Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med 2019;381:803-15. DOI: 10.1056/NEJMoa1902824

Re: ADVANCE (ClinicalTrials.gov Identifier: NCT03122262)

Enclosed is the original protocol, final protocol, summary of changes to the protocol, and statistical analysis plan (the original version was unchanged), as requested.

CLINICAL STUDY PROTOCOL

WRHI 060: A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF+FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy

PROTOCOL NO. WRHI 060

Sponsor: Wits Reproductive Health and HIV Institute (RHI)

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Version and Date of Protocol: Protocol Version 1.0; 29 April 2016

CONFIDENTIAL

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Contents

Protocol Approval

Study Title	**WRHI 060: A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF+FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy**
Protocol Number	WRHI 060
Protocol Date	Protocol Version 1.0; 29 April 2016

Protocol accepted and approved by:

Principal Investigator
Prof WD Francois Venter, FCP (SA)
Deputy Executive Director, Wits RHI
Associate Professor, Department of Medicine
University of the Witwatersrand, Johannesburg, South Africa

Declaration of Investigator

I have read and understand all sections of the protocol entitled "A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF+FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy" and the accompanying current information for investigators.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 1.0 dated 29 April 2016, the International Conference on Harmonisation harmonised tripartite guideline E6 (R1): Good Clinical Practice, and all applicable government regulations. I will not implement protocol changes without HREC approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorised to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications without the permission of the participant.

_____ 29 April 2016

Signature of Principal Investigator Date

Prof. WD Francois Venter

Printed Name of Principal Investigator

List of Abbreviations

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ART	antiretroviral therapy
BID	twice daily
CYP	cytochrome P450
DSMB	data and safety monitoring board
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HREC	Wits Human Research Ethics Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
TAF	tenofovir alafenamide
WHO	World Health Organisation
Wits RHI	Wits Reproductive Health and HIV Institute

Protocol Synopsis

Protocol number: WRHI 060
Title: A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy

Study Phase: Phase 3

Study Sites: 1-2 sites in Johannesburg, South Africa

Objectives: The primary objective of this study is to demonstrate the non-inferiority of dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) when compared with DTG and tenofovir disoproxil fumarate (TDF) plus FTC or compared with efavirenz (EFV) and TDF plus FTC in the first-line treatment of patients infected with human immunodeficiency virus (HIV)-1 as determined by the proportion of patients in each regimen with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48.

The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of each regimen.

Patient Population: Patients with HIV-1 infection will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria: Each patient must meet **all** of the following criteria to be enrolled in this study; there are no CD4 threshold criteria:

1. Age ≥12 years and ≥40 kg
2. Documented laboratory diagnosis of infection with HIV-1 (positive enzyme-linked immunosorbent assay HIV-1 antibody test) at screening
3. Plasma HIV-1 RNA (VL) ≥500 copies/mL
4. All pre-existing medical or laboratory abnormalities must be deemed to be stable by the investigator prior to study enrolment
5. Calculated creatinine clearance (CrCl) >60 mL/min (MDRD formula)
6. Ability to comprehend the full nature and purpose of the study, in the opinion of the investigator, and to comply with the requirements of the entire study.

Exclusion Criteria: Patients meeting any of the following criteria will be excluded from the study:

1. Previously received more than 30 days of treatment with any form of antiretroviral therapy (ART) or
2. Received any antiretrovirals within the last 6 months
3. Women who are pregnant at the time of the screening or baseline visit

4. Active tuberculosis and/or are on antituberculous therapy at the time of the screening or baseline visit
5. Taking and cannot discontinue prohibited concomitant medications listed in 7.3 at least 2 weeks prior to the baseline visit and for the duration of the study period
6. Clinically unstable, in the investigator's opinion
7. Current history of drug or alcohol abuse that, in the opinion of the investigator, may be an impediment to patient adherence to the protocol
8. Patients who participated in a study with an investigational drug within 60 days of screening or who are currently receiving treatment with any other investigational drug or device may be ineligible to participate. This is an investigator decision
9. Have a strong likelihood of relocating far enough to make access to the study site difficult
10. History or presence of allergy to the study drugs or their components.

Study Design

This is an open label randomised, non-inferiority (10% non-inferiority margin), phase 3 study to assess the efficacy and safety of DTG (50 mg once daily [QD]) administered in combination with TAF (25 mg QD) and FTC (200 mg QD) compared to DTG (50 mg QD) administered in combination with TDF (300 mg QD) and FTC (200 mg QD) and compared to EFV (600 mg QD) administered in combination with TDF (300 mg QD) and FTC (200 mg QD) over 96 weeks in patients with HIV-1 infection eligible for first-line ART .

Approximately 1050 male and female patients infected with HIV-1 who are eligible for first-line ART will be randomly assigned in a 1:1:1 ratio (approximately 350 patients per treatment group) to Treatment Group 1 (DTG + TAF + FTC) or Treatment Group 2 (DTG + TDF + FTC) or Treatment Group 3 (EFV + TDF + FTC). To ensure adequate representation of adolescents in any treatment group, randomisation will be stratified according to age greater or less than 18 years. The study includes screening and baseline visits, 8 study visits from Week 4 to Week 84, and an end-of-study visit at Week 96. Study medication pill counts will be performed at each follow up visit.

Screening: Screening will take place between Days –60 and –1, prior to the first study treatment administration. Within the 60-day period re-screenings may be done to confirm eligibility.

Baseline: At baseline (Day 0, Week 0), patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study, given a patient number, randomly assigned to either Treatment Group 1 or Treatment Group 2 or Treatment Group 3, and provided with unblinded study medication.

Treatment Period: Patients will begin treatment on the evening of Day 0, Week 0. However, the first dose may be delayed up to one week following randomisation. Patients will return to the site at pre-defined time intervals for clinical assessments and blood sampling. At all visits patients will be questioned about adverse events (AEs) to assess their wellbeing, and about concomitant medications.

Interim Analyses: To allow early stopping, 2 interim analyses will be performed on the primary efficacy endpoint: the first when approximately one-third of all patients have completed the Week 48 assessments and the second after approximately two-thirds of patients have completed the Week 48 assessments. Unblinded primary efficacy analysis and safety analyses will be provided to the data and safety monitoring board (DSMB), which is independent of the study team.

End-of-Study Visit: An end-of-study visit will occur either at the end of the study (Week 96) or earlier if the patient withdraws from the study, fails virologically, or a toxicity occurs that requires a medication change.

Efficacy Assessments: All laboratory end points will have a window of 4 weeks before and after that time point; 48-week data will include any plasma HIV-1 RNA levels done between 44 and 52 weeks; 96-week data will include any data between 92 and 100 weeks.

Primary Efficacy Endpoint: The primary efficacy endpoint will be the proportion of patients with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48. Patients who do not have an HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48.

Secondary Efficacy Endpoints:

- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm
- Proportion of patients with plasma HIV-1 RNA levels <200 copies/mL at Week 96
- Time to virologic failure (defined as confirmed HIV-1 RNA levels ≥1000 copies/mL at Week 12 - 24 or ≥200 copies/mL at or after Week 24)
- Change from baseline in plasma HIV-1 RNA levels at each visit
- Change from baseline in plasma CD4 levels at each visit.

Safety Assessments: Safety analyses will be performed on physical examination findings, vital sign measurements, clinical laboratory analyses, other investigations (such as DEXA scans) and monitoring AEs and concomitant medications throughout the study.

Throughout the Study:

- Adverse events (AEs) including serious AEs (SAEs)
- Vital sign measurements (blood pressure (BP) and heart rate)
- Targeted physical examination findings
- Mental health screening
- Sleep questionnaire
- Neuropathy screen
- Quality of life questionnaire
- Actigraphy (in a subset of patients)
- Laboratory analyses

Secondary Safety Endpoints:

- Mental health screening: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Sleep questionnaire: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Neuropathy screen: baseline, Weeks 4, 12, 24 and 48
- Quality of life questionnaire: baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in full blood count (all follow up visits)
- Change in biochemistry (all follow up visits)
- Change in serum and urine glucose (all follow up visits)
- Change in lipids weeks 0, 24, 48 and 96
- Changes in liver function tests measured at Weeks 0, 12, 24, 36, 48, 60, and 96 function tests measured at Weeks 0, 12, 24, 36, 48, 60, and 96
- Change in measures of renal function
    - Urine dipstix at each visit
    - Creatinine clearance (MDRD formula) at each visit
    - Urine Protein: Creatinine ratio (UPCR) at each visit
    - Urine Albumin: Creatinine ratio (UACR) at each visit
    - Retinol binding protein to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
    - β2 microglobulin to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
    - Fractional excretion of uric acid at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
    - Fractional excretion of phosphate at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
- Change in bone mineral density measured by DEXA scans at weeks 0, 48 and 96
- Women who fall pregnant on study will have monthly TAF, TDF and DTG levels done, and active follow-up and evaluation of their infants.

