TITLE: Safety, tolerability, and drug-drug interactions of short-course treatment of latent tuberculosis infection with high-dose rifapentine and isoniazid or standard isoniazid preventative therapy among HIV-infected patients taking dolutegravir-based antiretroviral treatment

Protocol number: 3HP-DTG-AUR1- 6-212
Short study name: DOLPHIN TOO
Protocol Version: 6.0
Date: 3 May 2019
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LIST OF ABBREVIATIONS AND ACRONYMS

3HP	3 month regimen of weekly isoniazid and rifapentine therapy
9H	9 month regimen of daily isoniazid therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	anti-retroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
Cl/F	oral clearance
Cmax	maximum (or peak) serum concentration
Cmin	minimum serum concentration
C_T	trough concentration
CAB	community advisory board
CBC	complete blood count
CDC	The Centers for Disease Control and Prevention
CRF	case report form
CRP	C-reactive protein
CXR	chest X-ray
DoH	Department of Health
DOT	directly observed treatment
DTG	dolutegravir
EAE	expedited adverse event
EFV	Efavirenz
FTC	Emtricitabine
FDA	(United States) Food and Drug Administration
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HP	isoniazid and rifapentine
IGRA	Interferon gamma release assay
INH	isoniazid
INSTI	integrase strand transferase inhibitor
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
k_a	absorption rate constant
Kg	Kilogram
3TC	lamivudine
LFT	liver function test
LTBI	latent tuberculosis infection
Mg	milligram

NRTI	nucleoside reverse transcriptase inhibitors
PI	principal investigator
PK	pharmacokinetics
PLWH	persons living with HIV
QFT	QuantiFERON
RIF	rifampicin
RPT	rifapentine
SAE	severe adverse event
SAHPRA	South African Health Products Regulatory Authority
SGOT	serum glutamic-oxaloacetic transaminase, *see also* AST
SGPT	serum glutamic-pyruvic transaminase, *see also* ALT
SMC	Safety Monitoring Committee
SOE	schedule of evaluations
TB	Tuberculosis
TDF	Tenofovir
TPT	TB preventative therapy
TST	tuberculin skin test
U&E	urea and electrolytes
ULN	upper limit of normal
USAID	United States Agency for International Development
Vd	volume of distribution
VL	HIV-1 viral load
WHO	World Health Organization

PROTOCOL SYNOPSIS

Protocol Title:	Safety, tolerability, and drug-drug interactions of short-course treatment of TB preventive therapy with high-dose once-weekly rifapentine (RPT) plus isoniazid or standard of care isoniazid preventative therapy (IPT) among human immunodeficiency virus (HIV)-infected patients taking dolutegravir-based antiretroviral treatment
Treatment Indication:	TB preventive therapy (TPT) in persons with HIV infection
Trial Objective:	Assess the safety, tolerability, and pharmacokinetics of three months of once-weekly isoniazid and rifapentine (3HP) or 9 months of Isoniazid alone (IPT) among persons taking dolutegravir (DTG) and tenofovir/emtricitabine (TDF/FTC) or tenofovir/lamivudine (TDF/3TC) for HIV infection
Trial Design:	Single-arm, single-center, Phase I/II clinical trial, in four groups. Individuals with HIV infection taking Efavirenz (EFV) and two nucleoside reverse transcriptase inhibitors (NRTI) who have undetectable (Groups 1 and 2) or detectable (Group 3 and 4) HIV viral load and an indication for TPT, will be switched to DTG with tenofovir/emtricitabine (Groups 1 and 2) or lamivudine/tenofovir (Groups 3 and 4). Group 1 and 2 will receive weekly HP for 12 total doses starting 8 weeks after initiating DTG. Individuals who are on an existing DTG-based plus two NRTI ART regimen for at least eight weeks (and have not received efavirenz or nevirapine for at least two months) who have an undetectable HIV viral load may also participate. Individuals with HIV infection who are ART treatment naïve at any HIV viral load level and have an indication for TPT will start DTG and be enrolled to receive standard IPT (Group 3) or HP (Group 4) initiated at the same time as DTG. Group 3 and 4 will be enrolled after follow up of Group 1 and 2 has been completed. Group 1 (n=30): The first 12 participants (Group 1A) will take dolutegravir 50 milligrams (mg) once daily (with tenofovir/emtricitabine) from Days 1-57. Semi-intensive PK sampling for dolutegravir will be performed on Day 57. Participants will continue once-daily dolutegravir and will receive once-weekly HP for 12 total doses beginning on Day 58. Semi-intensive PK sampling for dolutegravir will be performed on Day 72 (with the 3rd dose of HP) and Day 108 (following the 8th dose of HP). Trough concentrations (C_T) will be measured on Days 59, 74, and 78. PK assessments will be performed at weeks 9 and 11 for rifapentine and at week 11 for isoniazid. VL will be measured at baseline and weeks 11 and 24. Safety labs (complete blood count (CBC), urea and electrolytes (U&E) and creatinine and liver function tests (LFT)) will be obtained at baseline, and weeks 9, 11, 13, 16, 20 and 24. After the 12 Group 1A participants have completed the second semi-intensive PK visit, an interim PK, safety, and VL assessment will be

	performed to ensure that the 50 mg once daily dose is safe and meets PK targets. The subsequent 18 participants in Group 1 (Group 1B) will receive either dolutegravir 50 mg or a higher dose of dolutegravir, if dose adjustment is required (e.g. dolutegravir 50 mg twice daily just on HP dosing days, dolutegravir 50 mg twice daily seven days a week, etc.) A **second interim evaluation** focused on PK will occur after all Group 1B participants have completed the Week 11 semi-intensive PK visit. This evaluation will include all PK data from Group 1A, who will have completed their Week 16 semi-intensive PK visit plus PK data from Group 1B up to and including the Week 11 semi-intensive PK visit. A **third interim evaluation** focused on safety and virologic response will occur after all participants (Groups 1A, 1B, and 2) have completed the Week 11 visit. This evaluation will include all safety data and HIV viral load information collected up until that point from all participants. <u>Group 2 (n=30)</u>: These participants will receive dolutegravir and HP at the same doses and dose schedule as the participants in Group 1B. They will undergo safety assessments at baseline and weeks 9, 11, 13, 16, 20 and 24; HIV VL assessments will be performed at baseline and weeks 11 and 24. Sparse (trough) PK samples for dolutegravir will be collected on two occasions. <u>Group 3 (n=25):</u> The next 25 participants who are ART treatment naïve will start dolutegravir 50 milligrams (mg) once daily (with tenofovir/lamivudine on study Day 0. Sparse PK sampling for trough concentrations (C_T) of dolutegravir will be performed on Day 1 (24 hours after taking the first dose of DTG, and before taking the first dose of standard isoniazid). Sparse PK sampling for trough concentrations (C_T) of dolutegravir will be performed on Day 24 (Week 3), to parallel 72^1 hours after the 3rd dose of HP. The final sparse PK sampling for trough concentrations (C_T) of dolutegravir will be performed on Day 59 (Week 8), to parallel 72^1 hours after the 8th dose of HP. HIV VL will be measured at screening, and Weeks 3, 8, 12, 16, and 24. Safety labs (complete blood count (CBC), urea and electrolytes (U&E) and creatinine and liver function tests (LFT)) will be obtained at baseline. Creatinine will be repeated at Weeks 2, 4, 8, 12, 16 and 24 and LFTs will be repeated at weeks 4, 8, and 12. <u>Group 4 (n=50):</u> After Group 3 is fully enrolled, another group of 50 participants who are ART treatment naïve will start dolutegravir 50 milligrams (mg) once daily (with tenofovir/lamivudine) on Day 0. They will begin TPT with once weekly HP the day after starting DTG, on Day 1. Sparse PK sampling for trough concentrations (C_T) dolutegravir will be

	performed on Day 1 (24 hours after the first dose of DTG, before the first dose of HP). Sparse PK sampling for trough concentrations (C_T) of dolutegravir will be performed on Day 24 (72[1] hours after the third dose of HP). Sparse PK sampling for trough concentrations (C_T) of dolutegravir will be performed on Day 59 (72[1] hours after the eighth dose of HP). HIV VL will be measured at screening, and Weeks 3, 8, 12, 16, and 24. Safety labs (complete blood count (CBC), urea and electrolytes (U&E) and creatinine and liver function tests (LFT)) will be obtained at baseline. Creatinine will be repeated at Weeks 2, 4, 8, 12, 16, and 24, and LFTs will be repeated at weeks 4, 8, and 12. [1] (+/- 24 hours)
Patient Population:	Individuals with HIV infection who are taking EFV (or DTG) and two nucleoside reverse transcriptase inhibitors (NRTIs) for at least eight weeks and who have a suppressed HIV-1 viral load (VL) and individuals who are ART treatment naïve at any HIV viral load level. Participants must be ≥ 18 years old, weight ≥ 50 kilogram (kg), be HIV seropositive, and be candidates to receive TB preventive therapy (i.e. no evidence of active TB). Women of childbearing potential must be willing to use two forms of contraception. Key exclusion criteria include elevated creatinine, Karnofsky status <80, abnormal liver enzymes, thrombocytopenia, treatment of TB or latent TB infection within the past year, history of drug hypersensitivity.
Study treatment:	• HIV treatment: DTG will be dosed as described above and will be given with daily TDF/FTC or TDF/3TC. • TPT regimen: 3HP will be given once-weekly orally for a total of 12 doses, with doses as follows: Rifapentine: 900 mg; Isoniazid: 900 mg -or- Standard isoniazid preventative therapy as prescribed under national TPT guidelines
Trials sites:	• The Aurum Institute, NPC, South Africa, Clinical Research Division Tembisa Clinical Research Centre, South Africa

Criteria for evaluation:

Primary Objectives:

1) To evaluate the effect of RPT and INH given at doses of 900 mg once weekly (HP) on the pharmacokinetics (PK) of DTG
2) To describe the safety of DTG and 3HP co-administration

Secondary Objectives

1) To estimate the proportion of participants who maintain HIV-1 virologic suppression among patients treated with DTG-based ART plus 3HP (Groups 1 and 2)
2) To assess the proportion of HIV treatment-naïve participants who achieve virologic suppression at 12 and 24 weeks after starting DTG-based ART (Groups 3 and 4)
3) To describe the PK of isoniazid and rifapentine in the study population
4) To examine DTG dosing options when given together with once-weekly HP in people living with HIV (PLHIV) requiring LTBI treatment.

Exploratory Objective

1) To describe the rate of decline of plasma HIV-1 Viral load among antiretroviral treatment naïve participants receiving tuberculosis preventive therapy (Groups 3 and 4)

Primary Endpoints

1) Population plasma PK parameters of DTG in the presence or absence of once-weekly HP, including absorption rate constant (k_a), volume of distribution (Vd), and oral clearance (Cl/F) and between-subject variability terms; post-hoc Bayesian predictions of secondary PK parameters of DTG including daily AUC and C_{min} following HP dosing.
2) Grade 3 or higher adverse events (AE)

Secondary endpoints

1) HIV-1 RNA viral load
2) Population PK parameters of RPT and INH; post-hoc Bayesian predictions of secondary PK parameters (AUC, Cmax, Cmin), taking into account (for INH) NAT2 acetylator status
3) Dose options for DTG with once-weekly HP derived by simulation using nonlinear mixed effects models.

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1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Tuberculosis in HIV-infected persons

Tuberculosis (TB) and HIV infection continue to be major global health threats. While deaths related to HIV infection have decreased markedly over recent years, reductions in TB-related mortality have not kept apace, and in 2014, for the first time, TB surpassed HIV as the number one cause of infectious disease related death. TB disproportionately affects persons living with HIV (PLWH). Among 10.5 million people with TB in 2015, 1.4 million were HIV-positive, and of the 1.5 million people who died from TB, 400,000 (33%) were co-infected with HIV (1); TB remains the leading cause of death among HIV-infected persons. HIV substantially increases the risk of progression from latent tuberculosis infection (LTBI) to active disease. The World Health Organization (WHO) estimates that among individuals with LTBI, people living with HIV have a 26-fold higher risk of progression to TB disease than those without HIV (2). HIV and TB display potentially lethal synergy, with HIV-associated immunosuppression triggering markedly increased susceptibility to TB and TB accelerating HIV-associated morbidity and mortality.

In the global context, South Africa has one of the world's most pronounced TB epidemics, with the third highest TB incidence in the world and the greatest number of HIV-associated incident TB cases. Novel strategies are required to accelerate progression towards TB elimination in settings such as South Africa where HIV-associated TB disease is a major factor in failure to meet global targets to halt TB.

1.1.2 Isoniazid and rifapentine for the prevention of TB disease

For HIV-uninfected persons with LTBI, the lifetime risk of reactivation is approximately 5-10% (3,4), but for PLWH, the annual risk of progression to TB disease is 3-16% per year (5). Interestingly, the higher risk of TB disease commences almost immediately after HIV infection, even when CD4 cell counts are still high. This increased risk is the basis for WHO's recommendation to provide both ART and TB preventive therapy to PLWH who are unlikely to have active TB. ART quickly and dramatically reduces TB incidence in HIV-infected persons, and this is true in areas of both high and low TB endemicity (6-8). Even with ART, though, risk of TB remains higher in PLWH than in the general population.

Isoniazid preventive therapy (IPT) has been the mainstay of TB prophylactic therapy for decades. IPT, with isoniazid given at a dose of 5 mg/kg (maximum 300 mg) daily for 9 months (9H), has proven efficacy and is generally well-tolerated. Completion rates for 9H, though, remain poor (9,10) and are consistently lower than completion rates for shorter-course TB prophylactic regimens (11,12).

A regimen of high dose RPT plus high dose INH given weekly for three months (3HP) is approved for the treatment of LTBI among high risk persons by the US Food and Drug Administration (FDA), and is recommended by the US Centers for Disease Control. The 3HP regimen has been shown to be non-inferior to a regimen of 6-9 months of INH for the prevention of TB, with better completion rates (12,13). For the first time in 2015, WHO recommended 3HP as a treatment option for LTBI in high income, low burden countries (14), and by December 2017 will also recommend 3HP for low income, high burden countries. 3HP is both safe and effective in patients with HIV infection, and the regimen is better-tolerated than the nine-month regimen of daily isoniazid in this population (15); however, in the Phase 3 registration trial, participants with HIV were not allowed to be taking ART. Based on small drug interaction studies, 3HP can be used with nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI) and efavirenz or raltegravir (16-18). Because of its potent induction of cytochrome P450 isoenzyme 3A (CYP3A) (19), RPT cannot be used together with protease inhibitors.

1.1.3 Dolutegravir for the treatment of HIV infection

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) that is now a first-line therapy for treatment of HIV infection in many settings. DTG is included in preferred regimens for antiretroviral naïve patients by both the US Department of Health and Human Services and the International AIDS Society USA guidelines panels (20,21). Because it is well-tolerated, inexpensive to manufacture, and has a relatively high barrier to resistance, DTG is now being introduced in many settings around the globe. Notably, DTG was recently approved and launched in South Africa.

Primarily metabolized by UGT1A, with CYP3A as a minor route, DTG has been studied with daily-dosed rifampin in healthy HIV-uninfected volunteers (22). Given twice daily with standard-dose, daily rifampin, DTG total daily exposures were similar to or higher than those achieved with DTG given once daily alone. The safety, tolerability, and efficacy of DTG given at a dose of 50 mg twice daily together with daily rifampicin (RIF), given as part of full four-drug TB treatment (with isoniazid, pyrazinamide, and ethambutol), is currently being tested in the INSPIRING trial, a clinical trial involving patients with HIV-TB that is now fully enrolled (clinicaltrials.gov identifier: NCT02178592). Results are expected in late 2017. Whether or not DTG can be given together with RPT (dosed either daily or once-weekly as part of 3HP) without dose adjustment has not been determined. In a small study assessing the PK and safety of DTG when given at a dose of 50 mg once daily together with once-weekly isoniazid and rifapentine (each dosed at 900 mg, given for 3 total doses) in HIV-uninfected healthy volunteers, DTG trough (Cτ) concentrations were reduced by 43%, 74%, and 53% two, three, and six days after the dose, compared to when DTG was given alone (23). The lowest average Cτ, though, remained 5.3 times higher than the protein-adjusted IC_{90} for DTG, suggesting that even with these reductions in exposure, virologic suppression was likely to be maintained in patients with HIV taking standard-dose DTG. The combination, however, was poorly-tolerated, with flu-like syndrome seen in two of three volunteers following the third once-weekly dose. Exposures to RPT and its main metabolite were similar to reference PK data, but INH exposures were much higher than expected in the two subjects that developed flu-like syndrome (23). Brisk immune responses have been seen in healthy volunteers given rifamycins previously (22,24,25), and in patients with TB disease, rifamycin hypersensitivity is most common when rifamycins are dosed intermittently (26,27). The safety and tolerability of dolutegravir plus 3HP remains to be established in patients with HIV-LTBI co-infection; moreover, the dose of dolutegravir required to maintain HIV virologic suppression among patients with HIV-LTBI receiving 3HP must be determined before these drugs can be used together.

