administered dose on this study visit should occur between 22-26 hours prior to the study dose administration on this study visit. A brief, targeted physical examination including vital signs will be performed. If any concerns regarding study eligibility develop after these assessments, then Dr. Gupta or Dr. Desta will be notified immediately to determine if the remainder of the Intensive PK Study Visit should proceed.

An indwelling peripheral IV catheter will then be placed for blood draws during this study visit. Safety laboratories will be obtained prior to study drug administration. Blood will also be drawn at this time for archiving DNA samples for future studies of interest linking genetics with the PK evaluations and for archiving serum and plasma for other studies of future interest that may explain differences in PK between the study groups.

For both study groups, the FDC DTG+RPV will be administered with a standard meal (~600 calories, 25% fat) after an initial blood sample ('PRE') is obtained for drug trough levels and safety laboratories. This will be the last dose of study drug that the participant ingests (any remaining study drug should at this time be returned to the study team for proper disposal by the Investigation Drug Services Pharmacy). For the intensive PK sampling, blood will be obtained pre-dose of study drug and then at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours after study drug administration. Standardized renal diets (low sodium, low potassium, low phosphorus) will be provided for the remainder of this study visit for <u>both</u> study groups.

After these study procedures are completed, the participant will be reminded that they will be either called by phone or visited during a regularly scheduled dialysis session by a member of the study team in approximately 14 days to assess for any interval development of potential adverse effects after cessation of FDC DTG+RPV and to document any new medications given since the intensive PK visit that may explain such adverse effects.

3.6 Study Duration and Participant Retention

The maximum study period for each participant will be 60 days (screening phase of 30 days and on-study phase of at most an additional 30 days). In order to promote retention in the study, the participants will be financially compensated at the Screening Visit and at the Intensive PK Study Visit, but not for the Drug Dispensation Visit or for the phone call assessments.

## 4.0 SELECTION AND ENROLLMENT CRITERIA

### 4.1 Inclusion Criteria

1. Negative HIV antibody testing at screening.
2. For the ESRD requiring HD study group: ESRD requiring chronic hemodialysis for at least 6 months at an established center (not home dialysis).

   NOTE: The approximate date that hemodialysis was initiated should be reported, if known.

   For the normal renal function group: Estimated CrCl (using the Cockcroft-Gault equation) at screening ≥75mL/min.

3. Availability of alternative venous access (not used for dialysis) for the purpose of PK sampling.
4. The following laboratory values obtained within 30 days prior to study entry (obtained either at screening or done as part of routine clinical care):
   - AST (SGOT) and ALT (SGPT) less than or equal to ULN
   - Total bilirubin less than or equal to 1.5 x ULN
   - Hemoglobin greater than or equal to 8.0 mg/dL
5. A negative serum pregnancy test result at screening for all women of reproductive potential who have not reached menopause or undergone hysterectomy, bilateral oophorectomy, or tubal ligation.
6. Males and females, age 18-65 years.
7. Ability and willingness of participant to provide written informed consent.

### 4.2 Exclusion Criteria

1. Known allergy or hypersensitivity to either dolutegravir or rilpivirine
2. Use of peritoneal dialysis.
3. Serious illnesses, other than ESRD, requiring systemic treatment and/or hospitalization within 30 days prior to the Screening Visit.
4. Known liver cirrhosis, unstable liver disease (presence of ascites, encephalopathy, coagulopathy, esophageal/gastric varices), Child-Pugh Class A, B or C, or known biliary abnormalities (except for known Gilbert's syndrome or asymptomatic gallstones).
5. Hepatitis B surface antigen or hepatitis C antibody with detectable RNA at screening.
6. Known gastrointestinal disease that may lead to poor absorption of the study drugs.

7. Known hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption.
8. Any of the following gastrointestinal signs or symptoms of Grade ≥ 2 within 7 days prior to the Screening Visit or during study drug administration prior to the Intensive PK Study Visit:
    - nausea
    - vomiting
    - diarrhea
    - abdominal pain
9. Use of any of the following within 30 days of initiating study drug:
    - Medications known to appreciably inhibit or induce CYP3A enzymes, P-glycoprotein, UGT1A1 or UGT1A4 enzymes (e.g., anticonvulsants such as carbamazepine, phenytoin, oxacarbamazepine; antimycobacterials such as rifampin, rifabutin and rifapentine; antifungal agents such as ketoconazole, fluconazole and itraconazole; verapamil, clarithromycin, erythromycin)
    - St. John's Wort, echinacea, grapefruits or grapefruit juice, garlic supplements, ginseng, golden seal, and milk thistle
    - Cancer chemotherapeutic agents
    - Investigational agents
    - Immunomodulators, including systemic steroids greater than or equal to 100 mg/day of prednisone (Note: Topical and inhaled corticosteroids are allowed.)
    - Dofetilide
    - Positive pre-study drug screen. Drugs that will be screened for include amphetamines, barbiturates, cocaine and phencyclidine (PCP). Active injected drug users will be excluded from this study.
10. Use of proton pump inhibitors within 7 days of initiating study drug (H2 blockers are permitted).
11. Pregnancy and/or breast-feeding.

    A female may be eligible to enter and participate in the study if she:

    a. is of non-child-bearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or,

    b. is of child-bearing potential with a negative pregnancy test at Screening and agrees to use one of the following methods of contraception to avoid pregnancy (please see Appendix I for complete listing):

        - Complete abstinence from penile-vaginal intercourse from 2 weeks prior to administration of JULUCA, throughout the study, and for at least 2 weeks after discontinuation of all study medications;
        - Any intrauterine device with published data showing that the expected failure rate is <1% per year;
        - Male partner sterilization ***confirmed prior to the female subject's entry*** into the study, and this male is the sole partner for that subject;
        - Approved hormonal contraception;
        - Any other method with published data showing that the expected failure rate is <1% per year.