Clinicians will be blinded to screening and laboratory values that are not part of standard of care, unless assessed as severe (grade 3 and 4).

Special patient populations during study:

Pregnancy: Women will be counselled regarding the unknown risks regarding DTG and TAF exposure to the foetus should they fall pregnant, but if they do fall pregnant and elect to stay on the study, they will be offered additional study visits (monthly). Infants will be followed post partum for up to 18 months. Pharmacokinetic (PK) levels of TAF, TDF and DTG will be done at diagnosis of pregnancy in Treatment Groups 1 and 2 (according to which drug they are taking), and at routine study visits pre- and post partum.

TB: Patients on TB therapy at screening or baseline will be excluded. The management of each arm if the patient develops TB will be as follows:
Treatment Group 1: (DTG + TAF + FTC) – DTG daily dose will be increased to 50 mg twice daily; TAF will be switched to TDF 300 mg daily, for duration of TB treatment.
Treatment group 2: (DTG + TDF + FTC) – DTG daily dose will be increased to 50 mg twice daily, for duration of TB treatment.
Treatment group 3: (EFV + TDF + FTC) – no change.

Studies looking at PK of both DTG and TAF in the presence of rifampicin are underway; data from these studies will be evaluated by the scientific protocol committee, to see whether these changes in dose and drug are still necessary, during the course of the study. If not, treatment will be continued at initiation dose.

PK levels of TDF, TAF and DTG will be performed at TB diagnosis in Treatment Group 1 and 2 (according to which drug they are taking), as well as during and after TB treatment (if still on study), to assess changes in therapeutic levels with the changes.

Patients requiring single study drug substitutions: All these patients will be discontinued from the study, except in the case of TB patients as detailed above.

Study Medication, Dosage, and Route of Administration
Treatment Group 1: DTG 50 mg + TAF 25 mg + FTC 200 mg administered once daily orally over 96 weeks
Treatment Group 2: DTG 50 mg + TDF 300 mg + FTC 200 mg administered once daily orally over 96 weeks
Treatment Group 3: EFV 600 mg + TDF 300 mg + FTC 200 mg administered once daily orally over 96 weeks

Sample Size: Approximately 1050 patients randomly assigned in a 1:1:1 ratio (approximately 350 patients per treatment group). To ensure adequate representation of adolescents in any treatment group, randomisation will be stratified according to age greater or less than 18.

Statistical Methods:
The primary objective of the study is to establish non-inferior efficacy for the DTG + TAF + FTC arm compared with either of the active control arms (EFV + TDF + FTC or DTG + TDF + FTC). Both of these

control arms are included in 2015 World Health Organisation (WHO) guidelines for first-line treatment. Currently, EFV + TDF + FTC is the preferred regimen for all populations, while DTG + TDF + FTC is an alternative regimen with some restrictions where data are limited (pregnant women, people with TB co-infection). The study will also allow a comparison of the efficacy of DTG + TDF + FTC versus EFV + TDF + FTC, allowing three treatment comparisons in the study design.

The primary population for analysis will be Intent-to-Treat, including all randomised patients who received at least one dose of study medication.

The primary efficacy parameter will be the percentage of patients who have HIV-1 RNA suppression below 50 copies/mL at Week 48. Patients who either have confirmed HIV-1 RNA levels above 50 copies/mL, or who have missing data for any reason will be considered treatment failures. Patients who have switched off randomised treatment to a different treatment by Week 48 will be considered as treatment successes, provided that the HIV-1 RNA is below 50 copies/mL at Week 48.

In a previous clinical trial conducted at the same investigational center, the percentage of patients taking first-line antiretroviral treatment who had HIV-1 RNA suppression below 50 copies/mL by Week 48 was 80%.

A sample size of 350 patients per arm (1050 total) will provide at least 80% power to establish non-inferior efficacy for the DTG + TAF + FTC arm, compared to each of the other study arms. A non-inferiority margin of -10% is now standard in the design of phase 3 randomised trials of antiretrovirals. There will also be at least 80% power to establish non-inferior efficacy for the DTG + TDF + FTC arm compared to the EFV + TDF + FTC arm. An overall 1.7% significance level (two one-sided tests) will be used, to adjust for the three treatment comparisons being made.

1. Introduction

1.1 Background Information

Significant gains have been made in the last decade in terms of access to antiretroviral care within low- and middle-income countries (LMIC) through the support of local governments, international donors, and agencies. However, as the number of patients on antiretroviral (ARV) treatment (ART) rises, there has been increased attention paid to treatment optimisation, whereby drug dosage and manufacturing, clinical diagnosis and monitoring and health delivery systems are all interrogated for increased efficiencies. Savings from these efforts can be applied to treatment programmes, enabling more patients to receive life-saving therapy.

Since the recent publication of the START and TEMPRANO studies, which demonstrated that ART should be started irrespective of CD4 count,[1, 2] the WHO has announced preliminary guidance recommending everyone infected with HIV should start ART,[3] doubling those eligible for ART, with significant programmatic and financial implications.

Since WHO's 2013 recommendations for a harmonised first-line regimen in adults,[4] effective, more robust, tolerable, and potentially less expensive ARVs have been developed. However, data to recommend using these newer drugs in LMIC are not available. The needs of HIV-positive people are often very different in LMIC: populations include larger proportions of women of childbearing age, children, the severely immunosuppressed and people with TB and other co-infections. Typically, trials for new ARVs by originator manufacturers focus on registration in high-income countries, with data generated on dose selection, comparability and compatibility with other ARVs. Data supporting use in LMIC populations are missing with newer drugs.

Current first-line treatment in LMIC has several challenges:

- **Tolerability** Treatment has side effects, resulting in non-adherence or discontinuation. Better safety profiles would keep people on first-line longer
- **Cost** The cost of ARVs consumes the bulk of LMIC programme budgets. Current first-line cost is unlikely to decrease significantly
- **Robustness/Resistance** First-line is vulnerable to resistance. Finding a first-line regimen that is more robust and durable will limit transition to expensive and less well tolerated second- and third-line regimens
- **Evidence** Generating the evidence level required to change WHO/country guidelines requires large rigorous randomised controlled trials (RCTs), which are lacking for these drugs in LMIC
- **Fixed dose combinations** New individual drug options for LMIC are held by different originator manufacturers that have prioritised their own fixed dose combinations, which lack the cost benefit of optimised regimens.

New, simpler, safer, more potent and potentially more cost-effective antiretroviral therapy regimens are needed. Decreasing total drug doses of antiretroviral agents represents an untapped possibility for decreasing costs and toxicity, if efficacy can be maintained. Manufacturing costs for originator companies

comprise only a fraction of the price of the drug. However, with the rise of generic manufacturers, as well as increased licensing by originator companies to other pharmaceutical companies, the cost of raw materials to manufacture the drugs (active product ingredient, API) has become a more significant component of cost as prices have decreased. Thus, regimens that have an overall lower dose of medications could have a notable impact on the overall cost of ART, as well as often reducing side effects.

1.2 Current Therapy in South Africa

Access to ART has expanded rapidly within South Africa, with over 3 million patients initiated on therapy since 2004,[5] the largest ART programme in the world, with early suggestions of resultant increase in life expectancy[6] and even decreased incidence.[7] South Africa is now the largest procurer of ART generics in the world, along with PEPFAR and the Global Fund. The state programme has, since its inception, used WHO-recommended combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), a combination that demonstrates excellent virological suppression with good adherence. Current first-line therapy in adults is tenofovir disoproxil fumarate (TDF) and efavirenz (EFV), in combination with emtricitabine (FTC) or lamivudine (3TC), in a single tablet fixed dose combination,[8] as recommended by WHO.