Initial data from Groups 1 and 2 of this trial (DOLPHIN-ONE) provided reassurance that co-administration of DTG-based ART and 3HP was safe and well-tolerated in individuals who are already virologically suppressed—all participants maintained viral loads of < 40 copies/mL throughout HP dosing. This was so despite a slight lowering in DTG trough that was observed in participants given HP; the geometric mean DTG trough pre-HP and during HP were 1003 ug/mL (5^{th} to 95^{th} %ile 500-2080) and 546 ug/mL (5^{th} to 95^{th} %ile 134-1616), respectively. Geometric mean ratios of DTG trough 1, 2, and 6 days post-HP dose (in comparison to baseline DTG trough) were 0.85 (90% CI 0.42-1.20); 0.41 (90% CI 0.15-0.68), and 0.39 (90% CI 0.18-0.87). There was a mild impact of 3HP on the bioavailability of DTG, but no impact on the clearance. All but one DTG trough level during the HP coadministration were above the in vitro IC90 for the drug of 64 ug/mL. There were no Grade ≥3 AEs that were judged related to HP. The only 3 Grade 3 AE's that were observed were two participants with elevated creatinine, and one participant with hypertension. There was one Grade 2 flu-like reaction that was fleeting (24 hours) and self-limited. It occurred at Day 72 (after the 2^{nd} dose of HP), and notably did not recur with subsequent doses. CRP levels were monitored over the study period, given the previous cytokine-mediated hypersensitivity reactions (with elevated CRP) seen in healthy volunteers in Study 26 given HP and DTG. Median CRP

(IQR) at baseline, week 9, and week 11 were 4.8 (2.2-8.8), 2.8 (1.1-6.7), and 3.2 (1.0-7.9) mg/L, respectively, with a normal cutoff value for the test of < 5 mg/L. (32)

1.2 RATIONALE

TB remains the most common cause of death among individuals with HIV infection globally. More effective measures to prevent TB disease are needed in PLWH, as this population bears a disproportionate share of TB and TB-associated mortality.

Two Phase 3 trials showed that 3HP is effective and perhaps superior to daily IPT for the treatment of LTBI (12,13). Among HIV-infected participants in these two studies, adverse events were fewer with 3HP than with IPT (15). Further, adherence to 3HP surpasses that of daily IPT, making this regimen an attractive option in the arsenal to combat TB by reducing its incidence.

In both Phase 3 trials of 3HP, however, co-treatment with ART was not allowed. In the current era, provision of ART to all HIV-infected persons, regardless of CD4 count, is the standard of care. RPT is a strong inducer of metabolizing enzymes, so there is a risk of drug interactions with this drug. Once-weekly RPT, however, can be used safely with NRTI and efavirenz. It cannot be used together with protease inhibitors, but it can be co-administered with raltegravir without dose adjustment.

DTG is a potent INSTI that is increasingly available globally and may become a standard choice in low- and middle-income countries. DTG is metabolized principally by UGT1A1, with a minor contribution by CYP3A4. In one small study involving healthy HIV-uninfected healthy volunteers, DTG concentrations were modestly reduced with once-weekly INH and RPT, but the trough concentrations remained several-fold higher than the protein-adjusted IC_{90} for DTG, suggesting that even with these reductions in exposure, virologic suppression is likely to be maintained in patients with HIV without dose adjustment. The combination, however, was poorly-tolerated in the healthy volunteer study, with flu-like syndrome seen in two of three volunteers who completed the study. Brisk immune responses have been seen previously in healthy volunteers given rifamycins. The safety and tolerability of DTG plus 3HP remains to be established in patients with HIV-LTBI co-infection; moreover, the dose of DTG required to maintain HIV virologic suppression among patients with HIV-LTBI receiving 3HP must be determined before these drugs can be used together.

2 HYPOTHESIS, OBJECTIVES AND ENDPOINTS

2.1 Primary objectives

1) To evaluate the effect of RPT and INH given at doses of 900 mg once weekly (HP) on the pharmacokinetics (PK) of DTG
2) To describe the safety of DTG and 3HP co-administration

2.2 Secondary objectives

1) To estimate the proportion of participants who maintain virologic suppression among patients treated with DTG-based ART plus 3HP (Groups 1 and 2)

2) To estimate the proportion of treatment-naïve participants who achieve virologic suppression at 12 and 24 weeks after starting DTG-based ART (Groups 3 and 4)

3) To describe the PK of isoniazid and rifapentine in the study population

4) To examine DTG dosing options when given together with once-weekly HP in people living with HIV (PLHIV) requiring LTBI treatment.

Exploratory Objective

1) To describe the rate of decline of plasma HIV-1 viral load among antiretroviral treatment naïve participants receiving tuberculosis preventive therapy (Groups 3 and 4)

2.3 Endpoints

2.3.1 Primary

1) Population plasma PK parameters of DTG in the presence or absence of once-weekly HP, including absorption rate constant (ka), volume of distribution (Vd), and oral clearance (Cl/F) and between-subject variability terms; post-hoc Bayesian predictions of secondary PK parameters of DTG including daily AUC and Cmin following HP dosing.

2) Grade 3 or higher adverse events (AE)

2.3.2 Secondary

1) HIV-1 RNA viral load
2) Population PK parameters of RPT and INH; post-hoc Bayesian predictions of secondary PK parameters (AUC, Cmax, Cmin), taking into account (for INH) NAT2 acetylator status
3) Dose options for DTG with once-weekly HP derived by simulation using nonlinear mixed effects models.

3 STUDY PROCEDURES

3.1 Study timeline

	Year 1				Year 2	Year 2	Year 3	Year 4
Quarter	**1**	**2**	**3**	**4**	**1-3**	**4**	**1-4**	**1-4**
Preparation phase								
Enrolment								
Follow up								
Write up & analysis								

3.2 Study sites

The study will leverage existing infrastructure and established systems for enrolling and following up participants in the ongoing multi-centre WHIP$_3$TB trial of 3HP in HIV-infected patients being led by the Aurum Institute, funded by the United States Agency for International Development (USAID) entitled "A Randomised, Pragmatic, Open-Label Trial to Evaluate the Effect of Three Months of High Dose Rifapentine Plus Isoniazid Administered as a Single Round or Given Annually in HIV-Positive Individuals. Enrolment into the WHIP$_3$TB trial will be completed in mid-November 2017, when enrolment into this trial is anticipated to start.

Participants will be recruited from South African Department of Health (DoH) HIV clinics in relative close proximity to the Tembisa Clinical Research Centre. Key steps in the recruitment process include:

- referral of HIV positive patients by DoH staff to Aurum study recruiters stationed at the clinics. The Aurum recruiters will provide information about the study to those who have been referred and express interest in the study.
- The patient will be asked pre-screening questions relating to: age, weight, HIV status, pregnancy, breastfeeding and TB treatment.
- Potentially eligible patients will be transported to and screened at the Tembisa Research Clinical Centre, where informed consent is obtained in the participant's language of choice.

3.3 Participant selection

3.3.1 Fairness and inclusivity

All eligible and consenting participants will be enrolled regardless of race, gender, sexual orientation or religious belief.

3.3.2 Informed consent

Informed consent will be sought from potential participants using participant information leaflet and informed consents available in relevant languages. Written informed consent will be sought, with the assistance of a translator where necessary, using standard consent forms. Participants unable to read or write will be asked to make a mark or thumbprint in the presence of an independent witness.

3.3.3 Eligibility criteria

According to South African guidelines, people living with HIV who do not have active TB disease are eligible for TB preventive therapy.

Inclusion criteria include:

1. Age $\geq$ 18 years
2. Weight $\geq$ 50 kg
3. Documented HIV infection
4. At least 8 weeks of HIV treatment with efavirenz or dolutegravir plus two NRTI, or ART treatment naïve, depending upon the enrolling treatment Group
5. Undetectable or detectable HIV-1 viral load, depending upon the enrolling treatment Group

Exclusion criteria

1. Confirmed or suspected TB disease
2. Likely to move from the study area during the study period
3. Known exposure to TB cases with known or suspected resistance to isoniazid or rifampicin in the source case
4. TB treatment within the past year
5. TB preventive therapy within the last year
6. Sensitivity or intolerance to isoniazid or rifamycins
7. On nevirapine, etravirine, rilpivirine, PI-based, or raltegravir-containing ART regimens
8. Suspected acute hepatitis or known chronic liver disease; HBsAg positivity; severe hepatic impairment (Class C or greater) as determined by Child Pugh classification
9. ALT≥ 3 times the upper limit of normal (ULN)
10. Total bilirubin ≥ 2.5 times the ULN
11. Absolute neutrophil count (ANC) ≤ 750 cells/mm3
12. Creatinine clearance < 50 ml/min
13. Pregnancy or breastfeeding
14. Women of childbearing potential who are unable or unwilling to use two forms of contraception if indicated*
15. Self-reported alcohol use exceeding 28 units per week for men, or 21 units for women
16. Karnofsky status < 80
17. On prohibited medications e.g. dofetilide (see Appendix 1)
18. Known porphyria

*acceptable forms of contraception:

Male or female condoms or Diaphragm or cervical cap; **PLUS** 1 of the following methods:

- Subdermal implant (under the skin in the arm)
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches

Contraception is not required if a woman:

- has reached menopause, with no menstrual periods for one year;
- has had a hysterectomy;
- has had an oophorectomy;
- has had a tubal ligation
- Is sexually abstinent

3.4 Randomisation

This is a single-arm study. There will be no randomisation to arm.

3.5 Blinding

This study will not be blinded.

3.6 Study treatments

3.6.1 TB preventative therapy: 3HP

Table 1: Treatment regimens, doses, and duration of treatment

Tx Regimen	Treatment Dose	Study Group	Treatment Duration
3HP or	Once weekly rifapentine (at a dose of 900 mg) plus isoniazid (at a dose of 900 mg)	1 ,2 and 4	12 weeks
IPT	or standard dosing of isoniazid preventative therapy	3	or IPT per national guideline

In Group 1, all HP doses will be given via directly observed treatment (DOT) by study staff at the clinic.

In Group 2, the first four HP doses will be given via DOT by study staff at the clinic. Subsequent doses will be given by a trained DOT provider at home.

In Group 3, the initial dose of isoniazid will be given via DOT. All subsequent doses will be self-administered per usual routine of the national programme. Participants will keep a medication diary and receive a reminder call about dosing before the PK visit

In Group 4, the initial dose of HP will be given via DOT. All subsequent doses will be self-administered. Participants will keep a medication diary and receive a reminder call about dosing before the PK visit

3.6.2 HIV treatment: DTG plus 2 NRTI

Group 1: The first 12 participants (Group 1A) will take DTG 50 mg once daily (together with TDF/FTC). Following an interim analysis, the subsequent 18 participants (Group 1B) will receive either DTG 50 mg once daily or an adjusted dose of DTG, depending on results of the interim analysis (See Section 8.2.2).

Group 2: Participants will receive the same dose as participants in Group 1B.

DTG and TDF/FTC will be given as study drug until four weeks following completion of 3HP, at which time participants will transition their care to the local HIV program, but they may continue DTG and TDF/FTC, provided via post-trial access plan for 48 weeks after the last study visit, if it is not readily available in the local HIV clinic. Women of childbearing potential must agree to practice reliable contraception in order to participate in the program. Thereafter, participants may access DTG and TDF/FTC via the national HIV treatment programme or through their local clinic.

Group 3: Participants will receive the same dose as participants in Group 1B.

DTG and TDF/3TC will be given as study drug until completion of the Week 24 visit, at which time participants will transition their care to the local HIV program. Thereafter, participants may access DTG and TDF/3TC via the national HIV treatment programme or through their local clinic, as national DTG roll-out is expected in September 2019.

Group 4: Participants will receive the same dose as participants in Group 1B.

DTG and TDF/3TC will be given as study drug until completion of the Week 24 visit, at which time participants will transition their care to the local HIV program. Thereafter, participants may access DTG and TDF/3TC via the national HIV treatment programme or through their local clinic, as national DTG roll-out is expected in September 2019.

3.6.3 Pyridoxine

Pyridoxine (vitamin B6) is not an investigational product. Pyridoxine will be administered at a dose of 25 mg or 50mg with each dose of isoniazid. The dose of pyridoxine may be increased to 50 mg with each dose of isoniazid if symptoms of peripheral neuropathy develop.

3.6.4 Meals

HP doses will be taken with food, and doses of HP associated with PK evaluations will be provided with a standardized meal in Groups 1 &2.

In Group 4, participants will be educated about taking self-administered HP with a high fat containing meal. The medication reminder tool will have a column for recording the food/ quantity/ and time of the meal taken with each weekly dose.

3.7 Schedule of participant evaluations

The schedule of study visits and investigations are shown in Tables 2A (Group 1), 2B (Group 2), 2C (Group 3) and 2D (Group 4) below. Descriptions of procedures at study visits follow these tables.

Table 2A: Summary schedule of evaluations (SOE) for Group 1

	Screening	Enrolment	On-study period*													
Study week			1-8	9	10	11	12	13	14	15	16	17	18	19	20	24
CLINICAL EVALUATIONS																
Informed Consent	X															
History, concomitant medication list	X	X														
TB symptom screen	X	X		X												
Physical exam (complete)	X															
Physical exam (targeted)[2]				X		X		X			X				X	X
Adverse event assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence Questionnaire				X		X		X			X				X	
LABORATORY EVALUATIONS																
Hematology, liver function tests	X			X[1]		X		X			X				X	X
Creatinine and U&E	X			X[1]		X					X				X	
Hepatitis B surface antigen (HBsAg)	X															
C-reactive protein**	X			X		X										
Pregnancy test***	X	X	X***	X		X			X		X		X		X	X
HIV-1 antibody test (Documented)	X															
HIV-1 viral load	X					X										X
CD4 count	X															X
TB DIAGNOSTICS																
Chest x-ray	X															
Interferon gamma release assay (IGRA)	X															
PHARMACOLOGY																
NAT2 metabolizer genotype				X												
Semi-intensive PK sampling for DTG				X		X					X					
Sparse PK sampling for DTG				X		X	X									
PK sampling for rifapentine				X		X										
PK sampling for isoniazid						X										
STUDY DRUG DOSING																
Dolutegravir plus tenofovir/emtricitabine (daily)	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Isoniazid/rifapentine (once-weekly)* (via DOT)				X	X	X	X	X	X	X	X	X	X	X	X	

*All study visits will have a visit window of +/-2 days, **Serum will be stored for measurement of cytokines (e.g. interferon gamma, IL-6, TNF-alpha), ***for women of childbearing potential (repeat at enrolment if screening pregnancy test was more than 48 hours prior to enrolment); during weeks 1-8, pregnancy tests are performed at weeks 1, 3, 5, and 7

[1] Safety labs may be drawn on Day 56 or 57. If either or both days fall on a Sunday or Holiday, safety labs may be drawn on Day 55.

[2] May be conducted at other time points if required for completing adverse events assessments.