*Any contraception method must be used consistently, in accordance with the approved product label at least 28 days prior to the first dose of study drug and for at least 2 weeks after discontinuation of study medication.*

12. Moderate to severe depression, defined as a PHQ-9 ≥ 10 at Screening.
13. Significant change (i.e., more than a 50% change) in tobacco smoking habit within 6 weeks prior to the Screening Visit. Participants who have recently stopped smoking should have stopped smoking more than 6 weeks prior to the Screening Visit. Participants who have recently started smoking should have started more than 6 weeks prior to the Screening Visit.
14. QTc interval greater than 500 msec at Screening.

If participants are excluded due to the above criteria, they may be approached again in the future or have their study visit rescheduled within the allowable timeframe if these criteria are no longer applicable.

### 4.3 Co-enrollment Guidelines

Co-enrollment into other studies will be permitted provided no drugs prohibited on this study will be given in the other study/ies and that the required blood draws do not exceed safe limits when combined with those for this study.

## 5.0 STUDY TREATMENT

### 5.1 JULUCA Administration

The study drug JULUCA (or FDC DTG 50 mg + RPV 25 mg) – IND 151804 – will be provided by ViiV Healthcare and stored at the IU Investigational Drug Services Pharmacy located at IUH University Hospital. Each JULUCA tablet contains 50 mg of DTG and 25 mg of rilpivirine, and is a pink, oval, film-coated, biconvex tablet debossed with "SV J3T" on one side. A bottle contains 30 tablets with child-resistant closure (the bottle contains a desiccant). Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant. Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [USP Controlled Room Temperature].

This pharmacy will also dispense the study agent to the study participants. Study drug administration will be open-label. Unused study drug will be disposed of by the IU Investigational Drug Services Pharmacy.

One tablet of FDC DTG+RPV will be taken daily for at least 10 days prior to the Intensive PK Study Visit but for no more than 14 days. On dialysis days, the dosing should not occur during dialysis itself but otherwise can be taken before or after the dialysis session. **The timing of the dosing should coincide with the anticipated observed dosing time on the Intensive PK Study Visit. The study drug will be taken with a meal, taken at least 4 hours before or 12 hours after taking H2-receptor antagonists, and at least 4 hours before or 6 hours after taking polyvalent cations, including calcium-based phosphate binders. Use of sevalamer or similar phosphate binders are allowed.**

### 5.2 JULUCA Safety

The following summarizes the JULUCA safety data as presented in the October 2019 package insert. Please refer to the package insert for more detailed information (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Juluca/pdf/JULUCA-PI-PIL.PDF#page=1).

The primary adverse events associated with JULUCA involve skin disorders, hepatotoxicity, and depressive disorders as documented in the licensing trials of JULUCA in 1,024 HIV-positive, virologically suppressed trial participants who changed their current antiretroviral regimen to JULUCA in the open-label SWORD-1 and SWORD-2 trials. In the pooled analyses, the proportion of subjects who discontinued treatment due to an adverse event was 4% in subjects receiving JULUCA once daily and less than 1% in those who remained on their current antiretroviral regimen.

The most common adverse events leading to discontinuation were psychiatric disorders with these AE occurring in 2% of subjects receiving dolutegravir plus rilpivirine and less than 1% on the current antiretroviral regimen.

The most common adverse reactions (all grades) reported in at least 2% of subjects in the Week 48 pooled analyses from SWORD-1 and SWORD-2 were diarrhea (2% JULUCA vs. <1% current treatment; headache 2% JULUCA vs. 0% current treatment).

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented below (from Table 3 in the JULUCA package insert).

Table 3. Selected Laboratory Abnormalities (Grades 2 and 3 to 4; Week 48 Pooled Analyses) in SWORD-1 and SWORD-2 Trials

| **Laboratory Parameter Preferred Term** | **Dolutegravir plus Rilpivirine (n = 513)** | **Current Antiretroviral Regimen (n = 511)** |
|---|---|---|
| ALT | | |
| Grade 2 (>2.5-5.0 x ULN) | 2% | <1% |
| Grade 3 to 4 (>5.0 x ULN) | <1% | <1% |
| AST | | |
| Grade 2 (>2.5-5.0 x ULN) | <1% | 2% |
| Grade 3 to 4 (>5.0 x ULN) | <1% | <1% |
| Total Bilirubin | | |
| Grade 2 (1.6-2.5 x ULN) | 2% | 4% |
| Grade 3 to 4 (>2.5 x ULN) | 0 | 3% |
| Creatine kinase | | |
| Grade 2 (6.0-9.9 x ULN) | <1% | <1% |
| Grade 3 to 4 (≥10.0 x ULN) | 1% | 2% |
| Hyperglycemia | | |
| Grade 2 (126-250 mg/dL) | 4% | 5% |
| Grade 3 to 4 (>250 mg/dL) | <1% | <1% |
| Lipase | | |
| Grade 2 (>1.5-3.0 x ULN) | 5% | 5% |
| Grade 3 to 4 (>3.0 x ULN) | 2% | 2% |

ULN = Upper limit of normal.

Embryonic toxicity has also emerged as a potential concern with dolutegravir use during the first trimester of pregnancy, specifically neural tube defects. **As such, a discussion should be conducted with**

**the patient about use of contraception to prevent pregnancy or to undergo pregnancy testing prior to initiation of dolutegravir and JULUCA in women of child bearing potential.**

5.2 Prohibited Medications

- Medications known to appreciably inhibit or induce CYP3A enzymes, P-glycoprotein, or UGT1A1 and UGT1A4 enzymes (e.g., anticonvulsants such as carbamazepine, phenytoin, oxacarbamazepine; antimycobacterials such as rifampin, rifabutin and rifapentine; antifungal agents such as ketoconazole, fluconazole and itraconazole; verapamil, clarithromycin, erythromycin)
- St. John's Wort, echinacea, grapefruits or grapefruit juice, garlic supplements, ginseng, golden seal, and milk thistle
- Cancer chemotherapeutic agents
- Investigational agents
- Immunomodulators, including systemic steroids greater than or equal to 100 mg/day of prednisone (Note: Topical and inhaled corticosteroids are allowed.)
- Proton pump inhibitors