However, the combination has a low resistance barrier and poor adherence invariably results in virological failure. Data on the number of first-line failures in South Africa are still elusive but a study looking at several programmes suggested just over 2% of patients migrate across to second-line annually (a larger percentage are lost to follow-up).[9] There is speculation that this percentage will rise, as programmes get larger and adherence counselling is spread across more patiennts.[10] However, intolerance to boosted protease inhibitors (the backbone of second-line) is well described, and includes gastrointestinal and metabolic concerns. Recently, in response to a growing number of patients failing second-line therapy, genotype resistance testing and third-line drugs including darunavir, raltegravir and etravirine, have been made available within the South African state programme, at considerable expense.[8, 11]

1.3 Rationale for selected study drugs and regimens

We will test two potential new regimens using newly available drugs in combination, both safer and more robust, for effectiveness against the current WHO and South African standard of care (EFV + TDF + FTC), with the express intention of providing adequate 48-week data to alter current first-line recommendations. In parallel to this study, there are protocols dealing with TB, additional studies addressing pregnancy, and studies looking at children below the age of 12, all evaluating the safety, dosing and efficacy of these new antiretrovirals. However, none of these address the overall effectiveness of routine use of these combinations in first-line ART, in those over 12 years.

Also in parallel, is a programme to alert generic manufacturers and regulators (such as the South African Medicines Control Council (MCC) to the potential new regimens, so that registration and manufacturing does not delay the in-country tender process.

This study protocol and set of exclusion criteria reflect the realities of programmatic use of these drugs in LMIC, and will be studied in patients who would be routinely eligible for these regimens. This includes studying the use of the drugs in TB and hepatitis B co-infected patients, adolescents, as well as in women of childbearing age.[12] This will set a new standard for trials intended to demonstrate the benefit of new drugs under real world conditions.

Rationale for the individual drugs to be tested:[12]

The two new drugs are dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) to be used with existing FTC, replacing EFV and TDF in current standard of care if the study is successful.

- DTG is better tolerated with a greater resistance barrier than currently used EFV
- DTG requires a smaller dose than EFV (50 mg versus both recommended EFV doses (600/400 mg)), lowering manufacturers' costs
- TAF has shown renal and bone benefits over currently used TDF
- TAF requires a smaller dose than TDF (25 mg versus 300 mg), lowering manufacturers' costs
- API requirements will drop; this will reduce the need for investment in additional manufacturing capacity by drug manufacturers
- One major generic manufacturer is willing to guarantee the proposed DTG + TAF + FTC regimen will be at least 20% cheaper than EFV + TDF + FTC
- The better tolerability and higher barrier to resistance of TAF and DTG should result in improved patient outcomes and more durable treatment, with less progression to expensive and more toxic regimens
- Both TAF and DTG are being studied in children less than 12, with the possibility of aligning these drugs with adult regimens in future.

A new first-line regimen at 20% less than current regimens and with a higher barrier to failure will result in significant savings of around USD 80 million/year by 2019 for South Africa, with secondary cost savings from reduced movement to second-line and clinical costs of non-adherence.

Rationale for DTG as a replacement for EFV: DTG has shown improved efficacy and safety over EFV in the first-line SINGLE trial, on a backbone of abacavir (ABC) and lamivudine (3TC).[13] DTG appears to have a high resistance barrier, with no cases of DTG resistance documented in naive patients in high-income countries where the drug has been used for almost three years. The cost of DTG is likely to be the same or less than EFV, at scale, according to the Clinton Health Access Initiative (CHAI) and confirmed by discussions with generic manufacturers. We will use DTG in the study, and compare it with EFV, which is in the current preferred WHO first-line regimen. The soon-to-start NAMSAL study is comparing a lower dose of EFV (EFV 400 mg) to DTG 50 mg, to lower the cost and side-effect profile of EFV; this will not resolve the EFV resistance issue. Adolescents ≥12 years, and ≥40 kg will be included in the study, as dosing in this group has been studied. DTG dosing for children less than 12 years of age is currently under study, and submitted to the FDA by the originator company at the end of 2015.

Rationale for TAF as a replacement for TDF: Use of DTG with ABC (as used in the originator FDC product) is problematic in LMIC countries because of genetic testing requirement, concerns over risk of cardiac events, lack of available co-formulations, and significant cost over alternatives to ABC. Two potential

alternatives are TDF 300 mg once daily, which is widely available, or TAF, 25 mg once daily. TAF, which is a prodrug of tenofovir has demonstrated lower renal and bone toxicity compared to TDF. Results from SPRING2 and Flamingo study showed high efficacy of DTG when combined with TDF/FTC.[13, 14] However, there are no data using TAF with DTG. Clinical trials to study TAF dosing and safety in children are only just getting underway. TAF is being studied as part of an FDC with elvitegravir + cobicistat + FTC in children 6-12 years weighing >25 kg using the adult tablet. A trial to study TAF + FTC dosing and safety in adolescents 12 - 18 years and 6 - 12 years olds weighing >25 kg started in early 2015 and is expected to be completed in mid-2018.

Rationale for the regimen DTG + TAF + FTC: The combination DTG 50 mg with FTC 200 mg and TAF 25 mg would give a total once-daily dose of 275 mg - a significant improvement on pill size when compared with current standard of care, TDF 300 mg, FTC 200 mg [or 3TC 300 mg] and EFV 600 mg, totalling 1100 mg [1200 mg] daily. We are not aware of any RCTs evaluating TAF 25 mg + FTC as first-line treatment in any form. There are also no clinical trials evaluating TAF 25 mg + FTC in combination with DTG. TAF 25 mg + FTC is only being evaluated in switching studies that provide only limited evidence for efficacy in first-line treatment. To justify scale-up of manufacture of this combination, it would be important to have WHO recommendation, based on clinical trial data. Most of the phase 2 and phase 3 clinical development of TAF thus far has been based on clinical trials comparing TAF 10 mg with TDF 300 mg, both with FTC and elvitegravir boosted by cobicistat, which cannot be used in TB, and where data on pregnant women are limited. The FDC tablet will be substantially smaller than the current regimen (comparable in size to a multivitamin supplement) and will have an impact on patient and programme convenience. Alternative integrase inhibitors are either not suitable for LMIC, or only in earlier stages of development.

Rationale for the regimen DTG + TDF + FTC: TAF drives the cost reduction of the new regimen; however, having data to support DTG use with TDF would guarantee that the study would deliver at least a benefit in terms of robustness and toxicity reduction over current standard of care, with at least crude price parity. Currently, TDF has only been tested with DTG in around 400 patients in clinical trials, although the combination is used commonly in high-income countries, despite the lack of evidence. For WHO to recommend this as the preferred new initiation ART regimen, while switching millions of people to this combination from the current standard of care, requires robust evidence. This combination is being tested in the event that TAF, which has potentially important drug interactions with rifampicin, an altered side effect profile, and also has not been studied as extensively in children or pregnant women, proves not to be non-inferior in this study.

Rationale for using EFV + TDF + FTC: This is the current standard of care in first-line in all LMIC (FTC and 3TC are interchangeable in almost all guidelines; FTC is currently the preferred agent in South Africa in the state programme). We have consulted with WHO and multiple other stakeholder and donors. For countries to move away from this current regimen, which has performed well in the field and which now has a large evidence base, would require the new regimens to be compared head-to-head, even though EFV and TDF are likely to fall away from high-income country guidelines. WHO has recommended that we therefore include this study arm. Using this process, future regimens will be required to be tested against a standard of care.

2. Study Objectives

2.1 Primary Objective

The primary objective of this study is to demonstrate the non-inferiority of DTG and TAF plus FTC when compared with DTG and TDF plus FTC or compared with EFV and TDF plus FTC in the first-line treatment of patients infected with HIV-1 as determined by the proportion of patients in each regimen with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48.