Table 2B: Summary schedule of evaluations (SOE) for Group 2

	Screening	Enrolment	On-study period*													
Study week			1-8	9	10	11	12	13	14	15	16	17	18	19	20	24
CLINICAL EVALUATIONS																
Informed Consent	X															
History, concomitant medication list	X	X														
TB symptom screen	X	X		X												
Physical exam (complete)	X															
Physical exam (targeted)[2]				X		X		X			X				X	X
Adverse event assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence Questionnaire				X		X		X			X				X	X
LABORATORY EVALUATIONS[1]																
Hematology, liver function tests	X			X[1]		X		X			X				X	X
Creatinine and U&E	X			X[1]		X					X				X	
Hepatitis B surface antigen (HBsAg))	X															
C-reactive protein**	X			X		X										
Urine Pregnancy test***	X	X	X***	X		X			X		X		X		X	X
HIV-1 antibody test	X															
HIV-1 viral load	X					X										X
CD4 count	X															X
TB DIAGNOSTICS																
Chest x-ray	X															
IGRA	X															
PHARMACOLOGY																
NAT2 metabolizer genotype						X										
Sparse PK sampling for DTG						X					X					
Sparse PK sampling for rifapentine						X										
STUDY DRUG DOSING																
Dolutegravir plus tenofovir/emtricitabine (daily)	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Isoniazid/rifapentine (once-weekly)				X	X	X	X	X	X	X	X	X	X	X	X	

*All study visits will have a visit window of +/-2 days, **Serum will be stored for measurement of cytokines (e.g. interferon gamma, IL-6, TNF-alpha), *** pregnancy test for women of child bearing potential (repeat at enrolment if screening pregnancy test was more than 48 hours prior to enrolment); during weeks 1-8, pregnancy tests are performed at weeks 1, 3, 5, and 7

[1] Safety labs may be drawn on Day 56 or 57. If either or both days fall on a Sunday or Holiday, safety labs may be drawn on Day 55.
[2] May be conducted at other time points if required for completing adverse events assessments.

Table 2C: Summary schedule of evaluations (SOE) for Group 3

	Screening	Enrolment	On-study period*															
Study week		Day 0	Day 1	1	2	3	4	5	6	7	8	9	10	11	12	16	20	24
CLINICAL EVALUATIONS																		
Informed Consent	X																	
History, concomitant medication list	X	X																
TB symptom screen	X	X			X													
Physical exam (complete)	X																	
Physical exam (targeted)[1]					X	X					X				X	X		X
Adverse event assessment			X		X	X					X				X	X		X
Adherence Questionnaire					X	X					X				X	X		X
LABORATORY EVALUATIONS																		
Hematology, liver function tests	X					X[6]					X[6]				X[6]			
Creatinine and U&E	X					X					X				X	X		X
Hepatitis B surface antigen (HBsAg))	X																	
Urine Pregnancy test***	X	X	X***		X	X					X				X	X		X
HIV-1 antibody test	X																	
HIV-1 viral load	X					X					X				X	X		X
CD4 count	X																	
TB DIAGNOSTICS																		
Chest x-ray	X																	
IGRA	X																	
PHARMACOLOGY																		
Sparse PK sampling for DTG (+/-1d window)			X[2]			X[4]					X[5]							
STUDY DRUG DOSING																		
Dolutegravir plus tenofovir/lamivudine (daily)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SOC Daily isoniazid			X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*All study visits will have a visit window of +/-2 days, pregnancy test for women of child bearing potential (repeat at enrolment if screening pregnancy test was more than 48 hours prior to enrolment); and at each study visit

[1] May be conducted at other time points if required for completing adverse events assessments.

[2] Sparse PK for DTG to be collected 24 hours from the dose given on Day 0 (Before the first dose of isoniazid)

[3] First dose of isoniazid to be given by DOT after the DTG PK collection
[4] Sparse PK sampling for DTG at Week 3, on Day 24 (72 hours after the Day 21 dose is taken)
[5] Sparse PK sampling for DTG at Week 8, on Day 59 (72 hours after the Day 56 dose is taken)
[6] LFTs only

Table 2D: Summary schedule of evaluations (SOE) for Group 4

	Screening	**Enrolment**	**On-study period***															
Study week		**Day 0**	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**20**	**24**
CLINICAL EVALUATIONS																		
Informed Consent	**X**																	
History, concomitant medication list	**X**	**X**																
TB symptom screen	**X**	**X**																
Physical exam (complete)	**X**																	
Physical exam (targeted)[1]					**X**	**X**					**X**				**X**	**X**		**X**
Adverse event assessment			**X**		**X**	**X**					**X**				**X**	**X**		**X**
Adherence Questionnaire					**X**	**X**					**X**				**X**	**X**		**X**

LABORATORY EVALUATIONS																		
Hematology, liver function tests	X					X[6]					X[6]				X[6]			
Creatinine and U&E	X					X					X				X	X		X
Hepatitis B surface antigen (HBsAg))	X																	
Urine Pregnancy test***	X	X	X***		X	X					X				X	X		X
HIV-1 antibody test	X																	
HIV-1 viral load	X					X					X				X	X		X
CD4 count	X																	
TB DIAGNOSTICS																		
Chest x-ray	X																	
IGRA	X																	
PHARMACOLOGY																		
Sparse PK sampling for DTG (+/-1d window)			X[2]			X[4]					X[5]							
STUDY DRUG DOSING																		
Dolutegravir plus tenofovir/lamivudine(daily)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Isoniazid/rifapentine (once-weekly)			X[3]	X	X	X	X	X	X	X	X	X	X	X	X			

*All study visits will have a visit window of +/-2 days, pregnancy test for women of child bearing potential (repeat at enrolment if screening pregnancy test was more than 48 hours prior to enrolment); during weeks 1-8, pregnancy tests are performed at weeks 1, 3, 5, and 7

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[1] May be conducted at other time points if required for completing adverse events assessments.

[2] Sparse PK for DTG to be collected 24 hours from the dose given on Day 0 (Before the first dose of HP)

[3] First dose of HP to be given by DOT after the DTG PK collection

[4] Sparse PK sampling for DTG at Week 3, on Day 24 (72 hours after the third HP dose is taken)

[5] Sparse PK sampling for DTG at Week 8, on Day 59 (72 hours after the eighth HP dose is taken)

3.8 Study procedures

Overall study description

There will be four groups. Group 1 will provide semi-intensive PK data and intensive safety monitoring to allow for comparison of dolutegravir exposures together with HP vs. when it is given alone. Both Groups 1 and 2 will provide safety and tolerability data, HIV virologic outcome data, and information about rifapentine and isoniazid PK.

Group 1 (n=30): The first 12 participants (Group 1A) will take dolutegravir 50 mg once daily (with tenofovir/emtricitabine) from Days 1-57. Semi-intensive PK sampling for dolutegravir will be performed on Day 57. Participants will continue once-daily dolutegravir (with tenofovir/emtricitabine) and will receive once-weekly HP for 12 total doses beginning on Day 58. Semi-intensive PK sampling for dolutegravir will be performed on Day 72 (with the 3rd dose of HP) and Day 108 (following the 8th dose of HP). Trough concentrations (C_T) of DTG will be measured on Days 59, 74, and 78. VL will be measured at baseline and weeks 11 and 24. Safety labs (CBC, Urea, electrolytes, creatinine, and liver function tests) will be obtained at baseline, and weeks 9, 11, 13, 16, 20 and 24. Isoniazid and rifapentine PK assessments will also be performed. Urine pregnancy test for women of childbearing potential will be conducted at Weeks 1, 3, 5, 7, 9, 11, 14, 16, 18, 20, and 24.

After the 12 Group 1A participants have completed the second semi-intensive PK visit, an interim PK, safety, and VL assessment will be performed to ensure that the 50 mg once daily dose is safe and meets PK targets. The subsequent 18 participants in Group 1 (Group 1B) will receive either dolutegravir 50 mg or a higher dose of dolutegravir, if dose adjustment is required (e.g. dolutegravir 50 mg twice daily just on HP dosing days or dolutegravir 50 mg twice daily seven days a week)

Group 2 (n=30): These participants will receive dolutegravir and HP at the same doses and dose schedule as the participants in Group 1B. They will undergo safety assessments at baseline and weeks 9, 11, 13, 16, 20 and 24; HIV VL assessments at baseline and weeks 11 and 24. Sparse (trough) PK samples for dolutegravir will be collected on two occasions. Urine pregnancy test for women of childbearing potential will be conducted at Weeks 1, 3, 5, 7, 9, 11, 14, 16, 18, 20, and 24.

Group 3 (n=25): These ART treatment naïve participants will receive dolutegravir at the same doses and dose schedule as the participants in Group 1B. At enrollment/Day 0, they will initiate dolutegravir. On Day 1, they will initiate standard of care dosing of isoniazid preventative therapy under the national TPT guideline. They will undergo safety assessments at baseline, Weeks 2, 3, 8, 12, 16 and 24. HIV VL assessments at Weeks 3, 8, 12, 16 and 24. Sparse (trough) PK samples for dolutegravir will be collected on three occasions on Day 1, Day 24 and Day 59. Urine pregnancy test for women of childbearing potential will be conducted at Weeks 2, 3, 8, 12, 16, 20 and 24.

Group 4 (n=50): These ART treatment naïve participants will receive dolutegravir and HP at the same doses and dose schedule as the participants in Group 1B. They will begin dolutegravir on Day 0, then will start HP on Day 1. They will undergo safety assessments at baseline and weeks 2, 3, 8, 12, 16 and 24; HIV VL assessments at Weeks 3, 8, 12, 16 and 24. Sparse (trough) PK samples for dolutegravir will be collected on three occasions on Day 1, Day 24 and Day 59. Urine pregnancy test for women of childbearing potential will be conducted at Weeks 2, 3, 8, 12, 16, 20 and 24.

A **second interim evaluation** focused on safety and PK will occur after all Group 1B participants have completed the Week 11 semi-intensive PK visit. This evaluation will include all HIV viral load and PK data from Group 1A, who will have completed their Week 16 semi-intensive PK visit plus HIV viral load and PK data from Group 1B up to and including the Week 11 semi-intensive PK visit.

A **third interim evaluation** focused on safety and virologic response will occur after all participants (Groups 1A, 1B, and 2) have completed the Week 11 visit. This evaluation will include all safety data and HIV viral load information collected up until that point from all participants.

Screening visit

Written informed consent must be obtained before any screening procedures are performed.

1. Verify study entry eligibility criteria are met
   Record locator information for contacting participant throughout study
2. Conduct brief medical history and symptom directed physical examination, including concomitant medication history
3. Conduct TB symptom screen (current cough, fever, night sweats, or unintentional loss of weight)
4. Do a chest X-ray (CXR) in order to exclude active TB disease
5. Persons with symptoms or signs suggestive of TB or an abnormal chest X-ray are ineligible to participate in the study, and should be referred for investigation by health clinic staff according to local guidelines. Do not proceed with enrollment.
6. Collect blood for liver function testing (LFT), pregnancy test (as applicable), complete blood count (CBC), Urea, electrolytes, creatinine, hepatitis B surface antigen (HBsAg)), and interferon gamma release assay (IGRA). In the event where IGRA is not available, a tuberculin skin test (TST) may be substituted.
7. Conduct HIV rapid test to confirm HIV positive status.
8. Collect a blood sample for a CD4 count and viral load.
9. (For female participants only) collect urine for βHCG. Provide counseling and document regarding requirement for contraception and need to avoid pregnancy while taking DTG.

Screening evaluations must occur prior to the participant's starting study medications. Ideally the participant will be screened and enrolled onto the study at the same study visit, provided s/he meets all eligibility requirements. Regardless, screening evaluations to determine eligibility must be completed within 7 days prior to study enrolment, unless otherwise specified.

Enrollment (must occur within 7 days of screening)

1. Verify that study entry eligibility criteria continue to be met, update locator information for contacting participant throughout study, and collect concomitant medication history.
2. Repeat TB symptom screen (current cough, fever, night sweats, or unintentional loss of weight). Persons with symptoms or signs suggestive of TB are ineligible to participate in the study, and should be referred for investigation by health clinic staff according to local guidelines.
3. (For female participants only) collect urine for βHCG, only if a result is not available from within 48 hours of enrolment

Once enrolled, participants will be switched from their efavirenz-based ART regimen to dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) or, if ART treatment naïve, will initiate with a dolutegravir-based regimen (DTG/TDF/3TC), to begin on the day of enrolment and continue for up to the next 8 weeks. Participants already on a DTG-based regimen at the time of enrolment only need to take study-provided DTG/TDF/FTC for two weeks prior to skipping to Week 9 procedures.

Weeks 1-24

Group 1

Group 1 will have 30 participants.

Group 1A will be the first 12 participants enrolled to the study.
Group 1B will be the next 18 participants enrolled after Group 1A's data have been analyzed.
It is possible that the dolutegravir dosing structure may change for Group 1B, depending upon the results of Group 1A's PK data analysis.

Groups 1A and 1B will follow the study events as described here:

At enrollment, participants who are not already on a dolutegravir-based ART regimen will be switched from their current ART to begin receiving once daily dolutegravir 50mg + tenofovir/emtricitabine through the study. Participants will self-administer the new regimen for the first 55 days.

All weekly doses of rifapentine/isoniazid (HP) will be administered by the clinic staff under directly observed therapy (DOT)

Weeks 1-8
Participants will self-administer their Day 1-55 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) doses at home. For women of childbearing potential, provide counseling regarding requirement for contraception and need to avoid pregnancy while taking DTG; urine pregnancy tests at weeks 1, 3, 5, 7.

Week 9

Day 56
In preparation for the first semi-intensive PK sampling for dolutegravir, participants will take their Day 56 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) dose in the presence of clinic staff, by DOT. The exact time of dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note. The semi-intensive PK blood draws will begin exactly 24 hours from the Day 56 dose administration time.

The participant may be admitted to the PK unit at a time convenient to the participant, so that everything is in place for events to begin on time. If the participant is not admitted she or he should arrive early on Day 57 at least an hour ahead of the first PK blood draw. Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 57) until s/he receives instruction from the study team to take the dose during the Day 57 visit. The participant will need to bring her or his Day 57 and Day 58 doses to tomorrow's visit.

Safety labs (chemistry panel including liver function tests, creatinine and U&E) may be drawn on Day 56 or 57. If either or both of these days fall on a Sunday or Holiday, safety labs may be drawn on Day 55.

Day 57
The participant will spend Day 57 and the morning of Day 58 in the PK unit undergoing semi-intensive PK sampling #1 for DTG. Verify that s/he brought today and tomorrow's ART regimen to clinic.

The first DTG PK sample will be drawn at exactly 24 hours from yesterday's (Day 56) DTG dose. This will be time point 0 of today's series of sampling. Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

Instruct the participant to take today's DTG/TDF/FTC dose. Record the exact time of dose administration for Day 57 in the study's DOT Log and capture in the nursing narrative note.

The next PK sample is taken exactly 1 hour from taking the dose above. This is time point 1. Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

The next PK time points are at 2, 4, 6, and 10 hours after this morning's DTG/TDF/FTC dose. Record the exact times each sample was taken, even if it veers from the expected time for a blood draw. Urine pregnancy test for women of child bearing potential is to be conducted (Day 57).

Day 58
The final semi-intensive PK sampling #1 for DTG is in the morning of Day 58, at 23 and 24 hours after yesterday's (Day 57) DTG/TDF/FTC. Record the exact times each sample was taken, even if it veers from the expected time for a blood draw.

In this gap, or at any time during the events of Day 56 or 57 (but before the first dose of rifapentine), conduct the following assessments:
-TB symptom screen
- targeted physical exam
- adverse event assessment
- adherence to DTG questionnaire
- CBC
- chemistry panel including liver function tests, creatinine, and U&E (necessity may require Day 55 if day 56 falls on a Sunday or holiday)
- C-reactive protein (CRP)
- NAT2 metabolizer genotype

After the 24-hour sample has been taken, instruct the participant to take her Day 58 dose of DTG/TDF/FTC. The exact time of ART dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note.

At the same time, administer dose #1 of rifapentine/isoniazid (HP). Record the exact time of HP dose administration for Day 58 in the study's DOT Log and capture in the nursing narrative note. Rifapentine is taken with food.

The participant may be discharged. The participant may be readmitted to the PK unit in the evening to ensure the participant is in the PK unit the next morning for sparse PK sampling #1 for dolutegravir and rifapentine at 23 and 24 hours after this morning's doses of ART and HP. If the participant is not readmitted, the participant should be instructed to return to the clinic early the next morning for the sparse PK sampling.

Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 59) until s/he receives instruction from the study team to take the dose during the Day 59 visit. The day 59 dose can be taken after the sparse PK samples are taken at the 24-hour time point.

Day 59
If the participant was not readmitted the night before, the participant should arrive at the clinic early in the morning so that everything is in place for events to begin on time.

Sparse PK samples are taken at 23 and 24 hours after the DTG and HP doses were taken on D58.

Week 10

Participants continue to take daily self-administered DTG/TDF/FTC.
On day 65, participants receive HP dose #2 by DOT.

Week 11

Day 71

In preparation for the second semi-intensive PK sampling for dolutegravir, participants will take their Day 71 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) dose in the presence of clinic staff, by DOT. The exact time of dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note. The semi-intensive PK blood draws will begin exactly 24 hours from the Day 71 dose administration time. The participant may be admitted to the PK unit at a time convenient to the participant, so that everything is in place for events to begin on time. If the participant is not admitted she or he should arrive early on Day 72 at least an hour ahead of the first PK blood draw.