## 6.0 CLINICAL AND LABORATORY EVALUATIONS

### 6.1 Schedule of Events

| | **Study Visits** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Visit 1** Screening Visit | **Visit 2** Drug Dispensation Visit (within 30 days of Visit 1) | **Interval Assessment** D3/Dose 3 (±1 day) | **Interval Assessment** D9/Dose 9 (±1 day) | **Visit 3** | | **Follow-up Assessment** D26-30 |
| | | | | | D11 (up to D14) | D12 (up to D15) | |
| **Study Procedure** | | | | | | | |
| Informed Consent | X | | | | | | |
| Medical History | X | | | | | | |
| Concomitant Medications | X | X | X | X | X | | X |
| Adverse Event Review | | X | X | X | X | | X |
| Medication Use Log/Adherence Review | | | X | X | X | | |
| Vitals Signs & Brief Physical Examination | X | | | | X | | |
| ECG[1] | X | | | | | | |
| PHQ-9 Depression Screening | X | | | | | | |
| Venipuncture | X | | | | X | | |
| Pregnancy Testing (for women of childbearing age) | X | X | | | | | |
| HIV, Hepatitis B, Hepatitis C, and illicit drug screening[2] | X | | | | | | |
| Safety Laboratories[3] | X | | | | X | | |
| DNA Sample | | | | | X | | |
| Archived Blood Samples (serum, plasma) | X | | | | X | | |
| IV Placement | | | | | X | | |
| PK Sampling[4] | | | | | X | X | |
| Drug Dispensation[5] | | X | | | | | |
| Drug Administration | | | | | X | | |

[1] QTc must be less than 500 msec.

[2] HIV 4th generation antibody/antigen, hepatitis B surface antigen, hepatitis C antibody with reflex RNA, illicit drug screen

[3] Blood samples will be sent to IUH Pathology. Safety labs include: complete blood count with differential and platelets, comprehensive metabolic panel/liver function tests. Of note, for screening purposes to determine eligibility, if a complete blood count with differential and platelets and a comprehensive metabolic panel/liver function tests are available through routine clinical care within 30 days of the Screening Visit, then these laboratories do not need to be redrawn.

[4] PK samples will be obtained pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post study dose.

[5] Drug will be dispensed to patient at Visit 2 with instructions to take 1 tablet of FDC DTG+RPV daily at approx. the same time each day with a meal.

## 6.2 Definitions for Schedule of Events – Special Instructions and Definitions of Evaluations

### 6.2.1 Medical/Psychiatric History

A medical/psychiatric history must be present in the source documents. Record the following on CRFs at either the Screening Visit:

- Birthdate
- Sex
- Patient's self-report of ethnicity and race
- Diagnoses (all medical and psychiatric as stated by the participant and by review of available medical records)
- Tobacco, alcohol, illicit drug use
- For those in the HD Study Group
  - Cause of renal failure, if known
  - Most recently available hepatitis C antibody, hepatitis C RNA levels, hepatitis B surface antigen, and hepatitis B surface antibody results obtained as part of routine clinical care prior to the Screening Visit
  - When hemodialysis was first initiated
  - Type of arteriovenous access (tunneled catheter, fistula)
  - Filter type used at last dialysis
  - Rate of blood flow into dialyzer (mL/min)
  - Dialysis fluid flow rate and times of dialysis at last 3 dialysis sessions prior to the Intensive PK Study Visit

### 6.2.2 Concomitant Medications

At Screening, a medication history must be present in source documents. All new and/or discontinued prescription medications taken since the last study visit or contact with the participant will be recorded on CRFs with start and stop dates. The following information will be recorded on the CRFs at the Screening Visit:

- All prescription medications within 30 days of Screening
- All supplements (non-prescription), vitamins, and over the counter medications used within 30 days of Screening

### 6.2.3 Adverse Event Review

All new symptoms/signs since the last study visit assessment (either by phone or in-person) will be documented on CRFs, graded per DAIDS toxicity tables (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf), and reviewed as being potentially related to study drug (see section 7.0).

### 6.2.4 Clinical Assessments

#### 6.2.4.1 Height

Height will be recorded on CRFs at the Screening Visit.

6.2.4.2 Weight

Weight will be recorded on CRFs at the Screening Visit and at the Intensive PK Study Visit.

6.2.4.3 Resting Blood Pressure

Blood pressure will be recorded on CRFs at the Screening Visit and the Intensive PK Study Visit. Blood pressure measurements should be performed on the non-fistula/dialysis access arm for the HD Group. The participant should first sit quietly for five minutes. With the elbow and forearm resting comfortably on a flat table, the blood pressure should then be measured. After two minutes, repeat blood pressure measurement in the same arm. Therefore, two blood pressure measurements are to be documented in the CRFs.

6.2.4.4 Resting Heart Rate

Resting heart rates will be recorded on CRFs at the Screening Visit and the Intensive PK Study Visit. The participant should first sit quietly for five minutes prior to measurement of heart rate.

6.2.4.5 Brief Physical Examination

The following assessments will be performed at the Screening Visit and the Intensive PK Study Visit.

- Examination of the arm to be used for IV placement
- Relevant examinations related by any new signs and symptoms as stated by the participant

6.2.4.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be obtained at the Screening Visit, primarily to assess the corrected QT interval (QTc) as part of the initial safety evaluation and eligibility evaluation.

6.2.4.7 PHQ-9 Depression Symptom Survey

The PHQ-9 questionnaire will be administered at the Screening Visit as part of the initial safety evaluation and eligibility evaluation.

6.2.5.8 Laboratories

All study visit laboratory evaluations performed as part of this study must be present in source documentation, including HIV, hepatitis B, hepatitis C, illicit drug screen, white blood cell count, hemoglobin, platelet count, creatinine and estimated creatinine clearance (for the Healthy Group), glucose, AST, ALT, total bilirubin, and serum pregnancy testing.

All laboratories will be sent to the Indiana University Health Pathology clinical laboratory for immediate processing and analysis; results will be entered on CRFs and kept in secure cabinets.