2.2 Secondary Objective

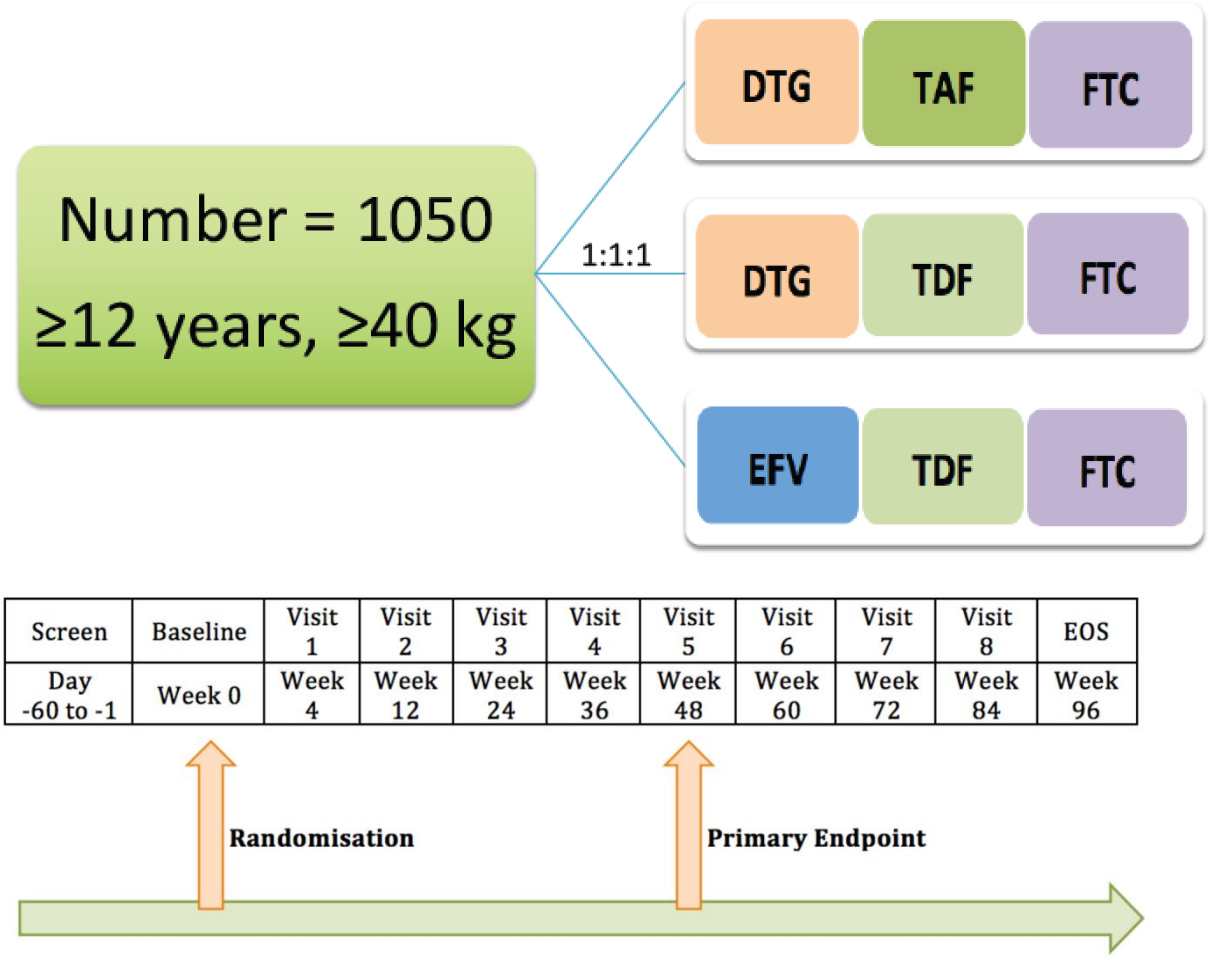
The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of DTG and TAF plus FTC when compared with DTG and TDF plus FTC or EFV and TDF plus FTC in each regimen.

3.0 Study Design

This is an open label, randomised, phase 3, three-arm, study, conducted over 96 weeks. *(See figure 1).*

The study includes a screening period (Days –60 to –1), a baseline visit (Week 0), and a 96-week treatment period.

Approximately one thousand and fifty male and female patients infected with HIV-1 eligible for first-line therapy, will be randomly assigned in a 1:1:1 ratio (approximately 350 patients per treatment group) to either Treatment Group 1 (DTG + TAF + FTC) or Treatment Group 2 (DTG + TDF + FTC) or Treatment Group 3 (EFV + TDF + FTC). To ensure adequate representation of adolescents in any treatment group, randomisation will be stratified according to age greater or less than 18 years. The randomisation will be electronically generated. All patients will be assigned a unique patient number by the randomisation system. After a patient number has been assigned, the number will not be reused even if the patient withdraws before receiving any study medication. All medications will be administered in an open label design.



Screen	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	EOS
Day -60 to -1	Week 0	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96

Figure 1: Study design

Table 1: Treatment Regimen

Study Medications	Tablet/Capsule Strength	Dosage Regimen
Treatment Group 1* (2 tablets)		
DTG	50 mg	Once daily
TAF	25 mg	Once daily
FTC	200 mg	Once daily
Treatment Group 2 (2 tablets)**		
DTG	50 mg	Once daily
TDF	300 mg	Once daily
FTC	200 mg	Once daily
Treatment Group 3 * (1 tablet)**		
EFV	600 mg	Once daily (at night)
TDF	300 mg	Once daily
FTC	200 mg	Once daily
Abbreviations: DTG, dolutegravir; TAF, tenofovir alafenamide fumarate; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; EFV, efavirenz. * TAF and FTC combined as a single tablet ** TDF/FTC combined as a single tablet *** TDF/FTC/EFV combined as a single tablet		

4.0 Selection of Study Population

Approximately one thousand and fifty patients infected with HIV-1 who qualify for first-line therapy, will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

There is no CD4 threshold for this study, in keeping with WHO guidelines, and as the South African government has signalled that this requirement will fall away in the next 2 years.

Before performing any study procedures, all potential patients will provide written informed consent, and will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The informed consent process and all questions raised must be documented. The study staff will also sign the ICF.

4.1 Inclusion Criteria

Each patient must meet **all** of the following criteria to be enrolled in this study:

1. Age ≥12 years and ≥40 kg

2. Documented laboratory diagnosis of infection with HIV-1 (positive enzyme-linked immunosorbent assay HIV-1 antibody test) at screening
3. Plasma HIV-1 RNA (VL) ≥500 copies/mL
4. All pre-existing medical or laboratory abnormalities must be deemed to be stable by the investigator prior to study enrolment
5. Calculated creatinine clearance (CrCl) >60 mL/min (MDRD formula)
6. Ability to comprehend the full nature and purpose of the study, in the opinion of the investigator, and to comply with the requirements of the entire study.

4.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Previously received more than 30 days of treatment with any form of antiretroviral therapy (ART) or
2. Received any antiretrovirals within the last 6 months
3. Women who are pregnant at the time of the screening or baseline visit
4. Active tuberculosis and/or are on antituberculous therapy at the time of the baseline visit
5. Taking and cannot discontinue prohibited concomitant medications listed in 7.3 at least 2 weeks prior to the baseline visit and for the duration of the study period
6. Clinically unstable, in the investigator's opinion
7. Current history of drug or alcohol abuse that, in the opinion of the investigator, may be an impediment to patient adherence to the protocol
8. Patients who participated in a study with an investigational drug within 60 days of screening or who are currently receiving treatment with any other investigational drug or device may be ineligible to participate. This is an investigator decision
9. Have a strong likelihood of relocating far enough to make access to the study site difficult
10. History or presence of allergy to the study drugs or their components.

5.0 Study Procedures **(see appendix 1)**

5.1 Screening

1. Informed consent process
2. Inclusion/exclusion criteria determination
3. Demography data
4. Pre-existing medical condition(s)
5. Concomitant medications
6. Physical examination, height, weight and vital sign measurements
7. Urine pregnancy test
8. Actigraphy (in a subset)
9. Clinical laboratory testing:

- Full blood count, biochemistry
- Liver function tests
- Confirm HIV-1 status with laboratory ELISA test
- HIV-1 RNA
- CD4 count
- Creatinine and calculated clearance (MDRD)

Re-Screening (Days -60 to -1)
During the 60-day screening period, a patient may be re-screened to determine eligibility. Re-screening will involve retesting of subsequent biological samples, and/or re-assessment of any inclusion and exclusion criteria that previously failed the patient.