Participant will be admitted to hospital on days 72 through the morning of day 73

Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 72) until s/he receives instruction from the study team to take the dose during the Day 72 visit. The participant will need to bring her or his Day 72 and Day 73 doses to tomorrow's visit.

Day 72

The participant will spend Day 72 and the morning of Day 73 in the PK unit undergoing semi-intensive PK sampling #2 for DTG, rifapentine and isoniazid. Verify that s/he brought today and tomorrow's ART regimen to clinic. Urine pregnancy test for women of child bearing potential.

The first DTG PK sample will be drawn at exactly 24 hours from yesterday's (Day 71) DTG dose. This will be time point 0 of today's series of sampling. Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

Instruct the participant to take today's DTG/TDF/FTC dose. Record the exact time of dose administration for Day 72 in the study's DOT Log and capture in the nursing narrative note.

At the same time, administer dose #3 of rifapentine/isoniazid (HP). Record the exact time of HP dose administration for Day 72 in the study's DOT Log and capture in the nursing narrative note. Rifapentine is taken with food.

This visit collects PK sampling for dolutegravir at 0, 1, 2, 4, 6, 10, 23, and 24 hours after the Day 72 DTG dose.
This visit collects PK sampling for rifapentine at 4, 10, 24 hours after HP dose #3 (Day 72)
This visit collects PK sampling for isoniazid at 1, 2, 6, 10 hours after HP dose #3 (Day 72)

Record the exact times each sample was taken, even if it veers from the expected time for a blood draw.

Day 73

The final sampling time for semi-intensive PK visit #2 for DTG will be in the morning of Day 73, at 23 and 24 hours after yesterday's (Day 72) DTG/TDF/FTC. The final PK sampling for rifapentine will be in the morning of Day 73, at 24 hours

after yesterday's (Day 72) HP dose. Record the exact times each sample was taken, even if it veers from the expected time for a blood draw.

In this gap, or at any time during the events of Day 72, conduct the following assessments:
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- C-reactive protein (with additional blood collected for storage for cytokine determination)
- HIV-1 viral load

After the 24-hour sample has been taken, instruct the participant to take her or his Day 73 dose of DTG/TDF/FTC. The exact time of ART dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note.
The participant can be discharged. The participant may be readmitted in the evening to ensure the participant is in the PK unit the next morning for sparse PK sampling #2 for dolutegravir at 23 and 24 hours after this morning's dose of DTG. If the participant is not readmitted, the participant should be instructed to return to the clinic early the next morning for the sparse PK sampling.

Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 74) until s/he receives instruction from the study team to take the dose during the Day 74 visit. The day 74 dose can be taken after the sparse PK samples are taken at the 24-hour time point.

Day 74
If the participant was not readmitted the evening before, the participant should arrive at the PK unit early in the morning so that everything is in place for events to begin on time.

Sparse PK samples are taken at 23 and 24 hours after the Day 73 DTG dose.

Day 77
In preparation for the third sparse PK sampling for dolutegravir, participants will take their Day 77 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) dose in the presence of clinic staff, by DOT. The exact time of dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note. The sparse PK blood draws will begin exactly 24 hours from the Day 77 dose administration time. The participant may be admitted to the PK unit to ensure the participant is in the PK unit the next morning in time for the sparse PK sampling. If the participant is not admitted, the participant should be instructed to arrive early at the PK unit the next day, so that everything is in place for events to begin on time. Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 78) until s/he receives instruction from the study team to take the dose during the Day 78 visit. The participant will need to bring her or his Day 78 dose to tomorrow's visit.

Week 12
Day 78
If the participant was not admitted the night before the participant should arrive at the PK unit early in the morning so everything is in place for events to begin on time.

Sparse PK samples are taken at 23 and 24 hours after the Day 77 DTG dose.
Participant resumes daily self-administered DTG/TDF/FTC after today's sampling is completed.

Day 79
Participant receives dose #4 of HP by clinic staff under DOT.

Week 13
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 86
Participant receives dose #5 of HP by clinic staff under DOT.
This is also a scheduled visit for the following assessments:
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests

Week 14
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 93
Participant receives dose #6 of HP by clinic staff under DOT.
Urine pregnancy test for women of child bearing potential.

Week 15
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 100
Participant receives dose #7 of HP by clinic staff under DOT.

Week 16
Participants will self-administer day 106 DTG/TDF/FTC as usual.

Day 107
The following samples will be collected:

- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- Urine pregnancy test for women of child bearing potential.

In preparation for the third semi-intensive PK sampling for dolutegravir, participants will take their Day 107 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) dose in the presence of clinic staff, by DOT. The exact time of dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note.

At the same time, administer dose 8 of rifapentine/isoniazid (HP). Record the exact time of HP dose administration for Day 72 in the study's DOT Log and capture in the nursing narrative note. Rifapentine is taken with food.
The semi-intensive PK blood draws will begin exactly 23 hours from the Day 107 dose administration time. The participant may be admitted to the PK unit to ensure s/he are in the PK unit in time for the PK blood draws on day 108.

If the participant was not admitted the day before, the participant should be admitted to the PK unit for day 108 through the morning of day 109 for PK evaluation.

Participants who were not admitted the day before should arrive early arrival to the PK unit on day 108, so everything is in place for events to begin on time. Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 108) until s/he receives instruction from the study team to take the dose during the Day 108 visit. The participant will need to bring her or his Day 108 and 109 doses to tomorrow's visit.

Day 108
The participant will spend Day 108 and the morning of Day 109 in the PK unit undergoing semi-intensive PK sampling #3 for DTG. Verify that s/he brought today's ART regimen to clinic.

The first DTG PK sample will be drawn at exactly 23 hours from yesterday's (Day 107) DTG dose. This will be time point -1 of today's series of sampling. Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

After 1 hour, the next PK sample will be drawn. This is time point 0, which is 24 hours from yesterday's DTG/TDF/FTC dose

Instruct the participant to take today's DTG/TDF/FTC dose. Record the exact time of dose administration for Day 108 in the study's DOT Log and capture in the nursing narrative note.

The next PK sample is taken exactly 1 hour from taking the dose above. This is time point 1. Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

The next PK time points are at 2, 4, 6, and 10 hours after this morning's DTG/TDF/FTC dose. Record the exact times each sample was taken, even if it veers from the expected time for a blood draw.

Day 109
The final semi-intensive PK sampling #3 for DTG be in the morning of Day 109, at 23 and 24 hours after yesterday's (Day 108) DTG/TDF/FTC. Record the exact times each sample was taken, even if it veers from the expected time for a blood draw.

After the 24-hour sample has been taken, the participant will resume daily self-administered DTG/TDF/FTC.

Week 17
Participant continues daily self-administered DTG/TDF/FTC

Day 114
Participant receives dose #9 of HP by clinic staff under DOT.

Week 18
Participant continues daily self-administered DTG/TDF/FTC

Day 121
Urine pregnancy test for women of child bearing potential.
Participant receives dose #10 of HP by clinic staff under DOT.

Week 19
Participant continues daily self-administered DTG/TDF/FTC

Day 128
Participant receives dose #11 of HP by clinic staff under DOT.

Week 20
Participant continues daily self-administered DTG/TDF/FTC

Day 135

Participant receives dose #12 of HP by clinic staff under DOT.
This is the final HP dose, completing the treatment course for LTBI.

This is also a scheduled visit for the following assessments:
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- Pregnancy test, for women of childbearing potential

Week 21

Participant continues daily self-administered DTG/TDF/FTC

Week 22
Participant continues daily self-administered DTG/TDF/FTC.

Week 23
Participant continues daily self-administered DTG/TDF/FTC

Week 24
Day 168
Participant continues daily self-administered DTG/TDF/FTC for the next 9 months, either through usual clinical care or through the study's open – access dolutegravir program if DTG is not yet available locally, with regular follow up through the national TB programme.

Women of childbearing potential must agree to practice reliable contraception in order to participate in the access program

Day 168 is also a scheduled visit for the following assessments:

-TB symptom screen
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests
- HIV-1 viral load
- CD4 count
- Urine pregnancy test for women of child bearing potential.

Group 2

Group 2 will have 30 participants.
Group 2's dolutegravir dosing schedule will be the same as Group 1B.

Group 2 will follow the study events as described here:

At enrollment, participants who are not already on a dolutegravir-based ART regimen will be switched from their current ART to begin receiving once daily dolutegravir 50mg or a revised dose and frequency + tenofovir/emtricitabine through the study. Participants will self-administer the new regimen for the next 55 days.

The first four weekly doses of rifapentine/isoniazid (HP) will be administered by the clinic staff under directly observed therapy (DOT). The remaining doses will be self-administered at home.

Weeks 1-8
Participants will self-administer their dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) doses at home. For women of childbearing potential, provide counseling regarding requirement for contraception and need to avoid pregnancy while taking DTG; urine pregnancy tests at weeks 1, 3, 5, 7.

Week 9
Participants will take their Week 9 DTG/TDF/FTC as usual.

Day 58 This is a scheduled visit for the following assessments:

- TB symptom screen
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- C-reactive protein
- Urine pregnancy test for women of childbearing potential

At this visit, participants receive dose #1 of rifapentine/isoniazid (HP) in the clinic, under DOT.
Record the exact time of HP dose administration for Day 58 in the study's DOT Log and capture in the nursing narrative note. Rifapentine is taken with food.

Week 10

Participants continue to take daily self-administered DTG/TDF/FTC.

Day 65
Participants receive dose #2 of rifapentine/isoniazid (HP) in the clinic, under DOT

Week 11
Day 71
Participants will take their Day 71 DTG/TDF/FTC as usual.

Day 72
In preparation for the first sparse PK sampling for dolutegravir tomorrow, participants will take their Day 72 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) dose in the presence of clinic staff, by DOT. The exact time of dose administration will be recorded in the study's DOT Log and captured in the nursing narrative note. The sparse PK blood draws will begin exactly 23 hours from the Day 72 dose administration time. The participant may be admitted to the PK unit to ensure they are in the PK unit in time for the sparse PK sampling.

Participants who are not admitted the night before should arrive early to the PK unit the next day, so everything is in place for events to begin on time. Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 73) until s/he receives instruction from the study team to take the dose during the Day 73 visit. The participant will need to bring her or his Day 73 dose to tomorrow's visit. Urine pregnancy test for women of childbearing potential.

Participants receive dose #3 of rifapentine/isoniazid (HP) in the clinic, under DOT, at the same time DTG/TDF/FTC is administered.
Record the exact time of today's DTG/TDF/FTC and HP dose in the study's DOT Log and capture in the nursing narrative note. Rifapentine should be taken with food.

This is also a scheduled visit for the following assessments:
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- C-reactive protein
- HIV-1 viral load
- NAT2 metabolizer genotype

Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 73) until s/he receives instruction from the study team to take the dose after the Day 73 sparse PK sampling. The participant should bring her or his Day 73 dose to tomorrow's visit.

Day 73
Participants who were not admitted the night before should arrive early in the morning at the PK unit so that everything is in place for events to begin on time. Urine pregnancy test for women of childbearing potential.

Sparse PK samples are taken for rifapentine at 23 and 24 hours after the DTG and HP dose was taken on D72.
Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

Observe participant's DTG/TDF/FTC dose today, after the PK sampling is completed.
Remind participant about tomorrow's D74 sparse PK visit for dolutegravir sampling.

Day 74
Participants who were not admitted the night before should arrive early in the morning at the PK unit so that everything is in place for events to begin on time.

Sparse PK samples are taken for dolutegravir at 47 and 48 hours after the HP dose was taken on D72.
Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

After today's PK sampling is completed, participant resumes daily self-administered DTG/TDF/FTC.

Week 12
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 79
At this visit, participants receive dose #4 of HP in the clinic, under DOT.
Record the exact time of HP dose administration for Day 79 in the study's DOT Log and capture in the nursing narrative note. Rifapentine should be taken with food.

This is the last DOT dosing for HP. The pharmacy will dispense the remaining HP doses to the participant, with instructions about dosing with food and proper drug storage at home. HP is stored below 30 degrees Celsius, away from light.

A dosing calendar will be prepared for the participant so s/he knows the precise days to take her or his HP. Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.

Instruct participant to bring the next dose of HP to the Week 13 visit with her, so s/he can take it after checking in with the study team.

Week 13
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 86
This is a scheduled visit for the following assessments:
- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests

If the participant is stable, she will be instructed to take her self-administered HP dose #5 today.

Week 14
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 93
This is the scheduled day for self-administered HP dose #6.

Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.
Women of childbearing potential must report to clinic for a urine pregnancy test.

Week 15
Participants continue to take daily self-administered DTG/TDF/FTC.

Day 100
This is the scheduled day for self-administered HP dose #7.

Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.

Week 16
Day 107
The following samples will be collected:

- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- Urine pregnancy test for women of childbearing potential.

In preparation for the second sparse PK sampling for dolutegravir sampling #2 tomorrow, participants will take their Day 107 dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) dose in the presence of clinic staff, by DOT.

Participant will receive dose #8 of rifapentine/isoniazid (HP) in the clinic, under DOT, at the same time DTG/TDF/FTC is administered.
Rifapentine should be taken with food.

The exact time of dose administrations will be recorded in the study's DOT Log and captured in the nursing narrative note. The sparse PK blood draws will begin exactly 23 hours from the Day 107 dose administration time.

The participant may be admitted to ensure that the participant is in the PK unit in time for the sparse PK sampling. For participants that are not admitted the day before, instruct the participant to arrive early to the PK unit the next day, so everything is in place for events to begin on time. Remind her or him to hold off taking the next day's DTG/TDF/FTC dose (Day 108) until s/he receives instruction from the study team to take the dose during the Day 108 visit. The participant will need to bring her or his Day 108 dose to tomorrow's visit. S/he will also bring her or his HP dose to clinic.

Day 108
Participants who were not admitted the day before should arrive early at the PK unit early in the morning so that everything is in place for events to begin on time.

Sparse PK samples are taken for rifapentine at 23 and 24 hours after the DTG and HP dose was taken on D107.
Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.

Observe participant's DTG/TDF/FTC today, after the PK sampling is completed.
Remind participant about tomorrow's D109 sparse PK visit for dolutegravir sampling.

Day 109
Participants who were not admitted the night before should arrive early in the morning at the PK unit so that everything is in place for events to begin on time.

Sparse PK samples are taken for dolutegravir at 47 and 48 hours after the HP dose was taken on D107.
Record the exact time the sample was taken, even if it veers from the expected time for this blood draw.
After today's PK sampling is completed, participant resumes daily self-administered DTG/TDF/FTC.

Participant resumes weekly self-administered HP for the Week 17 dose.

Week 17
Participant continues daily self-administered DTG/TDF/FTC.

Day 114
This is the scheduled day for self-administered HP dose #9.

Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.

Week 18
Participant continues daily self-administered DTG/TDF/FTC.

Day 121
This is the scheduled day for self-administered HP dose #10.

Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.
Women of childbearing potential must still report to clinic for a urine pregnancy test.

Week 19
Participant continues daily self-administered DTG/TDF/FTC.

Day 128
This is the scheduled day for self-administered HP dose #11.

Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.

Week 20
Participant continues daily self-administered DTG/TDF/FTC.

Day 135
This is the scheduled day for self-administered HP dose #12.

Participants may be sent a reminder text message or phone call the day before and possibly on the day of dosing.
Women of childbearing potential must still report to clinic for a urine pregnancy test.
This is the final HP dose, completing the treatment course for LTBI.

This is also a scheduled visit for the following assessments:
- targeted physical exam

- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests, creatinine, and U&E
- Pregnancy test, for women of childbearing potential

Week 21
Participant continues daily self-administered DTG/TDF/FTC.

Week 22
Participant continues daily self-administered DTG/TDF/FTC.

Week 23
Participant continues daily self-administered DTG/TDF/FTC

Week 24
Day 168
Participant continues daily self-administered DTG/TDF/FTC for the next 60 weeks, either through usual clinical care or through the study's open-access dolutegravir programme if DTG is not yet available locally.
Women of childbearing potential must agree to practice reliable contraception in order to participate in the access program, with regular follow up through the national TB programme.

This is also a scheduled visit for the following assessments:

- targeted physical exam
- adverse event assessment
- adherence questionnaire
- CBC
- chemistry panel including liver function tests
- HIV-1 viral load
- CD4 count
- Women of childbearing potential must still report to clinic for a urine pregnancy test.