6.2.5.8 Specimen Collection, Processing, Labeling, and Storage for Specimens for Future Analysis

DNA Sample

- Collection: Collect ONE (1) 7.0-mL K3 purple-top EDTA tube, FILL COMPLETELY. Place on ice immediately. Do not allow to clot. Do not spin.
- Processing: Prepare at least 4 aliquots of 1.5-mL each in 1.5-mL purple screw cap vials from the 7.0-mL whole blood EDTA tube and freeze at -80°C and store upright.
- Labeling: Label on each aliquot the protocol-subject number, date, specimen type "DNA".

Archived Plasma

- Collection:
  - For plasma #1, collect TWO (2) 6.0-mL, purple-top EDTA tubes, FILL COMPLETELY. After collection of blood, gently invert the tube 10 to 15 times and keep upright at room temperature until centrifugation. KEEP REFRIGERATED AT 4$^{O}$C AFTER DRAW IF UNABLE TO CENTRIFUGE IMMEDIATELY.
  - For plasma #2, collect an additional ONE (1) 2.7-ml, blue-top 3.2% buffered Sodium citrate (SCI) tubes, FILL COMPLETELY (for storage). Mix gently by inverting 8 times immediately after filling. DO NOT SHAKE the tube as this will break down fibrinogen in the sample. COMPLETE PROCESSING WITHIN 1 HR OF COLLECTION.
- Processing:
  - For plasma #1 tubes, spin 3000 x *g* for 10 minutes at 4ºC. Prepare at least 6 total aliquots containing at least 0.5-mL of plasma each and freeze at –80°C within 4 hours of collection.
  - For plasma #2 tube, spin at 1500 x *g* for 15 minutes at room temperature. Prepare at least 2 total aliquots containing at least 0.5-ml of plasma each and freeze at –80ºC within 60 minutes of collection.
- Labeling: Label on each aliquot the protocol-participant number, date, specimen type "E-PLA" and "S-PLA", and aliquot number as appropriate.

Archived Serum

- Collection: Collect ONE (1) 10.0-mL red-top tube without additive at room temperature. Let blood clot 30 minutes at room temperature in vertical position.
- Processing: Spin tube for 10 minutes at 1300 x *g* to separate serum within 1 hour of collection. Prepare at least 6 total aliquots containing at least 0.5-mL of serum. Separated serum MUST be refrigerated until frozen. Freeze at -80ºC as soon as possible within 8 hours of collection. REFRIGERATE ALIQUOTS IF FREEZING CANNOT BE ACCOMPLISHED IMMEDIATELY AFTER PROCESSING.
- Labeling: Label on each aliquot the protocol-participant number, date, specimen type "SER", and aliquot number.

DTG and RPV Plasma Drug Concentrations

- Collection: Collect ONE (1) 7.0-mL lavender-top tube without additive at each time point (at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours after study drug administration).
- Processing: Within one hour of collection, spin tube at 3000 rpm for 20 minutes at room temperature. Prepare at least TWO (2) aliquots in to amber brown glass tubes containing 0.5mL each and store immediately at -80°C. Utmost care will be made to protect blood and plasma samples from exposure to light.

- Labeling: Label on each aliquot the protocol-participant number, date, and appropriate time point (PRE, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, or 24).

Drug Concentration Measurement Methods

DTG and RPV and their relevant metabolites concentrations in plasma and urine will be measured in a 96-well plates format using a validated LC/MS/MS assay method [QTRAP 6500+ LC-MS/MS system (AB Sciex, Framingham, MA) with turboelectrospray source operated in both positive (confirmation) and negative (quantification) modes]. The equilibrium dialysis method will be used to determine the fraction unbound DTG and RPV in plasma. Both the LC/MS/MS assay and the equilibrium dialysis methods have been described for DTG by our group recently and will be modified and implemented in this study. Validated LC/MS/MS plasma assay of RPV is available in Dr. Desta's laboratory and this assay will be modified and validated to measure RPV in the equilibrium dialysis samples. At all times, processing plasma and equilibrium dialysis samples will be protected from light.

# 7.0 ADVERSE EVENT MANAGEMENT

## 7.1 General Considerations

### 7.1.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting definition of an AE include: Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
    - The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
    - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency

or drug abuse.

- Is associated with liver injury and impaired liver function defined as:
  - ALT > 3xULN and total bilirubin > 2xULN (>35% direct), or
  - ALT >3xULN and INR > 1.5.
  - Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT > 3xULN and total bilirubin > 2xULN, then the event is still to be reported as an SAE.

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

7.1.2 Assessment of Relatedness/Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to ViiV Healthcare. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ViiV Healthcare.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.1.3 AE/SAE Reporting

Development of any serious adverse event or any new onset adverse event of Grade ≥ 2 using the DAIDS adverse event reporting system (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) and judged to be possibly or definitely due to study drug will lead to immediate cessation of study drug and the participant will be withdrawn from the study without rechallenge.

In particular, CNS symptoms (mood, sleep disturbances), gastrointestinal symptoms, and safety laboratories (liver function tests, complete blood cell counts) will be assessed at the Screening Visit and the Intensive PK Study Visit. A withdrawn study participant will be replaced. For participants who are discontinued from the study due to adverse events, they will be followed (with repeat laboratory testing every 2 weeks as needed) until resolution of the event.

Clinical management decisions and decisions to discontinue participants from the trial will be made by the Principal Investigator(s). All serious adverse events (SAEs) will be documented on CRFs with unexpected SAEs forwarded to the IU IRB within 10 working days of the event; all other non-serious adverse events will be documented on the annual continuing review. All SAE, regardless of causality/relatedness, will be reported to ViiV Healthcare within 24 hours of the study team becoming aware of the event.

## 7.2 Pregnancy

Women who become pregnant while on study will be discontinued from further participation. To ensure participant safety, each pregnancy must be reported immediately to the study team upon learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the study team. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event or serious adverse event. Spontaneous abortions must be reported as a serious adverse event. These events will be reported to the Antiretroviral Pregnancy Registry and to ViiV within 24 hours of becoming aware using the APR reporting form (www.apregistry.com).