5.2 Baseline

1. Review inclusion/exclusion criteria
2. Review pre-existing medical condition(s)
3. Review concomitant medications
4. Symptom-led physical examination (including TB symptom screen), weight and blood pressure
5. Mental health screen
6. Sleep questionnaire
7. Neuropathy screen
8. Quality of life questionnaire
9. Urine pregnancy test
10. Hepatitis B surface antigen test (HBsAg)
11. Clinical laboratory testing
    - Lipid panel (fasting)
    - Glucose (fasting)
    - Liver function tests
    - Measures of renal function
        - Urine dipstix
        - Creatinine clearance (MDRD formula)
        - Urine Protein: Creatinine ratio (UPCR)
        - Urine Albumin: Creatinine ratio (UACR)
        - Retinol binding protein to creatinine ratio
        - β2 microglobulin to creatinine ratio
        - Fractional excretion of uric acid
        - Fractional excretion of phosphate
    - Urine, serum, plasma and PBMCs for storage (including neuropathy genetic/epigenetic blood specimen)
12. DEXA scan
13. Randomisation
14. Study medications dispensing and patient education on adherence

5.3 Follow-up Visit Procedures

1. Assess adverse events
2. Concomitant medications
3. Symptom-led physical examination (including TB symptom screen), weight and blood pressure
4. Mental health screen
5. Sleep questionnaire
6. Neuropathy screen at Weeks 4, 12, 24 and 48)
7. Quality of life questionnaire
8. Adherence questionnaire at Weeks 4, 48 and 96
9. Urine pregnancy test
10. Clinical laboratory testing:
    - Plasma HIV-1 RNA (all follow up visits)
    - CD4 count (Week 48 and 96)
    - Full blood count (all follow up visits)
    - Biochemistry (all follow up visits)
    - Serum and urine glucose (all follow up visits)
    - Lipids (Week 24, 48 and 96)
- Liver function tests (Weeks 12, 24, 36, 48, 60, and 96)
    - Urine for pregnancy screening at every visit, for women of child bearing potential
    - Measures of renal function
        - Urine dipstix
        - Creatinine clearance (MDRD formula) (all follow up visits)
        - Urine Protein: Creatinine ratio (UPCR) (all follow up visits)
        - Urine Albumin: Creatinine ratio (UACR) (all follow up visits)
        - Retinol binding protein to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
        - β2 microglobulin to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
        - Fractional excretion of uric acid at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
        - Fractional excretion of phosphate at Weeks 0, 12, 24, 36, 48, 60, 72, and 96
- Urine, serum, plasma and PBMCs for storage (including neuropathy genetic/epigenetic blood specimen at Weeks 4, 12, 24 and 48)

11. Other investigations
    - DEXA scans at Weeks 48 and 96
12. Study medications dispensing and patient education

5.4 Physical Examination and Vital Sign Measurements

A full physical examination will be performed at screening, and a targeted symptom directed physical examination where clinically indicated thereafter. Height and weight will be recorded at the screening visit and weight will be measured at all clinic visits from baseline to the last study visit.

Vital sign measurements (temperature, pulse rate, systolic and diastolic blood pressure) will be collected at screening. At all other study visits only blood pressure and pulse rate will be routinely measured, and other vital signs only if indicated clinically.

5.5 Efficacy Assessments

Efficacy will be assessed by the evaluation of plasma HIV-1 RNA level. The primary efficacy endpoint will be the proportion of patients with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48. Patients who do not have a HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48.

All patients with detectable HIV-1 RNA (>50 copies/mL) will receive adherence counselling, with a repeat test within 2 months of the date of counseling. If repeated HIV-1 RNA ≥500 copies/mL, a resistance test will be performed, and the patient terminated from the study. In instances where HIV-1 RNA copies cannot be amplified, investigator's discretion will apply. In patients who continue to have 50 - 1000 copies/mL, adherence intensification and 2-monthly testing will continue until suppression below 50 copies/mL, upon which study monitoring will occur as per protocol, or when persistently above 1000 copies/mL (2 measures), upon which the patient will be terminated from the study.

5.6 Additional Assessments

The burden of pain in HIV-positive populations is high. Pain is common (50-75% of individuals report a painful condition), is most commonly experienced as moderate to severe in intensity and patients often report more than one pain site. This pain burden associates with reduced quality of life. Certain painful conditions, such as HIV-associated sensory neuropathy, are more prevalent on some drug regimens and warrant monitoring. Intensity and interference of the associated pain may be measured by patient self report and by objective measurement of activity using actigraphy.

HIV-associated sensory neuropathy (HIV-SN) is a common neurological complication of HIV and its treatment, with a prevalence of >50% in a similar Johannesburg cohort. Incidence of HIV-SN is higher on some ARV regimens than others, and perception of pain may be altered by others, and so screening for HIV-SN will allow for comparison of neurotoxicity of the drug regimens. HIV-SN is frequently painful and treatments often ineffective. Genetic and epigenetic studies are important to help elucidate the pathogenesis of HIV-SN and the associated pain, and also to help determine potential drug targets. Such studies will be possible with screening for HIV-SN and extraction of DNA from patient blood samples.

Sleep issues are a common side effect of some ARVs, including DTG and EFV. Poor sleep quality and quantity affect (amongst other factors), quality of life, immunity and cognitive function; of particular importance in HIV-positive populations. Monitoring sleep, both through patient self report and objective measurement using actigraphy, is important.

Neuropathy screen
Patients will be assessed for the presence of neuropathy using the validated AIDS Clinical Trials Group (ACTG) Brief Peripheral Neuropathy Screen. This validated tool is widely used in clinical trials and encompasses assessment of both clinical signs (vibration sense, pin-prick detection, ankle-jerk reflexes) and symptoms (pain, numbness, paraesthesia), which if both are present are indicative of sensory neuropathy. The screening takes about 10 minutes per patient to complete. Assessment will be made at weeks 0, 4, 12, 24 and 48.

Actigraphy
Activity levels of patients will be measured using accelerometers during the screening period, and weeks 24 and 48. Accelerometers which are small (29 mm x 37 mm X 11 mm) and lightweight (22 g) will be worn on the patients' waists for a two-week period and only removed for bathing, showering or swimming. An appointment will be made for the return of the accelerometer following the two-week wear period. Actigraphy will only be assessed in a subset of patients.

Bloods for assessing epigenetic changes
At weeks 0, 4, 12, 24, and 48, 5 mL of blood will be taken to assess both for genetic and epigenetic associations with development of neuropathy and the pain associated with it. The extracted DNA will be analysed at the NHLS genotyping facility. Following DNA extraction, the DNA sample will be stored in the Human Genetics DNA Bio-Bank at the NHLS, Johannesburg, South Africa for the duration of the research study and bio-banked for future use.

Sleep
At all study visits, we shall assess sleep using two standardised sleep questionnaires which have been validated and previously used in South African cohorts. The faces sleepiness scale is a pictorial measure of sleepiness, which consists of cartoon faces showing various degrees of eye closure, yawning, a hand rubbing an eye, and a person asleep. The faces scale is therefore a particularly useful tool for individuals who are not fluent in English or those not proficient in reading. A further screening questionnaire will be used to identify patients with insomnia, who will then complete the insomnia severity scale. The questionnaires will take approximately 10-15 minutes to administer, in total.

5.7 Early withdrawal

Patients are free to withdraw from the study at any time for any reason. If a patient withdraws from the study early, all procedures for the end-of-study visit should be conducted. The investigator may also withdraw the patient at any time in the interest of patient safety, for virological failure or if the study is terminated. The primary reason for withdrawal must be recorded in the source document.

Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. Patients who miss any study visits will be followed up according to study site SOP "Participant recruitment and retention". At least 2 attempts (by telephone, personal visit, or e-mail) will be made before the patient is considered lost to follow-up. All follow-up attempts (method, date, and time) will be documented in the source document.

The investigator may withdraw a patient from the study, ideally after discussion with the principal investigator, if the patient:

- Is in violation of the protocol
- Experiences a serious or intolerable AE which interferes with study procedures
- Has laboratory safety assessments that reveal clinically significant changes from the baseline values, and is likely due to study drug
- Experiences virological failure, as described above
- Requires a medication that is prohibited by the protocol
- Has non-adherence to study protocol requirements and/or medication
- Withdraws consent or refuses to continue participation and/or procedures/observations.