Group 3

Group will have 25 participants.
Group 3's dolutegravir dosing schedule will be the same as Group 1B.

Group 3 participants will record daily isoniazid dose-taking in a medication memory tool.

Group 3 will follow the study events as described here:

Day 0
At enrollment, participants who are ART treatment naïve will begin taking ART with once daily dolutegravir 50mg + tenofovir/lamivudine through the study. Participants will self-administer the regimen for duration of the study. For women of childbearing potential, provide counseling and document regarding requirement for two forms of contraception (barrier PLUS another effective form) and the recommendation to avoid pregnancy while taking DTG.

Since this cohort of participants does not have an established custom of taking their ART dose at night, the study recommends that they take their daily ART and IPT around the same time each morning.

Day 1
A sparse PK sample will be collected exactly 24 hours after the time of the Day 0 DTG dose.

After the sparse PK sample is collected, participants will receive the first dose of standard isoniazid preventative therapy from the clinic staff under directly observed therapy (DOT). The remaining daily doses will be self-administered at home for the duration of the study, then continuing through the national TB programme to complete a 12 month course. Participants will record daily isoniazid dose-taking in a medication memory tool.

For women of childbearing potential, provide counseling and document regarding requirement for two forms of contraception (barrier PLUS another effective form) and the recommendation to avoid pregnancy while taking DTG.

Week 1
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC) and daily isoniazid doses at home, recording daily isoniazid dose-taking in the medication memory tool.

Week 2
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.

Day 20
Call participant to remind her/him to take DTG and IPT in the morning on Day 21, making sure to document date and time in her/his medication memory tool.

Week 3
Day 21
Confirm morning DTG and IPT dosing with participant.

Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine and LFTs.
Plan with participant for Day 24 Sparse PK collection (confirming and documenting that DTG and INH doses are being taken in the morning).

Day 24
A sparse PK sample will be collected exactly 72 hours after the time of the Day 21 DTG dose.

Weeks 4-7
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC) and daily isoniazid doses at home, recording daily isoniazid dose-taking in the medication memory tool.

Day 55
Call participant to remind her/him to take DTG and IPT in the morning on Day 56, making sure to document date and time in her/his medication memory tool.

Week 12
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine and LFTs.

Weeks 13-15
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC) and daily isoniazid doses at home, recording daily isoniazid dose-taking in the medication memory tool.

Week 16
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine.

Week 20
Participant continues daily self-administered DTG and INH.
Urine pregnancy testing for women of childbearing potential. Document counseling about contraception.

Week 24
Final study visit
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine.

Refer participants to national TB and HIV programme to continue ART and IPT.

Group 4

Group 4 will have 50 participants.
Group 4's dolutegravir dosing schedule will be the same as Group 1B.

Group 4 participants will record weekly HP dose-taking in a medication memory tool.

Group 4 will follow the study events as described here:

Day 0
At enrollment, participants who are ART treatment naïve will begin taking ART with once daily dolutegravir 50mg + tenofovir/lamivudine through the study. Participants will self-administer the regimen for duration of the study. For women of childbearing potential, provide counseling and document regarding requirement for two forms of contraception (barrier PLUS another effective form) and the recommendation to avoid pregnancy while taking DTG.

Since this cohort of participants does not have an established custom of taking their ART dose at night, the study recommends that they take their daily ART and IPT around the same time each morning.

Day 1
A sparse PK sample will be collected exactly 24 hours after the time of the Day 0 DTG dose.

After the sparse PK sample is collected, participants will receive the first dose of rifapentine/isoniazid (HP) from the clinic staff under directly observed therapy (DOT). The remaining weekly HP doses will be self-administered at home for the duration of the study to complete a 3 month (12 week course) on-study. Participants will record weekly HP dose-taking in a medication memory tool.

For women of childbearing potential, provide counseling and document regarding requirement for two forms of contraception (barrier PLUS another effective form) and the recommendation to avoid pregnancy while taking DTG.

Week 1
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC) and weekly HP doses at home.

Week 2
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.

Day 20
Call participant to remind her/him to take DTG and HP in the morning on Day 21, making sure to document date and time in her/his medication memory tool.

Week 3
Day 21
Confirm morning DTG and HP dosing with participant.

Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine and LFTs.
Plan with participant for Day 24 Sparse PK collection (confirming and documenting that DTG and HP doses are taken in the morning)

Day 24
A sparse PK sample will be collected exactly 72 hours after the time of the Day 21 DTG dose.

Weeks 4-7
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC) and weekly HP doses at home, recording weekly HP dose-taking in the medication memory tool.

Day 55
Call participant to remind her/him to take DTG and HP in the morning on Day 56, making sure to document date and time in her/his medication memory tool.

Week 8
Day 56

Confirm and document morning DTG and HP dosing with participant.

Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine and LFTs.
Plan with participant for Day 59 Sparse PK collection (confirming and documenting that DTG and HP dose are taken in the morning).

Day 59
A sparse PK sample will be collected exactly 72 hours after the time of the Day 56 DTG dose.

Weeks 9-11
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC) and weekly HP doses at home, recording weekly HP dose-taking in the medication diary.

Week 12
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine and LFTs.
Final HP dose was dose #12

Weeks 13-15
Participants will self-administer their daily dolutegravir/tenofovir/lamivudine (DTG/TDF/3TC).

Week 16
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine.

Week 20
Participant continues daily self-administered DTG.
Urine pregnancy testing for women of childbearing potential. Document counseling about contraception.

Week 24
Final study visit
Study visit for safety assessment, TB symptom screen, targeted physical exam, AE assessment, adherence questionnaire, HIV viral load measurement, and urine pregnancy testing for women of childbearing potential. Document counseling about contraception.
Lab check for creatinine.

Refer participants to national HIV programme to continue ART.

Post-Study Follow Up

For participants who continue on the study's open-access dolutegravir programme beyond Week 24 (Groups 1 and 2 only):
At 24 weeks and 60 weeks following the Day 168 visit, participants will be contacted to collect information on intercurrent events such as hospitalizations and to check on vital status. Bloods and Urine will be collected at every ARV collection visit to monitor pregnancy (rapid pregnancy testing) and creatinine levels for those participants who opt to take part in the study's open access dolutegravir programme up to week 60 or until DOH rolls out DTG. Test results will be used only to ensure the safety of participants and will not form part of the data for the study. Participants who state a concern will be referred to usual or routine care, if needed.

Visit windows

Careful tracking of each participant's daily schedule of events is essential
To every extent possible, the schedule of daily and weekly visits should follow the plan that is outlined above.

To accommodate weekends, holidays and unforeseen events, the HP dosing can move a day in either direction, but the PK visits associated with that HP dose should be at the intervals described in the protocol. For example, the Day 58 HP dose can be given on Day 59, but the PK visits associated with it should all be pushed one day ahead as well. The subsequent dose can still be on Day 65.

Unscheduled visits

Any time TB is suspected by the health clinic staff, the participant should be directed to the study clinic to facilitate TB investigation and referral for treatment as needed. If TB is diagnosed outside of the study, the participant is encouraged to report to the study clinic where the information will be recorded in study records. HP should be discontinued in participants with suspected or confirmed TB. These participants should be replaced so that the full sample size is met.

Participants and their families should be educated to contact the study team for any changes or symptoms, particularly those suggestive of adverse drug reactions, that occur between visits. The study team will bring participants into clinic for evaluation under an unscheduled visit.

3.9 Clinical assessments

Brief medical history
The medical history should include all prior TB, and acute or chronic liver disease. Hypersensitivity to any medications and their formulations must be documented. Participant weight will be obtained.

Symptom screen for TB
Routine screening for TB will use the WHO-defined symptom criteria: current cough, fever, night sweats, or unintentional loss of weight.

TB Investigations
Participants with signs or symptoms suggestive of TB (e.g. current cough, fevers, weight loss) require investigation for TB. They will not be enrolled on to the study. Rather, they will be referred to the routine health service for evaluations and management.

Symptom screen for AEs
A questionnaire will be used to identify study defined adverse events related to isoniazid, rifapentine and dolutegravir use. The questionnaire will include hypersensitivity reaction symptoms known to occur with rifapentine such as flu-like illness, hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis occurring in temporal relation to taking study drug on at least one occasion. We will also screen for isoniazid related adverse events, such as hepatitis, rash, peripheral neuropathy, seizures. Liver injury will be determined by measuring ALT, AST and total bilirubin at several

time-points, as described above in the Schedule of Evaluations. Questions regarding gastrointestinal intolerance, psychiatric disturbances, and insomnia will be asked, as these can occur with dolutegravir.

Concomitant medication history
A medication history including all prescription and nonprescription medications will be taken within 30 days prior to study entry, and will include actual or estimated start and stop dates. A complete HIV and active or latent TB treatment history will be taken, with start and stop dates of any antiretroviral or TB medication (estimated if the exact dates cannot be obtained).

Treatment completion history
In Group 1, all doses of HP will be administered under DOT by study staff. In Group 2, the first four doses of HP will be administered under DOT by study staff. After that, if the drugs are well-tolerated, treatment will be administered at home by a family member or friend trained in DOT. DTG and TDF/FTC or 3TC will be self-administered except on PK dosing days, at which times it will be given by study staff so the exact time of administration of DTG can be observed. In Groups 3 and 4, all doses of HP will be self-administered, except for the first dose which will be supervised by the clinic nurse.

3.10 Laboratory evaluations

IGRA (QuantiFERON Gold Plus)
At screening, all participants must provide a blood specimen of ≥3 mL for QuantiFERON (QFT) Gold Plus testing.

Liver function tests
AST (SGOT), ALT (SGPT), and total bilirubin will be performed at defined time points, as well as at any time during the treatment and post-treatment phase the participant exhibits signs suggestive of liver injury (e.g., fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, dark urine, chills) or has signs of jaundice.

Complete blood count
Complete blood count (CBC) will be performed at defined time points and will include hemoglobin, white count, absolute neutrophil count, and platelet count.

Urea, electrolytes and creatinine
Urea, electrolytes and creatinine will be performed at time points as defined in the SOE

C-reactive protein
This test will be performed at defined time points, in accordance with the SOE. At the time of collection of blood for CRP measurement, blood will also be collected and plasma stored for possible measurement of cytokines typically associated with an acute inflammatory response (e.g. interferon gamma, IL-6, TNF-alpha),

Urine for βHCG (pregnancy testing)
Women with reproductive potential will provide a urine sample for βHCG prior to having study drug dispensed at enrolment, and prior to having a CXR. Women of reproductive potential will be advised to use two methods of contraception to prevent pregnancy during the 3 months they are on the study regimen.

Table 3: Cumulative phlebotomy volumes

Group 1

LABORATORY EVALUATIONS	Screening	Week 9	Week11	Week12	Week 13	Week 16	Week 20	Week 24
Hematology,	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube		2ml EDTA tube	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube
Liver function tests , Creatinine and U&E C-reactive protein Screening, Week 9 and Week 11 **only**)	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube		2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube
Cytokine testing	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube					
Hepatitis B surface antigen (HBsAg)	3.5ml SST tube							
HIV-1 antibody test	2ml EDTA tube							
HIV-1 viral load	6ml EDTA		6ml EDTA					6ml EDTA
CD4 count	4ml EDTA							4ml EDTA
TB DIAGNOSTICS								
Interferon gamma release assay (IGRA)	6ml Lithium Heparin							
PHARMACOLOGY								
NAT2 metabolizer genotype		2ml EDTA						
Semi-intensive PK sampling for DTG		6ml K2 EDTA	6ml K2 EDTA			6ml K2 EDTA		
Sparse PK sampling for DTG		6ml K2 EDTA	6ml K2 EDTA	6ml K2 EDTA				
PK sampling for rifapentine		Included in the sparse and semi PK tube	Included in the sparse and semi PK tube					
PK sampling for isoniazid			Included in the sparse and semi PK tube					

Group 1 Blood volumes

Study Week	Volume *(closest estimation)* ml	Estimated Number of Teaspoons
Screening	28,5	6
Week 9	69	14
Week 11	73	15
Week 12	12	3
Week 13	4,5	1
Week 16	58,5	12
Week 20	4,5	1
Week 24	14,5	3
Total	**264,5**	**55**

Group 2

LABORATORY EVALUATIONS	Screening	Week 9	Week 11	Week 13	Week 16	Week 20	Week 24
Hematology,	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube	2ml EDTA tube
Liver function tests , Creatinine and U&E C-reactive protein Screening, Week 9 and Week 11 only)	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube
Cytokine testing	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube				
Hepatitis B surface antigen (HBsAg)	3.5ml SST tube						
HIV-1 antibody test	2ml EDTA tube						
HIV-1 viral load	6ml EDTA		6ml EDTA				6ml EDTA
CD4 count	4ml EDTA						4ml EDTA
TB DIAGNOSTICS							
Interferon gamma release assay (IGRA)	6ml Lithium Heparin						
PHARMACOLOGY							
NAT2 metabolizer genotype			2ml EDTA				
Sparse PK sampling for DTG			6ml K2 EDTA		6ml K2 EDTA		
Sparse PK sampling for rifapentine			Included in the sparse PK tube				

Group 2 Blood Volumes

Study Week	Volume *(closest estimation)* ml	Estimated Number of Teaspoons
Screening	28,5	6
Week 9	7	2
Week 11	39	8
Week 13	4,5	1
Week 16	28,5	6
Week 20	4,5	1
Week 24	14,5	3
Total	**126,5**	**26**

Group 3 Blood Volumes

LABORATORY EVALUATIONS[1]	Screening	Day 1	Week 3	Week 8	Week 12	Week 16	Week 24
Hematology,	2ml EDTA tube		2ml EDTA tube	2ml EDTA tube	2ml EDTA tube		
Liver function tests , Creatinine and U&E	2.5ml SST tube		2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube
Hepatitis B surface antigen (HBsAg)	3.5ml SST tube						
HIV-1 antibody test	2ml EDTA tube						
HIV-1 viral load	6ml EDTA		6ml EDTA	6ml EDTA	6ml EDTA	6ml EDTA	6ml EDTA
CD4 count	4ml EDTA						
TB DIAGNOSTICS							
Interferon gamma release assay (IGRA)	6ml Lithium Heparin						
PHARMACOLOGY							
Sparse PK sampling for DTG		6ml K2 EDTA	6ml K2 EDTA	6ml K2 EDTA			

Group 3 Blood Volumes

Study Week	Volume *(closest estimation)* ml	Estimated Number of Teaspoons
Screening	26	6
Day 1	6	2
Week 3	16,5	4
Week 8	16,5	4
Week 12	10,5	3
Week 16	8,5	2
Week 24	8,5	2
Total	**92,5**	**19**

Group 4 Blood Volumes

LABORATORY EVALUATIONS[1]	Screening	Day 1	Week 3	Week 8	Week 12	Week 16	Week 24
Hematology,	2ml EDTA tube		2ml EDTA tube	2ml EDTA tube	2ml EDTA tube		
Liver function tests , Creatinine and U&E	2.5ml SST tube		2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube	2.5ml SST tube
Hepatitis B surface antigen (HBsAg)	3.5ml SST tube						
HIV-1 antibody test	2ml EDTA tube						
HIV-1 viral load	6ml EDTA		6ml EDTA	6ml EDTA	6ml EDTA	6ml EDTA	6ml EDTA
CD4 count	4ml EDTA						
TB DIAGNOSTICS							
Interferon gamma release assay (IGRA)	6ml Lithium Heparin						
PHARMACOLOGY							
Sparse PK sampling for DTG		6ml K2 EDTA	6ml K2 EDTA	6ml K2 EDTA			

Group 4 Blood Volumes

Study Week	Volume *(closest estimation)* ml	Estimated Number of Teaspoons
Screening	26	6
Day 1	6	2
Week 3	16,5	4
Week 8	16,5	4
Week 12	10,5	3
Week 16	8,5	2
Week 24	8,5	2
Total	**92,5**	**19**

3.11 Treatment completion measures

Prior to treatment initiation, each participant will receive treatment adherence counselling which will include information regarding the treatment, side effects, assistance with methods to remember to take their medication, and discussion of any anticipated problems with taking medication. At each study visit, participants will be reminded to take all their medication. HP will be provided via DOT for all doses in Group 1 and for the first four doses in Group 2. Groups 3 and 4 will self-administer their medication at home and keep a medication memory tool to record their TPT dose- taking. For Group 3 on IPT and Group 4 on 3HP medication will be dispensed monthly. The memory tool serves as an aid to assist the participant with recall of each dose of medication taken. The memory tool will be used to corroborate self-reported adherence and pill counts but will not be used to measure adherence. Adherence will be measured by physical count of doses taken and returned (dose accountability) at monthly visits.