## 7.3 Allergy/Rash

Participants may continue for Grade 1 allergic reactions or rash (skin reaction) at the discretion of the study team. The subject should be advised to contact the study team immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

## 7.4 Liver stopping criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study drug and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
For any participant meeting one of the criteria outlined below, or if the Principal Investigator believes that it is in the best interest of the patients, the Principal Investigator must follow the required actions and follow up assessments also outlined in these tables. Any events meeting liver stopping criteria should also be reported to ViiV Healthcare on a Liver Stopping Criteria specific CRF.

Dolutegravir must be discontinued if:

- ALT ≥ 3xULN.
- If ALT ≥ 3xULN AND bilirubin > 2xULN (>35% direct bilirubin), i.e. Hy's case, report event as SAE.

| ***Required Actions and Follow up Assessments following ANY Liver Stopping Event*** | |
|---|---|
| ***Actions*** | ***Follow Up Assessments*** |
| • **Immediately discontinue DTG** | • Viral hepatitis serology, including: |

- **Subject should not be rechallenged due to the risk of a recurrent reaction**.
- Report the event to the [the IU IRB and ViiV Healthcare] within **24 hours of awareness**.
- Events of possible drug-induced liver injury with hyperbilirubinemia[2] will be reported to the [the IU IRB and ViiV Healthcare] as serious adverse events using the serious adverse event case report form.
- Complete the liver event case report form for all events meeting liver stopping criteria, and submit to the [the IU IRB and ViiV Healthcare] within one week of first becoming aware of the event
- Perform liver event follow up assessments.
- Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline
- Subject may continue in the study for any protocol specified follow up assessments.

**MONITORING:**

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) and perform liver event follow up assessments at the central laboratory as described to the right.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline.

- Hepatitis A immunoglobulin M (IgM) antibody;
- HBsAg and hepatitis B core antibody;
- Hepatitis C RNA;
- Hepatitis E IgM antibody.
- Cytomegalovirus IgM antibody.
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
- Syphilis screening.
- Drugs of abuse screen, including alcohol. Record alcohol use on the liver event case report form
- Serum acetaminophen adduct High Performance Liquid Chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [FDA, 2009]). The site must contact the medical monitor when this test is required.
- Serum creatinine kinase and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin ≥1.5xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins).
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Complete Liver Imaging and/or Liver Biopsy case report form.
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form

| | |
|---|---|
| | • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications, and alcohol use. |

Note:
Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or** ALT ≥3xULN **and** INR > 1.5, if INR measured which may indicate severe liver injury **must be reported as a serious adverse event**

7.5 Suicidal risk monitoring

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

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior, or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior.

If any participant experiences a possible suicidality-related adverse event (PSRAE) while participating in this study that is considered by the Investigator to meet ICH E2A (ICH E2A, 1994) definitions for seriousness, the Investigator will collect information using a PSRAE case report form (or agreed alternative) in addition to reporting the event on a serious adverse event case report form. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to the IRB within one week of the investigator diagnosing a possible suicidality-related serious adverse event.

## 8.0 CRITERIA FOR STUDY DISCONTINUATION

- Requirement for prohibited concomitant medications after Screening
- Failure by the participant to attend a scheduled study visit
- Request by the participant to withdraw
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant
- Clinical reasons believed life threatening by the physician
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results, including lack of adherence to the study agent

- At the discretion of the study investigators
- If the pregnancy test is positive or if the participant is found to be pregnant on study visit days
- Development of adverse events of Grade greater or equal to 2 after initiation of study drug and judged to be possibly due to study drug

## 9.0 STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT

### 9.1 General Considerations

Data management and statistical analyses will be the responsibility of Dr. Desta (Division of Clinical Pharmacology, Indiana University School of Medicine). Parameter estimates and relevant summary statistics will be reported for the PK, primarily using Geometric Mean Ratios and associated 90% CI, and side effects. Continuous variables will be summarized by means, medians, minima, maxima, and standard deviations. Categorical variables will be summarized by frequencies and percentages. Additional exploratory analyses will be performed when appropriate. Normality of variables will be checked and, if violated, nonparametric methods will be adopted. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature of the study. All PK analyses will be performed using Phoenix WinNonlin.

### 9.2 Study Design

The objectives of this study will be achieved by performing a matched, two-group study of 10 participants in the HD Group and 10 participants in the Healthy Group.

### 9.3 Sample Size Justification

No formal hypothesis testing will be utilized for this study. An estimation approach will be used to evaluate the effect of ESRD requiring hemodialysis on DTG and RPV PK. The target sample size of 10 evaluable subjects per study group was chosen based on feasibility to address the objectives of the study. This sample size is considered sufficient to determine whether the PK in subjects with severe renal impairment requiring HD is meaningfully different from subjects with normal renal function. The between-subject coefficients of variation of PK parameters from 50 mg tablet administration in DTG studies involving participants with normal renal function (11-14) were in the range of 20-35%, 16-30%, and 26-58% for the DTG PK parameters $AUC_{0\text{-}tau}$, Cmax, and Ctau respectively. The between-subject coefficients of variation of PK parameters from 25 mg tablet administration in RPV studies of participants with normal renal function (14-17) were in the range of 26-34%, 28-35%, and 26-41% for the RPV PK parameters $AUC_{0\text{-}tau}$, Cmax, and Ctau, respectively.

If the point estimate of the geometric mean ratios (GMR) of the two study groups is assumed to be 1 for each PK parameter, then the tables below show the 90% confidence intervals on a log scale for these GMR for sample sizes of 10 and 9 (if there is data loss) in each study group. For each parameter, we provide the actual lower bound of the confidence interval for the parameter using the lowest, highest, and pooled concentration estimates from the literature.