A patient can also be withdrawn at the discretion of the investigator.

5.8 Replacements

Patients who discontinue participation in the study for any reason after randomisation will not be replaced.

6.0 Safety Assessments

Safety evaluations will include the monitoring of AEs and concomitant medications, clinical laboratory assessments, physical examinations, vital sign measurements, and evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, and urine dipstix and creatinine clearance).

Investigators will be blinded to measures of UPCR, UACR, retinol binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and fractional excretion of phosphate and DEXA scans. Mental health screening, sleep questionnaire and neuropathy screen results will also be blinded, unless the study nurse or counsellor administering the questionnaire has serious concerns that the patient requires intervention, upon which they should immediately inform the investigator.

Safety issues will be discussed in detail among study doctors and with the patient before taking any decisions as to study continuation.

6.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient in a clinical investigation with a medicinal product regardless of its causal relationship to study medication. Patients will be instructed to contact the principal investigator or designee at any time after randomisation if any symptoms develop.

A treatment-emergent AE is defined as any event, including laboratory abnormalities, not present before exposure to study medication or any event already present that worsens in either intensity or frequency after exposure to study medication.

An AE is also any of the following occurring after study randomisation:

- Complications that occur as a result of a protocol-mandated procedure after randomisation to study medications
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of the study after randomisation to study medications
- Reasons for and complications arising from a termination of pregnancy due to medical and/or surgical reasons.

An AE does not include the following:

- Medical or surgical procedures performed. However, the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before screening visit that do not get worse
- Situations where an untoward medical occurrence has not occurred (eg, hospitalisation for elective surgery)
- Overdose of study medication without clinical sequelae
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason.

Adverse events will be assessed (reported and/or observed) and documented from enrolment once the patient is randomised to study medications, until exit from the study (i.e. early withdrawal or end-of-study visit at week 96). Any medical conditions observed at screening and which do not exclude the patient from the study will be documented as pre-existing medical conditions. All AEs will be followed to adequate resolution. Any ongoing AE at early withdrawal or the end-of-study visit will be further followed until satisfactory resolution or until the investigator deems the event to be chronic or the patient to be stable, up to a maximum of 30 days after the last visit.

AEs will be documented in chart notes and those of grade 3 and 4 and unexpected adverse drug events will be entered into the AE case report form (CRF).

6.2 Serious Adverse Events (SAE)

An SAE is defined as any AE that:

- Results in death
- Is immediately life threatening (includes events which put patients at risk of death at the time of the event but not events which may have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Of clinical significance in the opinion of the investigator.

Any SAE must be documented in an SAE CRF. All SAEs and unexpected ADRs will be reported to the Wits RHI Safety Committee (WSC), by email, within 24 hours from the time site personnel first learn of the event.

6.3 Assessment of AEs

The severity or intensity of an AE refers to the extent to which an AE affects daily activities. The severity of all AEs, including laboratory abnormalities, will be graded according to the Division of AIDS grading table (version 2.0, November 2014).

The relationship or association of the study medication in causing or contributing to the AE will be characterised using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study medication and the reported event.

Related: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

All SAEs that occur during the study (regardless of relationship to study medication) must be reported in detail and followed until the events resolve, stabilise, or become non-serious. All SAEs will be reported to the Human Research Ethics Committee (HREC) according to HREC requirements. Medical and scientific judgement should be exercised in deciding whether an AE, which does not meet the routine definition of an SAE but is important from a safety perspective and may jeopardise the patient or require intervention to prevent one of the other outcomes listed in the definition of serious, should be considered as serious.

6.4 Management of Pregnancy

DTG Preclinical toxicity studies for DTG in pregnancy did not reveal any significant concerns, and DTG was

classified as FDA pregnancy category B, prior to the removal of this classification from use. In registration trials and Compassionate Use programmes, among 38 pregnancies, 1 congenital anomaly, 18 live births without any anomalies, 9 elective terminations without any anomalies, 13 spontaneous abortions without any anomalies, and 3 ectopic pregnancies were described. In post marketing surveillance, 74 pregnancies were reported as of 16 January 2016, with 18 live births without any anomalies, 2 live births with congenital anomalies, 4 spontaneous abortions without anomaly, 1 spontaneous abortion with anomaly, 1 stillbirth without anomaly and 39 pregnancies ongoing or lost to follow up. According to the Antiretroviral pregnancy registry (APR), with first trimester DTG exposure, there were no defects seen in 10 live births, and one defect was noted in 18 live births with second and third trimester exposure (it is likely that the pregnancies reported to the APR overlap with those described above). Recent data from CROI from IMPAACT 1026 in 30 mother-infant pairs, had four varied congenital anomalies reported, and the researchers are still collecting data on these cases.[15]

TAF Preclinical toxicity studies for TAF did not reveal any significant concerns. TDF is used as a proxy for TAF carcinogenicity and peri-postnatal studies. According to the APR, with first trimester exposure to any TDF-containing regimen, 2.3% of 10 live births had birth defects, and 2.1% of live births with second and third trimester exposure.

Other studies Several other clinical studies using DTG and/or TAF in pregnant women are underway, which will include pregnant women receiving DTG and/or TAF. ARIA is a phase 3b study comparing DTG + ABC + 3TC to ATV/r + TDF + FTC in ARV naïve women (n=474). Women in the DTG arm who become pregnant on the study will roll over into a single-arm PK and safety study. It is anticipated that this study should recruit approximately 25 women. DOLphin is a small study that will randomise late presenting pregnant women to received either DTG or EFV-based regimens. It will look at PK in late pregnancy, post partum and during breastfeeding, and will be followed up by a larger study, DOLphin 2. IMPAACT 1026s and PANNA will enroll women who become pregnant whilst using DTG or TAF into PK studies. The NAMSAL study comparing DTG to EFV 400mg will continue women who become pregnant on their assigned study drug. WAVES, a phase 3 study of EVG + COBI + FTC + TDF versus ATV/r + FTC + TDF in women, has an open label extension with EVG + COBI + FTC + TAF. Those randomised to EVG + COBI + FTC + TDF will continue on this arm, while those on ATV/r + FTC + TDF will be re-randomised to continue ATV/r + FTC + TDF, or to receive EVG + COBI + FTC + TAF. Women who fall pregnant on the open label study will be allowed to continue on their randomised regimen in the study. Other studies to evaluate DTG and/or TAF in pregnancy are still in planning stages, including IMPAACT 2010, which has a similar design to this study in terms of study drugs, but only enrolling pregnant women. More data will also continue to accumulate from continued clinical use of DTG in countries where it is licensed and easily available.

This study All eligible women of childbearing potential (and where possible their partners) will be counselled about the potential risks associated with pregnancy during the trial and the uncertainty of long-term effects of antiretroviral therapy on infant outcome.

Women will be encouraged to not fall pregnant during their study participation. They will receive counselling and be provided with condoms and appropriate contraception. They will be advised to report to the study site staff as soon as possible if pregnancy is suspected.

Urine pregnancy tests will be performed in all female patients of childbearing potential at every visit from screening to the end-of-study (Week 96) or early withdrawal visit, and as required during the study according to local standard practice for clinical care or according to the investigator's discretion, where pregnancy may be suspected.

If a female patient becomes pregnant during the study and consents to further participation, they may elect to remain in the study. Women who become pregnant on DTG arms and elect to stay in the study will have their DTG levels taken monthly. Those on the DTG + TAF + FTC arm who become pregnant will have monthly TAF levels in addition to DTG levels. DTG and TAF drug levels will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions.

Children born to study participants
Children will be followed up to 18 months and assessments regarding congenital anomalies, potential toxicities due to ART exposure *in utero* and through breastfeeding, growth and development will be assessed.

The following will be conducted at 3 monthly visits (birth + 5 days; 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, see appendix 2):

- Gestational assessment
- Feeding assessment
- Infant/child ART exposure (maternal ART or infant prophylaxis)
- Anthropometry:
    - Birth weight and length and head circumference
    - Weight, length and weight for length at each study visit (3 monthly)
- Congenital anomalies assessment
- Developmental screen and assessment
- Toxicity assessment: Creatinine clearance, FBC at birth, 3 months
- DEXA scan: 6 months

Children will be referred as necessary, if any abnormality is suspected.