In Groups 1 & 2, for doses that fall on visit days, staff will dispense the appropriate dose and observe and note its ingestion. A minimum of 4 days must have elapsed after the participant's previous dose to allow for directly observed dosing at the clinic visit. All ART agents will be self-administered except on DTG dosing days preceding collection of PK samples (that is, on the morning of the semi-intensive PK sampling or the day before the sparse PK sampling). Participants who miss a dispensing visit will be contacted by phone or home visit by research staff and reminded to visit the study clinic to collect treatment.

Groups 3 and 4 will receive their first DTG and TPT dose under DOT, then self-administer their ART and TPT at home,

keeping a medication memory tool to record their TPT dose- taking.

In all arms, several measures will be used to monitor treatment completion, including:

- Proportion of dispensing visits attended
- Self-reported treatment completion at each monitoring visit.
- Pill counts. Participants will be asked to bring their unused study medication with them. Study staff will count the remaining pills to estimate the number of scheduled doses taken.

3.12 Retention activities

Detailed locator information will be collected on all participants. Participants with cell phones will have their number verified at the screening visit and reconfirmed at every study visit. Participants who report potential drug side effects or symptoms suggestive of TB will be advised to come to the research clinic for care. Participants who miss a study visit will be called (or the nominated contact if the participant is not reachable) to remind them to come for the study visit. Where necessary and feasible, a home visit will be conducted to retain the participant in the study.

4 STUDY PRODUCT

4.1 Acquisition, formulation, distribution, storage and accountability

RPT will be donated by or procured from Sanofi. Specifically, the company will provide rifapentine (RPT, Priftin®) in boxes containing 3 blister packs of 8 tablets each (24 tablets at 150 mg each). Three boxes per participant will be required to complete a 12-week course of treatment. The study medication will be shipped by Sanofi to a central depot in South Africa. Aurum bears responsibility for shipping the required doses to study sites.

Winthrop isoniazid will be obtained locally. Winthrop isoniazid is packaged in 28 count 'securitainer' bottles (at 300 mg each). The study medication will be delivered from Sanofi South Africa to a central depot in South Africa. Aurum bears responsibility for shipping the required doses to study sites.

Rifapentine and isoniazid will be stored at dry conditions at temperatures between 15-30° C.

DTG will be donated or procured from ViiV Healthcare, LLC. It is provided in 50 mg tablets.

Quality assured pyridoxine will be obtained from a supplier in South Africa, and shipped to site along with the isoniazid and rifapentine.

Study medication will be managed and controlled according to the Aurum Standard Operating Procedures for Distribution, Storage and Accountability. Study sites are responsible to maintain records of all study products received, returned and destroyed (if unused or returned).

4.2 Concomitant medication

DTG and TDF/FTC or 3TC will be provided by the study for 24 weeks (All groups 1, 2 , 3 and 4). Participants will have post-study access (Groups 1 and 2 only) to DTG and TDF/FTC for 60 weeks through a donation from ViiV Healthcare. For groups 3 and 4, access to DTG will be made available through the DOH. Women of childbearing potential must agree to practice reliable contraception in order to participate in the post-study access program. Thereafter, participants will access DTG through the national HIV programme that will be scaling up DTG from May 2018. In the unlikely event that DTG is not available to participants through the routine health services, participants may be switched back to the antiretroviral therapy regimen they were on prior to joining the study. In addition to DTG, only NRTI will be permitted during the study period. If a participant is required to switch to an ART regimen that is incompatible with study drug, the 3HP will be stopped and the participant offered six months of INH.

All concomitant medication that is started or the dose changed should be recorded. Prior to starting any new medication, the list of prohibited and precautionary medications (Appendix 1) should be consulted to minimize the potential for drug-drug interactions.

5 SAFETY

5.1 Responsibilities for ensuring the safety of study participants

The national regulatory authorities, the sponsor, the institutions through which the research is performed, Site Principal Investigator and clinical teams share responsibility for ensuring that participants in this trial are exposed to the least possible risk of adverse events that may result from participation in this protocol.

The site principal investigator has a personal responsibility to closely monitor study participants and an inherent authority to take whatever measures necessary to ensure their safety. The principal investigator has the authority to terminate, suspend or require changes to the study for safety concerns Site principal investigators determine severity and causality for each adverse event.

The protocol is approved by the District and Provincial Department of Health Research Committees. A referral network has been established for referring persons with adverse events and suicidal ideation to the hospital or local clinic. The Department of Health (DoH) has provided a letter guaranteeing access to DTG when it becomes available in South Africa.

5.2 Safety profile of study regimens

In June 1998, the US Food and Drug Administration (FDA) approved rifapentine for the treatment of tuberculosis, the first new drug approved for tuberculosis in more than 25 years. In addition, the 3HP regimen is registered by the US FDA and is recommended for the prevention of TB disease by the US Centers for Disease Control and Prevention (CDC) and will be recommended by the WHO for low burden, middle and high- income countries in the integrated guidelines for the programmatic management of LTBI, expected to be released by end of November 2017. Tolerance of HP regimen was comparable to INH in the CPCRA/ACTG trial. Finally, Sanofi has submitted the regulatory dossier for rifapentine to the South African Health Products Regulatory Authority (SAHPRA) for approval to use in the 3HP regimen.

Isoniazid has been used in the treatment and prevention of tuberculosis for over 50 years, and its adverse event profile is well known. Rash, fever, jaundice, and peripheral neuritis are the most common INH-related adverse reactions. Concurrent administration of pyridoxine (vitamin B6) prevents INH-related peripheral neuropathy as well as nearly all other nervous system disorders attributable to INH administration. In this study, pyridoxine will be administered at a dose of 25 mg with each dose of INH. The dose of pyridoxine may be increased to 50 mg with each dose of INH if symptoms of peripheral neuropathy develop.

RPT, like other rifamycins, causes red-orange discoloration of body fluids. In trials where RPT was combined with INH and other antituberculosis drugs, rates of adverse reactions were similar between rifampin and RPT, with increased liver aminotransferase activity in about 5% of patients (29).

3HP. In TBTC 26, 3HP was also well-tolerated among study participants compared to 9H. A synopsis of relevant adverse events and their frequencies is listed in Table 1.

Table 1. Drug-related adverse events in trials of RPT/INH for LTBI treatment

Adverse Event	*TBTC 26 (HIV-negative) n=1861**	*TBTC 26 (HIV positive) n= 207*	*Martinson, et al Soweto study (HIV-positive) n=328*
Hepatotoxicity	11 (0.59%)	3 (1.4%)	5 (1.5%)
Rash	15(0.8%)	1 (0.5%)	0 (0%)
Possible hypersensitivity	85(4.6%)	2 (1%)	0 (0%)

* confirmed HIV-negative

Dolutegravir on rare occasions can cause hypersensitivity and rash; other side effects include drug-induced liver injury, mild to moderate gastrointestinal intolerance, psychiatric disorders (including most commonly insomnia), and immune reconstitution inflammatory syndrome (IRIS). Dolutegravir can cause mild elevations of creatinine related to a benign effect on creatinine secretion with blockade of the OCT2 renal transporter. Participants switched to DTG who do not remain virally suppressed or who develop severe or serious adverse events related to DTG may be switched to EFV. In May 2018, ViiV Healthcare became aware of a potential safety issue related to neural tube defect (NTD) in infants born to women with exposure to dolutegravir at the time of conception that was identified from a preliminary unscheduled analysis of a study conducted among pregnant women in Botswana (Tsepamo study, 4 NTD among 426 pregnancies on dolutegravir). This represented an incidence of about 0.9% with an expected background rate of about 0.1%. In the reproductive toxicology studies, including embryofetal development studies performed in animals prior to drug licensure, there were no adverse development outcomes, including NTD, but dolutegravir was found to cross the placenta. Up to now, data from the Antiretroviral Pregnancy Registry (APR), clinical trials, and post marketing use have not indicated a potential safety issue, but data from these sources are limited. The FDA recommends that women of childbearing potential have a pregnancy test before starting dolutegravir and that women of childbearing age who decide to take a dolutegravir-containing regimen consistently use effective contraception while on HIV treatment (www.fda.gov).

Tenofovir/emtricitabine (TDF/FTC) can cause new onset or worsening renal impairment and Fanconi syndrome. Lactic acidosis and hepatomegaly with steatosis have been reported. Decreases in bone mineral density and mineralization defects have been seen in patients treated with TDF. It is recommended that all individuals be tested for chronic hepatitis B infection prior to starting TDF/FTC. Hepatitis exacerbation with liver failure can occur with abrupt stopping of TDF/FTC among patients with hepatitis B infection.

Tenofovir/lamivudine (TDF/3TC) can cause new onset or worsening renal impairment and Fanconi syndrome. Lactic acidosis and hepatomegaly with steatosis have been reported. Decreases in bone mineral density and mineralization defects have been seen in patients treated with TDF. It is recommended that all individuals be tested for chronic hepatitis B infection prior to starting TDF/3TC. Hepatitis exacerbation with liver failure can occur with abrupt stopping of TDF/3TC among patients with hepatitis B infection.

5.3 Adverse event (AE) reporting

The study will base AE reporting on SAHPRA requirements which have been developed to ensure timely and accurate reporting of adverse experiences to monitor patient safety. The purpose of AE reporting in this study is to ensure the safety of participants, and not to identify new AEs related to isoniazid, rifapentine, or dolutegravir. Although the 3HP regimen has been approved by a stringent regulator (US FDA) for the treatment of LTBI, and has demonstrated an acceptable safety profile in previous studies, we will monitor for adverse events in the study.

5.3.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a study agent and which does not necessarily have a causal relationship with the treatment received.

5.3.2 Study defined AEs

We will capture study-defined adverse events including hepatitis, hypersensitivity reactions, peripheral neuropathy, psychosis, flu-like reactions, gastrointestinal disturbances and seizures. All Grade 2 or higher clinical or laboratory adverse events will be captured. All participants will be monitored for symptoms suggestive of hepatitis up to and including 30 days after the last day the INH/RPT is taken.

Participants, research staff and health care workers will be educated to immediately discontinue preventive therapy should they develop symptoms suggestive of hepatitis or rifamycin hypersensitivity syndrome. Participants with symptoms and signs suggestive of hepatitis will be investigated appropriately. In addition, active screening for liver injury will be conducted at several time points in the study in the form of ALT, AST and total bilirubin assays. Participants who have a severe or serious adverse event related to DTG may be switched back to an EFV.

5.3.3 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
- Other medically important conditions. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

5.3.4 AEs requiring expedited reporting

We will report all study-defined SAEs, including death from any cause, among individuals who received INH and/or RPT as part of the study, and who had a study-defined SAE occurring on or after the first date that individual took INH and/or RPT until one month after the last day the INH/RPT was taken. Any grade 2 or higher hepatitis or hypersensitivity reaction; any grade 3 or 4 psychosis, flu-like reaction, or seizure will also be reported to the Principal Investigator, and Sponsor, and Johns Hopkins PI and study coordinator within 24 hours (one business day) of site's knowledge. Reporting of pregnancy will follow similar expedited reporting within 24 hours (one business day of site's knowledge) to the Principal Investigator, and Sponsor, and Johns Hopkins PI and study coordinator.

5.3.5 AE Reporting period

The reporting period for AEs is from time of participant enrollment to the end of trial follow up for that participant. AEs occurring prior to exposure to the study agents in this trial do not require reporting. Similarly, immune reconstitution inflammatory syndrome (IRIS) events do not require reporting as they are anticipated events for ART.

5.3.6 Submission of updated information on SAEs

Sites must follow each SAE until the SAE is resolved or stable. For each SAE reported, sites are required to submit an updated report to the Local Medical Monitor as soon as significant additional information becomes available by ticking the box marked 'follow-up' and emailing to the Local Medical Monitor as information becomes available. The following are examples that must be submitted:

- An updated report documenting the stable or resolved outcome of the SAE, unless the initial report included a final outcome
- Any change in the assessment of the severity grade of the SAE, or
- Additional significant information on a previously reported SAE (e.g., cause of death).

Extra, annotated information and/or copies of test results may be provided separately.

5.3.7 Recurrent SAEs

For an event previously reported to the Local Medical Monitor, if the SAE fully resolved but then re-occurs with an outcome meeting expedited reporting criteria, the SAE must be reported as a new event.

5.3.8 Timeframe for SAE reporting

Clinical research sites must report SAEs no later than 24 hours after the site becomes aware of an event that meets protocol-defined criteria for reporting to the Sponsor and Johns Hopkins PI and study coordinator. SAEs will be submitted to all applicable ethical and regulatory agencies within 72 hours of the site becoming aware of the event. SAEs will be submitted to all applicable ethical and regulatory agencies within 72 hours of the site becoming aware of the event.

5.3.9 Site investigator assessment and signature

A site physician investigator or sub-investigator must review and verify the completed SAE Form for accuracy and completeness and then sign the report. In the rare event that such physician(s) are not available for signature, sites may submit the SAE requiring reporting without the signature to meet reporting timeframe requirements. However, the completed SAE Form with signature and any necessary corrections or additions must be submitted within 72 hours. The site Principal Investigator (or designee) is responsible for designating at least one other physician at the site who can complete the form and provide signature to provide uninterrupted coverage of monitoring of SAEs.

5.3.10 Procedures

1. The site PI or designee evaluates the AE and determine whether it fulfils the criteria for seriousness.
2. If the SAE criteria is met, the SAE Form should be completed and signed by the responsible investigator.
3. The completed and signed SAE form should be emailed to the Local Medical Monitor within 72 hours.

5.4 Follow up of participants who become pregnant

Females who become pregnant while receiving 3HP will discontinue 3HP and be switched to six months of isoniazid preventive therapy. Women who become pregnant while receiving DTG will discontinue DTG and be switched to efavirenz-based antiretroviral therapy. Females will be encouraged to continue on- study and complete the evaluations per the schedule of events. At the end of the pregnancy, the outcome and AEs for the participant and the infant will be recorded on an outcome case report form (CRF).

Pregnancies that occur on study in participants receiving ART should be reported to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: +1-910-679-1598; Fax: +1-44-1628-789-666 or +1-910-256-0637.

6 TOXICITY MANAGEMENT

6.1 Toxicity grading tables

Severity and laboratory tests will be graded per the Division of AIDS (DAIDS) Table for Grading Adult and Pediatric Adverse Events, Version 2.1 (dated March 2017, and available at http://rsc.tech-res.com/safetyandpharmacovigilance/).

6.2 Toxicity management

6.2.1 Gastrointestinal

For nausea/vomiting and/or diarrhea ≥Grade 3 or for Grade 2 toxicity if symptoms were not present at the previous visit, all study drugs should be withheld until the symptoms have resolved. Reintroduce study drugs with caution. Antiemetic and antidiarrheal medication may be used at the site investigator's discretion.

If nausea and vomiting occur because of hepatitis, every effort should be made to reintroduce the study drugs after the symptoms return to baseline levels.

6.2.2 *Cutaneous*

For Grade 2 or 3 cutaneous events that occur after enrollment into the study, all study drugs should be withheld until the toxicity resolves. Study drugs should be reintroduced with caution. Grade 4 cutaneous or Grade 4 mucocutaneous rash is a major toxicity, and all study drugs should be permanently discontinued. Study drugs may be discontinued at the discretion of the site investigator. Similarly, study drugs that are temporarily interrupted may be reintroduced at the discretion of the site investigator.

6.2.3 *Rifamycin hypersensitivity syndrome*

A flu-like syndrome consisting of attacks of fever, chills and malaise, sometimes with headache, dizziness or bone pain, has been associated with intermittent rifampin administration, and been reported in a rifapentine + isoniazid regimen study (29). However, in a study conducted in South Africa to evaluate a 3HP regimen for treatment of LTBI, there were no reports of flu-like illness.[28] Nevertheless, careful monitoring of signs and symptoms of possible flu-like illness will be conducted in this study.

For participants who develop signs or symptoms suggestive of RHS (e.g., fever, myalgia, rash, hypotension, clinical hepatitis):

- Hold study drug regimen
- Assess for RHS (see note below for definition) through clinical evaluation and laboratory testing, including comprehensive metabolic panel, CBC with manual differential, and other tests that, at the discretion of the site investigators are necessary to exclude likely alternative diagnoses (e.g., should symptoms suggest influenza, a nasopharyngeal aspirate for viral testing could be sent).
- If Grade 3 or higher AE meets the case definition for RHS (and symptoms are not clearly attributable to an alternative diagnosis), permanently discontinue the study drug regimen and notify the Core Team.