Dolutegravir

| | If N=10 | | If N=9 | |
|---|---|---|---|---|
| $AUC_{0\text{-}tau}$, µg·h/mL | | | | |
| Lowest | 38.43 | (0.89, 1.11) | 38.16 | (0.88, 1.12) |
| Highest | 43.80 | (0.85, 1.15) | 43.37 | (0.83, 1.16) |
| Pooled | 40.43 | (0.84, 1.16) | 40.02 | (0.84, 1.16) |
| Cmax, µg/mL | | | | |
| Lowest | 2.89 | (0.83, 1.17) | 2.86 | (0.83, 1.17) |
| Highest | 3.63 | (0.86, 1.14) | 3.60 | (0.84, 1.15) |
| Pooled | 3.26 | (0.86, 1.14) | 3.23 | (0.86, 1.14) |
| Ctau, µg/mL | | | | |
| Lowest | 0.64 | (0.68, 1.32) | 0.62 | (0.66, 1.34) |
| Highest | 0.80 | (0.75, 1.25) | 0.79 | (0.74, 1.26) |
| Pooled | 0.74 | (0.76, 1.24) | 0.73 | (0.75, 1.25) |

Values are lower bounds for 90% confidence interval based on historical estimates (11-14), along with 90% confidence intervals around the null ratio of 1 (no change).

Rilpivirine

| | If N=10 | | If N=9 | |
|---|---|---|---|---|
| $AUC_{0\text{-}tau}$, ng·h/mL | | | | |
| Lowest | 1719 | (0.81, 1.19) | 1697 | (0.80, 1.20) |
| Highest | 2463 | (0.86, 1.14) | 2441 | (0.85, 1.15) |
| Pooled | 1958 | (0.82, 1.18) | 1935 | (0.81, 1.19) |
| Cmax, ng/mL | | | | |
| Lowest | 103 | (0.74, 1.26) | 101 | (0.72, 1.28) |
| Highest | 168 | (0.85, 1.15) | 166 | (0.84, 1.16) |
| Pooled | 128 | (0.82, 1.18) | 126 | (0.81, 1.19) |
| Ctau, ng/mL | | | | |
| Lowest | 51.6 | (0.74, 1.26) | 50.6 | (0.72, 1.28) |
| Highest | 86.2 | (0.86, 1.14) | 85.4 | (0.85, 1.15) |
| Pooled | 64.3 | (0.80, 1.20) | 63.4 | (0.79, 1.21) |

Values are lower bounds for 90% confidence interval based on historical estimates (14-17), along with 90% confidence intervals around the null ratio of 1 (no change).

Based on the pooled half-width estimate of 24% for the 90% CI for DTG, even if the Ctau GMR was as low as 0.50 based on the study by Weller in patients with reduced renal function (6), then the lower bound of 0.26 (0.50-0.24) would still be above the 0.25 requirement to maintain virologic efficacy as determined by Song et al. [Pharmacokinetics (PK) and PK-Pharmacodynamic (PD) Relationship of Dolutegravir (DTG) in Integrase Inhibitor (INI)-Naive Subjects. Song et al. 53rd ICAAC, Denver, CO, 2013].

## 9.4 Criteria for Stopping the Study

No early stopping rules will be implemented.

## 9.5 Patient Characteristics and Significant Protocol Violations

Demographics and other baseline data will be summarized descriptively for all enrolled participants. Comparisons between the two groups will be performed using Pearson's chi-square tests and Student's t-tests. Significant protocol violations will be documented.

## 9.6 Analysis Plan for the Primary Objective

To address the primary objective of the study, we will focus on trough concentration (24 h after the observed inpatient dosing of FDC DTG and RPV, or Ctau) for each study drug as this parameter is most closely predictive of clinical efficacy (e.g. virologic suppression). Ctau concentrations will be calculated as the value occurring at the terminal sample point. A sampling window of 30 minutes before to 30 minutes after the 24-hour observed post-dose will be used to estimate Ctau. Concentrations obtained during that time period will be expected to be acceptable deviations (within 2%) from nominal time for Ctau. Other pharmacokinetics, including Cmax, $AUC_{0\text{-}tau}$, CL/F, steady state average concentration calculated as $AUC_{0\text{-}tau}$/duration of the dosing interval (24 hour), and fractions unbound will be obtained for secondary PK analyses. PK parameters will be either observed (Cmax, Ctau) or derived from non-compartmental analysis using Phoenix WinNonlin 8.1 ($AUC_{0\text{-}tau}$ and CL/F PK parameters will be log-transformed). 95% percent confidence intervals and other summary statistics will be calculated and reported on both the log and original scales. PK parameters will be compared for both total and free/unbound concentrations between the two study groups using t-tests and ANCOVAs as appropriate. GMRs with 90% confidence intervals will be calculated for the comparison of interest (HD Group: Healthy Group).

## 9.7 Analysis Plan for Secondary Objective

Safety assessments will be performed using the safety dataset.

## 9.8 Interim Analysis

No interim analysis will be performed.

## 9.9 Subgroup Analysis

No subgroup analyses are planned.

## 9.10 Data Management

A comprehensive web-based data management system will be developed for this study using REDCap which will allow controlled entry through the internet. REDCap provides a secure, web-based environment that provides an intuitive data entry interface and has real-time validation rules (with automated data type and range checks). The system offers easy data manipulation with logged auditing, functionality for reporting, monitoring and querying subject records. An experienced Database Administrator provides database creation, daily backup, and installation of security patches.

A unique identifier will be assigned to each study participant and their associated study specimens. Patient identifiers will be located only within the participant's study file in a separate, locked cabinet within the Division of Clinical Pharmacology. Hardcopies of laboratory source records will also be stored in a locked file

cabinet. Initial screening, consenting of potential subjects, and data abstraction and recording will be completed by the primary investigators or by the research study coordinators from the ICRC.

## 10.0 HUMAN PARTICIPANTS RESEARCH AND PROTECTION

### 10.1 General Considerations/Investigator Training

The Human Participants Research outlined in this proposal does not meet the definition of a clinical trial. This is an observational study comparing the PK and safety of two study groups over a short period of time. Therefore, a formal Data and Safety Monitoring Board is not required, although appropriate monitoring through the Data and Safety Monitoring Plan with independent monitor as described below will be fully implemented. This trial will be posted on ClinicalTrials.gov and updated regularly as needed for protocol updates and results. All Indiana University personnel involved with this application have successfully completed the training and examination involved with the Collaborative Institutional Training Initiative Course.