6.5 Management of TB

DTG: DTG is currently being studied in patients on TB treatment in a separate study, comparing a DTG-based regimen versus EFV-based treatment, and this study should be completed in 2016. Additional PK studies in patients with TB are in progress or planned. Current recommendations are that DTG be dosed twice daily if given with rifampicin (RIF).

TAF: Currently there are no data on interactions between TAF and RIF, but a significant interaction is predicted based on modelling from PK interactions between TAF and carbamazepine. A study in healthy volunteers is currently planned, which will examine the interaction between TAF and RIF, followed by a study in patients with TB.

This study Active TB is an exclusion criterion for entry to this study. Patients will be screened for active TB at every visit, using the 4-question screening tool in the South African guidelines. Those screening positive will be investigated in accordance with the guidelines.

The management of each arm if the patient develops TB on study drug will be as follows:
Treatment Group 1: (DTG + TAF + FTC) – DTG daily dose will be increased to 50 mg twice daily; TAF will be switched to TDF 300 mg daily, for duration of TB treatment.
Treatment group 2: (DTG + TDF + FTC) - DTG daily dose will be increased to 50 mg twice daily, for duration of TB treatment.
Treatment group 3: (EFV + TDF + FTC) – no change.

PK levels of TDF, TAF and DTG will be performed at TB diagnosis in Treatment Group 1 and 2 (according to which drug they are taking), as well as during and after TB treatment (if still on study), to assess changes in therapeutic levels with the changes.

Studies looking at PK of both DTG and TAF in the presence of RIF are underway; data from these studies will be evaluated by the scientific protocol committee, to see whether these changes in dose and drug are still necessary. If not, treatment will be continued at initiation dose.

6.6 Management of single drug substitutions

Any modification of the antiretroviral regimen will result in patient exclusion, except in TB, in the manner described above.

6.7 Safety of patients in the study

To ensure safety of patients, this study will be conducted to standards of ICH-GCP, South African GCP, Good Participatory Practice and other applicable regulatory and ethical standards. In addition, there will be a DSMB to oversee the safety aspects of the clinical trial. The DSMB is run by the NIH, with international representation, and comprises members who are independent of the study site and staff.

There will be a Steering Committee, including the PI and other stakeholders, which will oversee the conduct of the study, and ensure continual updates concerning the study implementation.

In addition, an Endpoint Adjudication Committee (EAC), also known as a Clinical Endpoint Committee (CEC), will be established. This is an independent group of experts that reviews the clinical trial data in order to give expert opinions about clinical safety or efficacy events of interest. The endpoint review committee will have two to four members comprising of an independent chair, an expert in the disease being studied and a member of the trial management or steering committee.

7.0 Study Treatments

All study medications are to be orally self-administered as directed according to the package insert. Open label study medication will be supplied to the patient at baseline and Week 4 - 84. All medications used in this study will be provided as open label medications. Patients will be instructed to bring all used and unused study medication bottles with them to each study visit.

Table 2: Study Medication Supplies

Product	Formulation	Manufacturer
Dolutegravir	50 mg tablets	ViiV Healthcare
Tenofovir disoproxil fumarate plus emtricitabine (FDC)	300/200 mg tablets	Gilead Sciences or generic manufacturer, to be determined
Tenofovir alafenamide fumarate plus emtricitabine (FDC)	25/200 mg tablets	Gilead Sciences
Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC)	600/300/200 mg tablets	MSD or generic manufacturer, to be determined
Abbreviations: FDC, fixed dose combination		

Currently, it is anticipated the originator companies will donate study drugs. If this does not occur, alternative supplies are available, including from generic manufacturers; however, colour and size of the medication may change from that detailed below. Regulators will be advised accordingly, if this is the case.

Dolutegravir

Each tablet contains dolutegravir sodium equivalent to 50 mg of DTG. The tablet, if supplied by ViiV Healthcare, is a yellow, round biconvex shape, film coated tablet about 9 mm diameter, de-bossed with “SV 572” on one side and “50” on the reverse side. The tablets do not require any special storage conditions.

Tenofovir disoproxil fumarate plus emtricitabine (FDC)

Tenofovir disoproxil fumarate plus emtricitabine (FDC) is a co-formulation of TDF 300 mg and FTC 200 mg as a film-coated tablet. The medication, if supplied by Gilead Sciences, is packed in a white plastic bottle of 112 tablets, and will be stored at room temperature (below 30 ^{0}C).

Tenofovir alafenamide fumarate plus emtricitabine (FDC)

Tenofovir alafenamide fumarate plus emtricitabine (FDC) is a co-formulation of TAF 25 mg and FTC 200 mg as a film-coated tablet. The medication, if supplied by Gilead Sciences is packed in a white plastic bottle of 112 tablets, and will be stored at room temperature (below 30 ^{0}C).

Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC)
Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC) is a co-formulation of TDF 300 mg, FTC 200 mg and EFV 600 mg as a film-coated tablet. The medication, if supplied by MSD is packed in a white plastic bottle of 112 tablets, and will be stored at room temperature (below 30 ^{0}C).

All study medications will be stored per manufacturers' specifications in the package insert.

7.1 Medication Supplies

The study site will acquire study medication from multiple sources, including the originator companies and generic manufacturers. All study medications will be administered in an unblinded fashion and supplied as commercial drug, over-labelled for clinical trial use in accordance with local regulatory requirements.

At the site, all study medications must be kept in a secure cabinet or room with access restricted to only necessary study site personnel. Storage instructions for site personnel and patients will be provided on the label. Study medication labels will contain information to meet the applicable regulatory requirements.

7.2 Study Medication Accountability

The investigator will maintain accurate records of receipt of all study medications, including dates of receipt. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study medications will be reconciled and retained or destroyed according to applicable regulations. Patient compliance will be evaluated through review of drug dispensing and administration records.

7.3 Prior, Concomitant and Subsequent Therapy

DTG As DTG is neither an inducer nor inhibitor of CYP3A, there are no significant interactions with hormonal contraceptives. However, as an in vitro inhibitor of OCT-2 (organic cation transporter), DTG increases metformin concentrations and dose adjustment of metformin should be considered when starting and stopping co-administration of DTG with metformin. Metformin intake is not a contraindication to study participation. Renal function should be monitored as per protocol. Antacids containing magnesium or aluminium, as well as calcium, iron, zinc and multivitamin supplements should be dosed at least 2 hours after or 6 hours before DTG dosing, due to complex binding to polyvalent cations.

TAF TAF is transported by P-gp and BCRP. Medicinal products that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption. *In vitro* and clinical PK drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving TAF with other medicinal products is low. TAF

is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is not an inhibitor of CYP3A4 *in vivo*. TAF is a substrate of OATP *in vitro*.

The following medications are not to be used during the course of the study:

- Investigational drug within 2 weeks of the first study drug dose (baseline)
- Anticonvulsants
    - Carbamazepine
    - Oxcarbazepine
    - Phenobarbital
    - Phenytoin
- Midazolam
- Triazolam
- Pimozide
- Ergot alkaloids
    - Ergotamine
- Herbal products
    - St. John's Wort
- Probenicid

Drugs with nephrotoxic potential should be used with care.

8.0 Statistical Analysis Plans

All plasma HIV-1 RNA levels end points will have a window of 4 weeks before and after that time point; 48-week data will include any plasma HIV-1 RNA levels done between 44 and 52 weeks; 96-week data will include any data between 92 and 100 weeks.

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48. Patients who do not have an HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48.

8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm
- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (<200 copies/mL) at Week 96

- Time to virologic failure (defined as confirmed HIV-1 RNA levels ≥1000 copies/mL at week 12 - 24 or ≥200 copies/mL at or after week 24)
- Change from baseline in plasma HIV-1 RNA levels by visit
- Change from baseline of CD4 count by visit.

8.3 Safety Endpoints

The main safety endpoint is the assessment of the tolerability and safety of the three treatment combinations as measured by the nature and frequency of AEs and changes in questionnaires, vital sign measurements, physical examination findings, clinical laboratory analyses and concomitant medications.