Note: RHS is defined as follows:

- Hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, or neutropenia that occurred in relation to study drug regimen; *or*
- More than four of the following that occurred in relation to study drug (one of which must be assessed as having been > Grade 2): weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, rash, itching, syncope, cough, palpitations, or chills.

6.2.4 *Drug-Associated Fever*

If ≥Grade 3, all study drugs should be held until the temperature returns to normal. Study drugs should be reintroduced with caution. Recurrence of symptoms on reintroduction will result in permanent discontinuation of the responsible agent.

6.2.5 *Liver Toxicity*

All study drugs will be stopped permanently if any of the following liver chemistry criteria are met:

- ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required)
    - NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
- ALT ≥3 × ULN with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
- ALT ≥5 × ULN; regardless of symptoms

  In the case of liver toxicity, appropriate evaluations for alternative causes may be pursued (viral hepatitis, alcohol exposure, etc.).

6.2.6 *Decline in Renal Function*

Participants who experience an increase in creatinine from baseline of 45 μMol/L (or 0.5 mg/dL) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine ratio should be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study core team to discuss additional follow-up and medical management.

Subjects who have a decline in estimated GFR (using the CKD-EPI method) of >50% must return for a confirmatory creatinine assessment as soon as possible. A urinalysis and urine albumin/creatinine ratio should be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then dolutegravir should be withheld, unless a clear alternative cause is identified. Other confounding factors (e.g., other medications, dehydration, concurrent medications) should be investigated. A switch from TDF to an alternative NRTI should be considered. Restarting dolutegravir will be at the discretion of the investigator, taking all factors into consideration.

6.2.7 *Peripheral Neuropathy*

Peripheral neuropathy associated with INH is usually avoided by the concurrent administration of vitamin B6. In this study, all participants will take vitamin B6 concomitantly with INH. Participants with peripheral neuropathy <Grade 2 may be entered into the study, but should be monitored carefully for progression of the neuropathy.

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

For Grade 3 or 4, discontinue all study medication until toxicity resolves to Grade ≤2. If peripheral neuropathy does not resolve despite discontinuation of study drugs, study drugs may be reintroduced at the site investigator's discretion.

6.2.8 *Suicidal Ideation*

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in participants 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 participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour. If the participant expresses suicidal ideations or intents, the data will be captured as AEs. Any suicide thought or attempt that qualifies as an expedited adverse event (EAE) will be reported using the standard EAE mechanism.

6.2.9 *Other*

For toxicities that do not fall into one of the scenarios above, management will be as follows:

Grades 1 and 2: Participants may continue DTG and 3HP or isoniazid, at the discretion of the site investigator with careful follow-up.

Grades 3 and 4: Study drugs should be held until symptoms have resolved (or until ≤Grade 2 or within normal limits). Study drugs may be permanently discontinued at the discretion of site investigator. Site investigators are strongly encouraged to discuss discontinuations and reintroductions of study treatment with the core investigators to ensure consistency across sites.

If study drugs are suspended for any reason, participants will have 16 weeks from enrolment to complete 12 weeks of HP If the break in treatment is longer than 4 weeks, the participant will need to be rescreened for TB before recommencing HP.

6.3 Criteria for discontinuation of study treatment or for study discontinuation

Permanent treatment discontinuation

- Drug-related toxicity requiring treatment discontinuation, as defined in 6.1.2 above
- Requirement for prohibited medications
- Pregnancy or breastfeeding. HP and DTG will be discontinued and ART regimen switched to an efavirenz containing regimen available through routine care.
- Diagnosed with active TB disease
- Completion of treatment phase as defined by the protocol
- Request by participant to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol

Premature study discontinuation

- 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
- 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

All participants who discontinue therapy will be followed up according to their assigned schedule until the end of the study.

7 DATA MANAGEMENT

7.1 Source documentation

All clinical and laboratory information required by this protocol is to be present in the source documents. All protocol-required visits are to be recorded on the case report forms (CRFs) and keyed into the database unless otherwise specified.

7.2 Data capture

Building on the information technology infrastructure available at Aurum, we will use Merge eClinicalOS, an integrated web-based data management system. The site will be responsible for entering protocol-required quantitative data into a study database. The interim and final analytical datasets will be stored on password-protected, encrypted servers housed at The Aurum Institute. Scheduled backups will be performed on a daily, weekly, and monthly basis. Any personal identifiers will be suppressed from the analytic dataset prior to the data analysis phase of the study. Any paper registers, forms, or records that are reviewed to abstract data or cross-check missing data will not be removed from the secure, programmatic area where they are stored.

7.3 Quality control

Data will be validated on entry, using range and consistency checks. Quality control procedures will include review of CRFs for completion and correctness and source data verification. Logical data checks will also be performed on the data. Incomplete and incorrect queries will be sent to sites electronically for error resolution within the study database. Errors will be reviewed and corrected on a weekly basis. The study will be monitored by internal monitors.

7.4 Data monitoring

The study will be monitored regularly by Aurum and an independent CRO throughout the study period.

The following will be monitored:
100% Source Data Verification (SDV) for all (n=60) enrolled participants. For these participants, the following will be conducted:

- Informed Consent Form (ICF) review for 100% of participants.
- On-site source data verification (SDV) of source documents: paper source versus electronic Case Report Form (eCRF)
- Eligibility criteria (full eligibility will be assessed for 100% of enrolled participants)
- Review of randomisation documentation and verification of correct treatment arm allocation
- Monitoring of Investigational Product (IP) accountability and pharmacy documentation for all enrolled participants.
- Monitoring of safety laboratory results, requisition forms and shipping documentation
- Verifying that all biological samples have been collected (e.g. urine, blood, sputum and serum samples) as per protocol

7.5 Record retention

Study records (source documents, signed informed consent forms, IRB/IEC correspondence and approval letters, and screening logs) will be kept in a secure location accessible only to authorised study staff, investigators, and monitors. Secure archives are available on-site at Aurum for preliminary storage after study closure, before moving them to an off-site, secure storage facility. All records will be archived in a secure storage facility for at least fifteen (15) years after the completion of the study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample size calculations

Group 1:

Our sample size estimates in Group 1 are aimed to provide data to support precise estimation of the pharmacokinetic model parameters for DTG in the presence and absence of once-weekly HP. These models, once validated, will further be used to examine DTG dosing options for treatment of HIV-infected patients co-infected with LTBI who will receive DTG together with 3HP, pending appropriate safety assessment.

DTG dose options in the presence of once-weekly HP are based on:

- Mean DTG Ctau of 0.3 mcg/mL associated with virologic suppression in SPRING-1, Taking variability into account, if 90% confidence intervals of the effect (GMR) on DTG $C\tau$ caused by any intrinsic or extrinsic factor is completely above 0.25, the effect of that factor is not considered clinically significant, and DTG dose adjustment by that factor is not necessary.

The sample size assessment was done by evaluating different study designs (varying number of subjects and time points) using clinical trial simulations. We employed the stochastic simulation-estimation "sse" methodology for clinical trial simulation and re-estimation to evaluate sample sizes required to evaluate key pharmacokinetic parameters with precision adequate for decision making on use of HP + DTG in HIV infected patients. This methodology simulates the data from planned trial with proposed design (number of samples, participants) followed by the estimation of the parameters under the true and alternative models. This is repeated at least 1000 times and parameter estimates relative standard errors and between subject variability (BSV) estimates are assessed.

The proposed design for DTG requires evaluable 24 subjects with 6-11 time points/occasion to estimate pharmacokinetic parameters with required the precision defined as relative standard errors < 10% for typical values and RSE < 25 % for random effects (between subject variability). An additional 6 participants will be recruited to allow for

drop-outs or unevaluable PK samples. An evaluable participant is someone who has participated in at least two semi-intensive PK visits.

Group 2:

The sample size for Group 2 is aimed at ensuring that with the combined safety data from Groups 1 and 2, there are adequate safety data to rule out a grade 3 adverse event risk of 10% or higher in participants with HIV who have achieved virologic suppression.

The reported risk of all hypersensitivity reactions in HIV-infected persons taking HP is 1%. With a total sample size of 60 in the safety analysis, we will have at least 80% power to rule out a grade 3 adverse event risk of 10% or higher. So, with 30 participants in Group 1, we will need 30 participants in Group 2.

Group 3:

The sample size for Group 3 (N=25) is aimed at ensuring that there is an adequate comparison group for Group 4, in which TPT and DTG are started simultaneously, but in the comparison group the TPT is IPT, the current prevailing standard of care. INH is not expected to affect significantly the PK of DTG, so this group will serve as a control for DTG C_{min} sampled at parallel timepoints in patients on DTG-based regimens not taking HP.

Group 4:

The sample size for Group 4 (N=50) is aimed at ensuring that with the combined safety data from Groups 1 and 2, there are adequate safety data to rule out a grade 3 adverse event risk of 10% or higher in participants with HIV who are treatment-naïve and have not yet achieved virologic suppression.

The reported risk of all hypersensitivity reactions in HIV-infected persons taking HP is 1%. With a total sample size of 50 treatment-naïve participants in the safety analysis, we will have at least 80% power to rule out a grade 3 adverse event risk of 10% or higher.

The secondary objective is to estimate the proportion of participants who achieve virologic suppression. Since this trial is not designed to compare outcomes between the study arms, no formal statistical hypotheses are tested. Assuming 90% of participants achieve virologic suppression at week 24, we will have 80% power at a two-sided alpha of 5% to detect virologic suppression in 75% or more participants in Group 4.

8.2 Data analysis

8.2.1 Overview

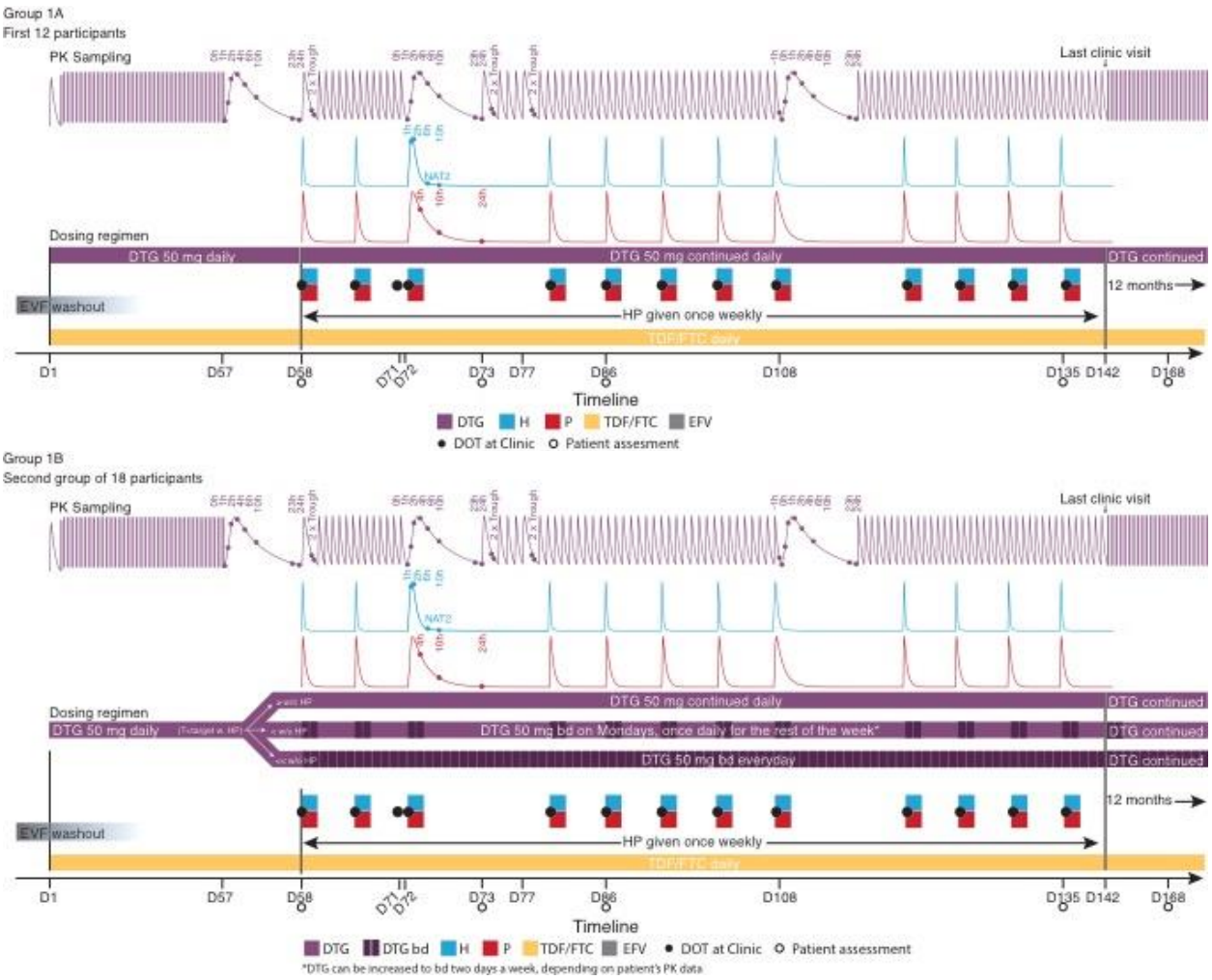
This is a Phase I/II trial assessing the pharmacokinetics and safety of dolutegravir-based ART when it is given together with twelve once-weekly doses of HP. The overall goal is to determine the dosing of DTG that will reach target concentrations over the seven days following HP dosing and to ensure that DTG given with 3HP is safe and well-tolerated to support 3HP's broad introduction in HIV-infected populations, many of whom will be taking DTG-based ART, and many of whom will be treatment-naïve and candidates for DTG-based regimens as preferred first-line therapy per 2018 WHO guidelines.

8.2.2 Pharmacology objectives and data

The Pharmacology objectives include Primary Objective 1 and Secondary Objectives 2 and 3, as follows:

- To evaluate the effect of RPT and INH given at doses of 900 mg once weekly (HP) on the pharmacokinetics (PK) of DTG (Primary Objective 1)
- To describe the PK of isoniazid and rifapentine in the study population (Secondary Objective 2)
- To determine the dosing for DTG, when given together with once-weekly HP that achieves target exposures in patients with LTBI-HIV co-infection, using nonlinear effects modeling. Mean DTG Ctau of 0.3 mcg/mL was associated with virologic suppression in SPRING-1, Taking variability into account, if 90% confidence intervals of the effect (GMR) on DTG Cτ caused by any intrinsic or extrinsic factor is completely above 0.25, the effect of that factor is not considered clinically significant, and DTG dose adjustment by that factor is not necessary. (28). (Secondary Objective 3).

PK sampling for Group 1A and 1B are demonstrated in the following figure:



Data that will be available to support the PK analyses include the following:
PK data for dolutegravir (Group 1):

- Semi-intensive PK data for DTG alone (Days 57-58): 0, 1, 2, 4, 6, 10, 23, 24 hours post-dose; blood for NAT2 genotyping
- Sparse PK sample on Day 59 (double trough, 23 and 24 hours after the previous day's dose) (this reflects DTG trough one day following first dose of HP)
- Semi-intensive PK data for DTG with the third dose of HP (Days 72-73): 0, 1, 2, 4, 6, 10, 23, 24 hours post-dose
- Sparse PK sampling on Day 74 (double DTG trough, two days after the third HP dose):
- Sparse PK sampling on Day 78 (double DTG trough, six days after the third HP dose)

- Semi-intensive PK data for DTG following the eighth dose of HP (Days 108-109) (Note that PK sampling here starts one day after the HP dose, not concurrent with the HP dose): -1, 0, 1, 2, 4, 6, 10, 23, 24 hours post-dose

PK data for dolutegravir (Group 2):

- Sparse PK sampling on Day 74 (two days following the 3rd HP dose): Double trough
- Sparse PK sampling on Day 109 (two days following the 8th HP dose): Double trough

PK data for dolutegravir (Group 3):

- Sparse PK sampling (single DTG trough) on Day 1 (24 hours following the 1st IPT or HP dose)
- Sparse PK sampling (single DTG trough) on Day 24 (72 hours following the 3rd IPT dose)
- Sparse PK sampling (single DTG trough) on Day 59 (72 hours following the 8th IPT dose)

PK data for dolutegravir (Group 4):

- Sparse PK sampling (single DTG trough) on Day 1 (24 hours following the 1st IPT or HP dose)
- Sparse PK sampling (single DTG trough) on Day 24 (72 hours following the 3rd IPT or HP dose)
- Sparse PK sampling (single DTG trough) on Day 59 (72 hours following the 8th HP dose)

PK data for rifapentine (Group 1):

- Sparse PK: Double RPT trough on Day 59 (following first HP dose)
- Semi-intensive sampling on Day 72 (with third HP dose): 4, 10, and 24 hours post-dose

PK data for rifapentine (Group 2):

- Sparse PK: RPT double trough on Day 73

PK data for isoniazid (Group 1):

- Semi-intensive PK on Day 72: 1, 2, 6, and 10h post-dose.