### 10.2 Risks to the Participants

#### 10.2.1 Human Participants Involvement and Characteristics

- A total of 20 HIV-negative participants will be recruited to participate in this study.
    - All participants must be between 18-65 years inclusive, do not have HIV infection, and have a screening PHQ-9 score <10.
    - There will be 10 enrolled participants in the Hemodialysis Group (HD Group) and 10 in the Healthy Group without renal insufficiency. Participants who do not complete the Intensive PK Study Visit will be replaced.
    - The chief exclusion criteria include known cirrhosis, gastrointestinal disease that would impair absorption of the study drug, and use of prohibited medications.
    - Potential participants will be recruited from the dialysis clinics affiliated with the IU Division of Nephrology or after self-referring in response to recruitment advertisements. All study procedures will occur in the Indiana Clinical Research Center at Indiana University Health University Hospital.

#### 10.2.2 Sources of Materials

- All data for this study will be obtained only after written, informed consent is provided by each participant. Existing medical records will be reviewed for demographics, medical diagnoses, medications, and dialysis parameters. Blood samples will be obtained for testing for HIV infection, chemistries, liver function tests, cell counts, pregnancy testing, and PK parameters. Serum, plasma, and DNA will be obtained for future studies of interest. Questionnaires to assess depression, medication adherence, and tobacco/alcohol/illicit drug use will be implemented. An electrocardiogram will be obtained to assess for QT prolongation prior to study drug administration.
- Results from pertinent medical records and procedures performed for these studies, as outlined above, will be recorded on the human participants involved in the projects in this application.
- Data will be stored in a password-protected computerized database via REDCap that will include only the participants' study identification number (names and other identifiable information will not be included). Therefore, the SID# will be the only link to the participant. Only the principal

investigators, co-investigators, and research personnel who will directly obtain the necessary data will have access to the participant identities. All data obtained for this study will be obtained only after written, informed consent is provided by each participant.

- Records will be reviewed manually. Blood specimens will be obtained via peripheral venipuncture. Questionnaires will be completed in private settings. These data will be collected solely for the purpose of the proposed research projects.

10.2.3 Potential Risks

- Risks associated with the study drug, FDC DTG+RPV (JULUCA). These primarily consist of psychiatric disorders (worsening depressive symptoms, headache, and insomnia), gastrointestinal and liver events (nausea, vomiting, diarrhea, hepatotoxicity, jaundice, abdominal pain, fever), and skin reactions (primarily rash).
- Other risks:
    - Loss of participant confidentiality.
    - Blood drawing/needle sticks associated risks, which include pain, bruising, infection, and phlebitis.
    - The amount of blood to be drawn at Screening is 30 mL (two tablespoons). The amount of blood to be drawn during the Intensive PK Study Visit is approximately 120 mL (six tablespoons), respectively. The total amount of blood to be obtained over the study period would then be approximately 150 mL (8 tablespoons), which is well within the accepted standards for blood donation.
    - Participants may also feel unease in completing the questionnaires.
- The principal alternative to these procedures would be not to participate in the research.

10.3 Adequacy of Protection Against Risks

10.3.1 Recruitment and Informed Consent

- Recruitment will only begin once the Indiana University Institutional Review Board has approved this study. All HD participants will be recruited from the dialysis clinics associated with the IU Division of Nephrology or in response to recruitment advertisements. Healthy Group participants will be recruited from the community through general advertising on CTSI All In for Health website along with the CTSI All IN for Health voluntary registry IU IRB Protocol Number 1105005444. If the primary dialysis provider for the patient believes he or she is eligible for the study and allows the patient to be approached for screening, one of the study investigators or a study coordinator will approach each potential participant during his or her regularly scheduled clinic visit or dialysis session. If eligibility is confirmed, then the purpose, procedures, and risks and benefits of the study will be discussed with the participant. Participants will have ample opportunity to ask questions and to have all concerns addressed. If the participant wishes to pursue screening, then written informed consent will be obtained (and a copy given to the participant) prior to screening as screening requires fasting; if this is not possible, a waiver from IRB to allow fasting prior to provision of written, informed consent will be requested. All consent forms will be stored in a locked file cabinet.

10.3.2 Protection Against Risk

10.3.2.1 Confidentiality. To minimize the risk to participant confidentiality, patient identifiers will be removed once his or her data is abstracted and recorded, and only the random study identification number (generated when consent is provided) will be used. All hardcopy study data will be kept in a secured and locked file cabinet. All electronic data will be kept in a password-protected computer database. The only link between patient identifiers and the randomized study identification number will be kept in separate files. Identifiers will never be used in the analysis or presentation of study results.

10.3.2.2 Blood draws. The risks of blood drawing will be minimized by having only experienced medical personnel perform this procedure. The amount of blood that will be drawn falls well within safety standards for blood donation.

10.3.2.3 Questionnaires. Participants may feel uneasy or discomfort in completing the depression, treatment adherence, and physical activity questionnaires. To minimize this risk, questionnaires will be completed in private settings with any questions regarding completion of the questionnaires addressed by trained study team personnel.

10.3.2.4 Study drug toxicity. We do not anticipate serious adverse events to occur with JULUCA due to its known safety profile in HIV-positive patients. To minimize these risks further, we will exclude those participants who may be at higher risk of such toxicities, including those with a PHQ-9 score $\geq 10$, those with abnormal liver function tests or known cirrhosis, those with abnormal blood cell counts, and those with a QTc >500 msec on standard 12-lead ECG. We will also exclude those who are pregnant/breastfeeding. In addition, we will closely monitor for any intolerances/side effects during the 14 day period when study drug is to be taken. We will call or visit with the participant on Days 3 and 9 after Drug Dispensation to determine if any new symptoms or side effects may have developed due to study drug. We will also assess for drug toxicities at the beginning of the Intensive PK Study Visit. We will then assess for later developing toxicities at a final phone call or in-person visit ~14 days after the Intensive PK Study Visit. Appendix 2 lists key risks and risk mitigation strategies for use of dolutegravir.

10.3.2.5 Adverse event financial management, grading, and reporting. In the event of an adverse event, necessary medical and professional intervention will be provided immediately and billed to the participant's medical insurance (if available). If the participant does not have insurance, care will be provided via the indigent care program at Eskenazi Health Hospital. Standard procedures for reporting deviations from protocols will be followed; serious adverse events that meet the Indiana University IRB prompt reporting requirements will be reported within 30 business days. All adverse events will be graded using The Division of AIDS Table for Grading Adult Adverse Experiences is located at: http://roc.s-3.com/members/download/adulttox.pdf.

10.3.2.6 Data and Safety Monitoring. Dr. Michael Eadon of the Division of Nephrology at Indiana University will serve as the independent chair and monitor for this trial. He will receive reports approximately every six-eight months regarding the progress and participant safety during the trial.

10.4 Potential Benefits of the Proposed Research to the Participants and Others

- Direct benefits to the participants are not expected. However, they may benefit from knowing that their participation will accrue knowledge that could benefit those with ESRD requiring HD.

- The proposed research may lead to the proper dosing and utilization of JULUCA in patients with ESRD requiring HD. These would include HIV-positive patients who require options for treatment who are intolerant to other HIV medications and HIV-negative patients for whom JULUCA or its component drugs may be used as part of pre-exposure or post-exposure prophylaxis to HIV infection. These results then would benefit society directly by impacting clinical practice.

## 10.5 Importance of the Knowledge to be Gained

- The knowledge that will be gained from this study will determine how to dose properly DTG and RPV (the components of JULUCA) in patients requiring HD for ESRD. Currently used dosing is based on single-dose PK studies and thus may not reflect true steady-state PK and proper dosing in this population. Improper dosing may lead to reduced efficacy and worse toxicities. As such, this study would potentially impact the clinical care of HIV-positive patients who require options for treatment and to HIV-negative patients needing alternative therapies for pre-exposure and post-exposure prophylaxis to HIV infection. Given that 'treatment is prevention', proper use of these drugs could benefit society by reducing transmission of HIV. Therefore, the importance of the knowledge gained outweighs the risks to the participants.

## 10.6 Data and Safety Monitoring Plan

Progress of these studies, including data monitoring, participant enrollment, protocol deviations, and all SAE, will be reviewed by a panel including the PIs (Drs. Gupta and Desta) and a nephrologist at Indiana University not directly connected with this study (Dr. Michael Eadon of the Division of Nephrology, Indiana University School of Medicine). Reports, which will include descriptions of all adverse events, will be prepared for review by this panel approximately every 6-8 months. Any study participant prematurely discontinued due to an adverse event will be reviewed immediately. Standard procedures for reporting deviations from protocols to the Indiana University ICRC, IRB, and the sponsor will be implemented. Serious Adverse Events (SAEs) will also be reported to the IRB within 30 working days and subsequently forwarded to the sponsor as required. All SAE will be reported to ViiV within 24 hours of the study team becoming aware of the event.

## 10.7 Inclusion of Women and Minorities

There are no exclusion criteria based on sex, gender identity, racial category, or ethnicity.

## 10.8 Inclusion of Children

As the objectives of this study are to address the PK of FDC DTG+RPV in adults with ERSD requiring HD, only participants ≥ 18 years will be eligible for enrollment. Changes in drug disposition may occur due to physiologic changes occurring during childhood and adolescents, and so those < 18 years will be excluded.

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**Appendix 1: Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential**

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to Females of Reproductive Potential (FRP) with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011
7. Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

## Appendix 2: Dolutegravir Risk Assessment

Dolutegravir (TIVICAY)

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Investigational Product: dolutegravir<br>Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information | | |
| Hypersensitivity and rash | Hypersensitivity reactions has been observed uncommonly with DTG. Rash, generally mild to moderate in intensity, was commonly reported in DTG Phase IIb/III clinical trials. No episodes of severe rash, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme, were reported in these clinical trials. | Subjects with history or presence of allergy/sensitivity to any of the study drugs or their components are excluded<br><br>Specific toxicity management guidance is provided for hypersensitivity reactions and rash<br><br>The subject informed consent form includes information on this risk and the actions subjects should take in the event of a hypersensitivity reaction or associated signs and symptoms. |
| Drug induced liver injury and other clinically significant liver chemistry elevations | Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy containing DTG regardless of dose or treatment population. | Subjects meeting any of the following criteria during the screening period are excluded from participating<br><br>• Alanine aminotransferase (ALT) above the upper limit of normal (ULN) or total bilirubin ≥1.5xULN<br><br>Positive for HBV (hepatitis B virus surface antigen positive [+HBsAg]) or positive HCV (positive hepatitis C antibody test) within 3 months of the Day 1 study visit<br><br>Specific/detailed liver stopping criteria and toxicity management guidance are provided for suspected drug induced liver injury or other clinically significant liver chemistry elevations |
| Neural Tube Defects | In the ongoing observational study conducted in Botswana, preliminary results show that in babies born to women who were taking DTG when they became pregnant there was an increased risk of | Pregnancy testing should be performed before initiation of DTG therapy in all women of child bearing potential (negative pregnancy test at screening and randomization). |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Investigational Product: dolutegravir<br>Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information | | |
| | neural tube defects compared with the background rate.<br><br>Dolutegravir was tested in a complete package of reproductive toxicology studies, including embryofetal development studies. No adverse development outcomes, including neural tube defects, were identified from reproductive toxicology studies. In reproductive toxicity studies in animals, DTG was shown to cross the placenta.<br><br>Data available from other sources including the Antiretroviral Pregnancy Registry (APR), other cohorts and clinical trials are insufficient to confirm or refute this potential risk. | Women who are pregnant or who plan to become pregnant, are excluded.<br><br>All women of reproductive potential should use effective contraception (Appendix 1).<br><br>The subject informed consent form provides information about this potential risk. |