PK data for isoniazid (Group 2):

- Day 73: Blood for NAT2 genotyping (better predictor of drug exposures than single PK sample)

8.2.3 Pharmacology analytical plan, including interim analysis

Interim analysis plan:

Analysis plan:

Where descriptive statistics are used to summarize group characteristics and differences, they will be presented as follows: for continuous variables, the mean and standard deviation, median, quartiles, and range (minimum, maximum) will be included, and for categorical variables, the number and percent will be presented for each category.

PK Analysis

Descriptive statistics will be presented for proportion of participants at each sparse PK sampling timepoint with DTG C_{min} < 300 mg/mL and proportion of participants at each timepoint with DTG C_{min} < 64 ng/mL.

Population PK Analysis

The population PK analysis and assessment of drug-drug interactions will be performed using the non-linear mixed effects modeling approach. This approach estimates the typical (mean) value of parameters as well as their inter-individual

variances. Individual data with different pharmacokinetic designs may be combined including individuals contributing sparse data only.

A population pharmacokinetic model for DTG will be developed based on available data from entire study using the step-wise approach described below. This will include development of the DTG model in absence of HP (data from the very first occasion) and extension of the model with DTG data in presence of weekly HP where effect of RPT presence will be evaluated as a covariate on DTG clearance and/or bioavailability. Since major aim of the analysis is assessment of DDI, only limited covariate analyses exploring the influence of potential predictors of PK variability will be performed, if ranges of potential covariates are reasonable (weight, age) – this will be decided by analysist upon availability of the data. Once a final model, including the quantification of the drug-drug interaction is determined, model evaluation through assessment of objective function mapping, predictive checks and nonparametric bootstrapping will be conducted.

The general procedure that will be followed for the development of the PK model for Dolutegravir is outlined below:

The following strategy will be utilized for the model building process:

1. PK data from all patients receiving DTG in Group 1A in absence of 3HP (12 subjects) will be pooled.

2. Structural model development will be conducted using the pooled DTG data. PK modeling will begin with a one - compartment model with first-order (linear) elimination and first-order absorption. More complex PK models will be evaluated, including two – and three compartment models. Range of absorption models will be tested, including first order absorption with a lag time, zero order absorption, mixed zero and first order input, etc. More mechanistic models, including transit compartment model and Erlang absorption model might also be tested if needed. Once basic structure of the model is determined, model evaluation will be performed to assure adequate fit of DTG data alone and compared to published DTG population PK parameters. Structural model refinement will be performed if required. – Key Model 1

3. DTG data in presence of HP (Occasion 1-3) will be pooled with the initial data. The structural model will be applied to these data and the fit of the key Model 1 to these data will be evaluated. We expect that this fit will not be optimal due to expected DDI. Structural model refinement will be performed. This will include following options: estimation of DTG CL and F in presence of HP as a single parameter, estimation of DDI time course – e.g. impact of HP on DTG CL and its dynamics – appearance and disappearance of change in DTG CL and/or F. To perform this, we will evaluate different functions including linear, nonlinear, bell –shape, exponential functions of time. If needed, we will develop mechanistic model quantifying impact of RPT actual concentration on magnitude and time course of DDI. This model will be evaluated to assure adequate description of DTG-3HP DDI magnitude and dynamics. – Key Model 2

4. Model refinement and model evaluation steps will be performed.

5. Key Model 2 will be used to simulate full DTG time course during 12 weeks of 3HP administration in large virtual population using anticipated population variability for DTG in PK parameters as reported in the literature. We will derive time below target concentrations as detailed in Section 8.1 and compare to DTG with and without 3HP administration. We anticipate that DTG concentrations might be decreased when co-administered with 3HP with specific time patterns (more decrease two days following RPT dose).

6. Based on this comparison, alternative dosing options will be simulated to assess a pragmatic dosing regimen for DTG in presence of 3HP aligned with the target and goal detailed in Section 8.1. Evaluation of following regimens

may be explored: a.) BID 50 mg DTG for 12 weeks, b) BID 50 mg DTV only on the day of 3HP administration and c.) BID 50 mg DTG for 1-2 weeks, followed by 50 mg QD

7. If needed, an alternative dosing regimen may be used in next 12 subjects (Group 2A) and these data will be used to update and refine DDI model. Using this model, we will evaluate and confirm if adequate concentrations have been achieved with alternative dosing regimen using the same methodology as described above. Once this has been confirmed, this dosing regimen will be used for the remainder of the study.

Software and technical details:

The software package NONMEM, version 7, level 4 (Globomax, 7250 Parkway Drive, Suite 430, Hanover, MD 21076 USA) will be used in the analysis and is installed on a PC platform using GCC 2.96 under Red Hat Linux 9. The R-based (v 2.12.0, www.r-project.org) version of Xpose, Xpose 4.4.3, will be used to produce standard goodness-of-fit plots. Perl (v 5.8.8, www.perl.org) and Perl-speaks NONMEM (PsN, sourceforge.net/projects/psn) will be used for model evaluation and automatic covariate model-building. Microsoft Office Excel (Microsoft Corporation, Redmond, WA, USA) may be used for additional exploratory analysis and post-processing of NONMEM output.

Estimation methods in NONMEM will be first-order conditional (FOCE) with additive or log-additive models for residual variability and first-order conditional with interaction (FOCEI) with proportional and additive + proportional models for residual variability [3, 4] and if supported by the data. In case of prohibitive computer intensive runs with FOCE, the first-order estimation method may be used during model development. In such case, critical modeling steps will be reassessed using FOCE (with or without interaction).

Stability of NONMEM models will be assessed based on:

- Acceptable basic goodness of fit plots
- Number of significant digits ≥ 3 for all θ's
- Successful covariance step
- Estimates of θ's not close to a boundary
- Condition number (ratio of largest to smallest eigenvalue) < 1000
- Correlation less than 0.95 between any two parameters
- Stability check performed for a selected basic model: investigation of model stability from different initial values:

Model selection will be based on:

- The comparison of full vs. reduced models is based on the Log-Likelihood Criterion: the difference in the minimum value of the objective function between hierarchical models is asymptotically chi-square distributed with degrees of freedom equal to the difference in number of parameters between models.
- Decrease in unexplained variability. Extension of a model by adding independent variables should usually be accompanied by a decrease in random inter- and/or intra individual variability;
- Goodness of fit plots, e.g. relevant residuals against time randomly distributed around zero.
- Scientific plausibility of the model
- Exploratory Graphical Analysis
- Structural Model Development
- Statistical model development
- Covariates analysis
- Final Model Refinement
- Sensitivity Analysis of Fixed Parameter Values
- Model Evaluation

8.2.4 Statistical plan (non-PK endpoints)

The non-pharmacology objectives in this study are Primary Objective #2 and Secondary Objective #1, as follows:

Primary Objective #2: To assess the safety of DTG and 3HP co-administration.
The outcome of interest for this objective will be Grade 3 or higher AEs, analyzed as a recurring outcome. As we do not anticipate significant loss to follow up based on Group-1 and 2 evaluations, we will first estimate the proportion of participants receiving DTG plus 3HP who experience the outcome of interest using the formula "*Number of participants experiencing any AE ≥ Grade 3 / Total number of participants enrolled"* with binomial exact 95% confidence intervals. We will use Poisson regression to identify demographic, clinical and PK variables associated with higher incidence of AEs adjusting for potential confounders (age, BMI, CD4 count, VL etc.), with emphasis on time-updated and cumulative H, P and DTG concentrations. We will additionally perform a descriptive analysis of the types of AEs observed in the study, with emphasis on hepatotoxicity and hypersensitivity reactions, by participant characteristics at enrollment. Categorical data will be presented as frequencies and proportions. Continuous data will be presented as medians and inter-quartile ranges for non-normally distributed data, or as means and standard deviations for normally distributed data. A final safety report among Group 1 and Group 2 participants (n=60), Group 3 participants (n=25), and Group 4 participants (n= 50) will be prepared following the 12th HP dose. Proportion of participants discontinuing treatment for treatment-related AE's will be described and summary statistics provided.

Secondary Objective #2: To estimate the proportion of HIV treatment-naïve participants who achieve HIV-1 virologic suppression at 12 and 24 weeks after starting DTG-based ART plus 3HP (Groups 3 and 4).
We will use the FDA Snapshot algorithm to estimate the proportion of participants with virologic suppression, defined as HIV-1 RNA <50 copies/mL, at week 12 and week 24 calculated by the formula "*Number of participants with virologic suppression / Total number of participants enrolled"* with binomial exact 95% confidence intervals. We will use Cox-proportional hazards regression to estimate the median time to viral suppression. Exploratory analyses will be performed to estimate the rate of log-decline in HIV-1 RNA PCR with and without HP using mixed effects regression with random intercept and slope, and the median log-decline at each timepoint the viral load is assessed using the Willcoxon sign-rank test to account for within individual correlations.

9 STUDY MANAGEMENT

9.1 Investigator team

The investigator team of collaborators and will meet at least monthly via teleconference to discuss implementation progress. The meetings will be chaired by the PI.

9.2 Project and site implementation teams

The core project management team will oversee project implementation. The team will include the Managing Director: Clinical Trials Division, Trial Operations director, Site PI, Programme Manager, and Data Manager. The project management team will meet at least fortnightly by teleconference or face to face.

The Site implementation team will be comprised of the site investigators and clinic coordinators responsible for the implementation of the project at trial sites. The site implementation team will oversee the day-to-day operational aspects of the study at the trial site.

9.3 Safety Monitoring Committee (Aurum/JHU)

The existing WHIP$_3$TB Safety and Monitoring Committee (SMC) will be responsible for reviewing interim and final data. The SMC consists of a Chair, plus 2 additional members, which includes an independent statistician, pharmacology expert, and one clinician experienced in the field of TB/HIV. The members will not be involved with the trial in any way and don't have any competing interests that could impact on the trial. Members will be reimbursed for travel, accommodation and a per diem only. The SMC charter for the WHIP$_3$TB trial will be amended to accommodate the safety and PK study.

After 12 participants in Group 1 have completed the PK visit following the 3rd HP dose, an interim PK, safety, and VL assessment will be performed to ensure that the 50 mg once daily dose is safe and is sufficient to maintain virologic suppression. The SMC will meet to review PK, virology, and safety data following this assessment. Based on these interim reviews, the SMC will make recommendations to study leadership regarding further conduct of the trial, including on whether there are safety reasons for the trial to pause, stop, or be adjusted, or if dose adjustment should be made for subsequent participants.

After Groups 1B and 2 have completed the Week 11 visit, a second interim analysis for safety and HIV viral load assessment will be performed and reported to the study sponsor.

A second interim PK evaluation will occur after all Group 1B participants have completed the Week 11 semi-intensive PK visit. This evaluation will include all PK data from Group 1A, who will have completed their Week 16 semi-intensive PK visit.

9.4 Community Advisory Board (CAB)

The CAB represents the interests of the community in the trial, and provides a forum in which community members can provide feedback on the trial protocol and study conduct. The CAB also may be involved in educating the community about participation in the trial. The CAB will include patient representatives.

The proposed trial site for this study has an existing CAB.

A representative from the CABs will be invited to provide a community perspective in terms of trial conduct.

10 ETHICS

10.1 Regulatory considerations

This study will be conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH-GCP, SA-GCP and local regulatory requirements as applicable.

Written or witnessed verbal informed consent will be obtained from each participant prior to any protocol-specified procedures being conducted.

The protocol and informed consent forms will be reviewed and approved by the IRB or IEC of each participating clinical site prior to any protocol-specified procedures being conducted. Site investigators are responsible for ensuring that the protocol is reviewed by an IRB/IEC with the appropriate composition (per site guidelines). The investigator will inform the IRB/IEC as to the progress of the study at applicable intervals as defined by IRB/IEC policy.

Investigators will obtain approval from the Research Ethics Committees of the University of Witwatersrand, South Africa In addition, the study will need to be approved by the Medicines Control Council. Approval will also be sought from the Provincial and District Ethics Committees.

10.2 Risks and benefits for participants

The 3HP regimen has been approved by a stringent regulator (US FDA) and is recommended for TB preventive therapy in the United States. The potential benefits of PLWH taking 3HP is a reduced risk of developing TB disease. The 3HP regimen has been found to be safe in other studies. In a recent DTG-3HP PK study, 2 of 3 participants developed a hypersensitivity syndrome. The potential harm to participants may include developing drug induced adverse reaction, particularly hypersensitivity reactions due to RPT.

Participants in the study, regardless of treatment arm, will receive compensation for travel expenses required to attend scheduled study visits. We may contact participants, by cell phone if possible, periodically during the study to confirm contact details.

Dolutegravir is approved by the US FDA and the South African Health Products Regulatory Authority for first line treatment of HIV 1-infection, when prescribed in conjunction with two NRTIs.

The current key risks for DTG include serious skin reactions and hypersensitivity reaction; hepatobiliary disorders (drug induced liver injury [DILI] and other clinically significant elevations in transaminases, including Hepatitis B virus/Hepatitis C virus (HBV/HCV) related immune reconstitution inflammatory syndrome [IRIS]); Depression, suicidal ideation and suicidal behaviour; and a potentially serious drug: drug interaction (D: DI) with dofetilide. Dolutegravir was associated with neural tube defects in one study and should be avoided in pregnant women until further information is available. Further information on these, and other known or theoretical risks associated with the use of DTG, is included in the approved Local Prescribing Information in countries where DTG is marketed.

10.3 Confidentiality

All study records will be managed in a secure and confidential fashion. All records will be stored at the participating clinics and offices at provincial level in locked filing cabinets. Access to the records will be restricted to specified study team members. Case report forms will be identified using the participant's study number only, with locator information stored separately.

10.4 Study discontinuation

The study may be discontinued at any time by the funder, sponsor, investigators, or by any of the relevant regulatory bodies.

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12 APPENDIX

Appendix 1. Prohibited and precautionary medications

Prohibited Medications

While on rifapentine (RPT), currently only efavirenz (EFV)-based antiretroviral therapy (ART) regimens are permitted. Nevirapine, etravirine, rilpivirine, and other ART regimens (e.g., PI-based, raltegravir-containing) are prohibited.

Precautionary Agents with INH

Carbamazepine
Chlorzoxazone
Disulfiram
Ketoconazole
Phenytoin
Warfarin
Theophylline
Selective serotonin re-uptake inhibitor antidepressants (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Precautionary Agents with RPT

Medication Class	Precautionary Medications
Antiarrhythmics	Disopyramide
	Mexiletine
	Quinidine
	Tocainide
Antibiotics	Chloramphenicol
	Clarithromycin
	Dapsone
	Doxycycline
	Fluoroquinolones
Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Antipsychotics	Haloperidol
Azole Antifungals	Fluconazole
	Itraconazole
	Ketoconazole

Medication Class	Precautionary Medications
Barbiturates	Phenobarbital
Benzodiazepines	Diazepam
Beta-Blockers	Propranolol
Calcium Channel Blockers	Diltiazem
	Nifedipine
	Verapamil
Cardiac Glycoside Preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Oral hypoglycemic agents	Sulfonylureas
Hormonal Contraceptives/ Progestins	Ethinyl estradiol
	Levonorgestrel
Immunosuppressants	Cyclosporine
	Tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Phosphodiesterase-5 (PDE-5) Inhibitors	Sildenafil
Thyroid preparations	Levothyroxine
Tricyclic Antidepressants	Amitriptyline
	Nortriptyline

<u>Prohibited Medications with dolutegravir</u>

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital

- Phenytoin
- St. John's wort (*Hypericum perforatum*)

Dofetilide and pilsicainide are prohibited as DTG may inhibit renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.