8.4 Sample Size

In a previous clinical trial conducted at the same investigational center, the percentage of patients taking first-line antiretroviral treatment who had HIV-1 RNA suppression below 50 copies/mL by Week 48 was 80%.

A sample size of 350 patients per arm (1050 total) will provide at least 80% power to establish non-inferior efficacy for the DTG + TAF + FTC arm, compared to each of the other study arms. A non-inferiority margin of -10% is now standard in the design of phase 3 randomised trials of antiretrovirals. There will also be at least 80% power to establish non-inferior efficacy for the DTG + TDF + FTC arm compared to the EFV + TDF + FTC arm. An overall 1.7% significance level (two one-sided tests) will be used, to adjust for the three treatment comparisons being made.

8.5 Analysis Sets

The following analysis sets will be used in the statistical analyses:
All-randomised set: The all-randomised set will consist of all randomised patients, regardless of whether or not any study treatment dosing was completed. Patients will be analysed according to the treatment they were randomly assigned to.
Per-protocol set: The PP set will consist of all randomised patients who fully comply with the inclusion and exclusion criteria, have received at least 80% of all doses of study treatment up to Week 48, and have an evaluable plasma HIV-1 RNA level assessment at Week 48. Criteria will be defined in more detail in the statistical analysis plan (SAP). Patients will be analysed according to the treatment they received.
Safety set: The safety set will consist of all patients who receive at least one dose of randomly assigned study treatments. All safety analyses will be performed using the safety set. Patients will be analysed according to the treatment they received.

All efficacy analyses will be performed using the all-randomised and PP sets. All safety analyses will be performed using the safety set.

8.6 Statistical Analysis

The primary objective of the study is to establish non-inferior efficacy for the DTG + TAF + FTC arm compared with either of the control arms (DTG + TDF + FTC or EFV + TDF + FTC). Both of these treatments are included in current World Health Organisation for first-line treatment. Currently, EFV + TDF + FTC is most widely recommended, while DTG + TDF + FTC is listed as an alternative treatment. The study will also allow a comparison of the efficacy of DTG + TDF + FTC versus EFV + TDF + FTC. Hence there are three treatment comparisons included in the study design.

The primary population for analysis will be Intent-to-Treat, including all randomised patients who received at least one dose of study medication.

The primary efficacy parameter will be the percentage of patients who have HIV-1 RNA suppression below 50 copies/mL at Week 48. Patients either who have HIV-1 RNA levels above 50 copies/mL, or who have missing data for any reason will be considered treatment failures. Patients who have switched off randomised treatment to a different treatment by Week 48 will be considered as treatment successes, if the HIV-1 RNA is below 50 copies/mL at Week 48.

6.7 Primary Efficacy Analysis

The primary endpoint is the proportion of patients with undetectable plasma HIV-1 RNA levels (<50 copies/mL) at Week 48. The difference in proportions of patients who achieve the primary endpoint across the 3 treatment groups will be analysed. This variable will also be tabulated, displaying the proportions of patients with undetectable plasma HIV-1 RNA levels (with 95% CI) by treatment group, the estimate (with 95% CI) for the difference in proportion across all three treatment groups, and the corresponding non-inferiority test p-values.

The consistency of the treatment effect across subgroups will be investigated. All efficacy analyses will be performed using the all-randomised and PP sets.

8.8 Safety Analyses

Treatment-emergent AEs will be tabulated by treatment, system organ class, preferred term, seriousness, severity, and relationship to treatment. Tabulations will contain the number and percentage of patients with an event as well as the number of events. All AEs will be listed.
Shift tables (change from baseline value to on-treatment values) based on laboratory normal ranges will be presented for each laboratory measurement at each assessment time. In addition, laboratory parameters will be summarised by descriptive statistics.

Changes in vital sign measurements, physical examination data, previous and concomitant treatments, medical history, mental health, sleep, neuropathy screen and quality of life questionnaires, actigraph readings, urine dipstix, clinical laboratory parameters, lipids, creatinine

clearance (MDRD formula), measures of renal function, and DEXA will be summarised by treatment group and visit, where relevant.

8.9 Interim Analyses

A data safety monitoring board (DSMB) will monitor the study in order to ensure that harm is minimised and benefits maximised for the study patients. Membership of the DSMB will be completely independent of the study staff. The NIH has agreed to use its existing International DSMB to oversee the study.

To allow early stopping, 2 interim analyses will be performed on the primary efficacy endpoint: the first when approximately one-third of all patients have completed the Week 48 assessments and the second after approximately two-thirds of patients have completed the Week 48 assessments. Unblinded primary efficacy analysis and safety analyses will be provided to the DSMB that is independent of the study team. The study will be unblinded to investigators and patients throughout the study to Week 96. The DSMB will issue recommendations concerning trial continuation.

Stopping rules*:*

The Peto rule will be used to adjust the p-value of the final analysis for the two interim analyses. The study would only be stopped for efficacy reasons if the efficacy of one arm (using the primary efficacy endpoint) was significantly worse than either of the two other treatment arms, with a p-value <0.001.

No formal stopping rules will be used by the DSMB for safety outcomes.

9.0 Data Management

At every visit, patients' information will be recorded in source documents including chart notes and laboratory test results. Data from CRFs and other data sources will be entered into an electronic database as specified in the study site's data management SOP. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the database. The electronic database will be designed and managed in a system to be agreed on and provided by a Contract Research Organisation (CRO).

Each person involved with the study will have an individual logon and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

10.0 Other Study Activities

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the regulatory authorities or the Human Research Ethics Committee (HREC).

The principal investigator or designee and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. All computers are password-protected and records can only be accessed by authorised study staff.

10.2 Reporting

The protocol and relevant supporting documents will be submitted to the Medicine Control Council (MCC) and HREC for approval. The study protocol will be registered with the South African National Clinical Trial Registry (www.sanctr.gov.za) / National Human Research Ethics Committee (www.ethicsapp.co.za) and ClinicalTrial.gov. Six-monthly progress reports will be submitted to MCC and HREC for the duration of the study, and as requested. Annual recertification will be obtained from HREC. Upon completion or premature termination of the study, the investigator will provide HREC with a summary of the study's outcome, and the regulatory authorities with any reports required.

10.3 Investigator Documentation

Prior to beginning the study, the principal investigator will be asked to comply with ICH E6(R1) 8.2 by providing the following essential documents, including but not limited to:

- An original investigator-signed investigator agreement page of the protocol
- An HREC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patients
- HREC approval
- *Curriculum vitae* for the principal investigator and each investigator. Current licensure must be noted on the *curriculum vitae*. They will be signed and dated by each investigator at study start-up, indicating that they are accurate and current
- Laboratory certifications and normal ranges for any laboratories used by the site.

10.4 Monitoring of the Study

The study monitor has the obligation to follow the study closely. In doing so, the monitor will visit the study facility at periodic intervals, in addition to maintaining necessary telephone and email contact. The

monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal investigator and study staff. All aspects of the study will be carefully monitored for compliance with applicable government regulation with respect to current ICH GCP guidelines and current standard operating procedures.

10.5 Protocol Amendments

Amendments to the protocol must be submitted in writing to the MCC and HREC for approval before patients are enrolled into an amended protocol, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. This should be fully documented.

10.6 Protocol Violations and Deviations

The principal investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The principal investigator or designee may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to trial patients without prior HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the HREC for review and approval and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the HREC and agreed to by the principal investigator or designee. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion, exclusion or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient, when the patient or principal investigator or designee has failed to adhere to significant protocol requirements (inclusion and exclusion criteria) and the patient was enrolled without prior approval, or when there is non-adherence to regulations or some ICH GCP guidelines.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigator or designees will be notified in writing by the monitor of violations and deviations. The HREC should be notified of all protocol violations and deviations in a timely manner.

10.7 Inspection of Records

Principal investigator or designee and institutions involved in the study will permit trial-related monitoring, audits, HREC review, and regulatory inspections by providing direct access to all study records.

10.8 Records Retention

All correspondence (e.g. with HREC, or MCC) relating to this clinical study should be kept in appropriate study folders. Records of patients, source documents, CRFs, and drug inventory sheet pertaining to the study must be kept on file. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, if required by the applicable regulatory requirements. If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who is willing to accept the responsibility.

10.9 Study Termination

Although Wits RHI has every intention of completing the study, Wits RHI reserves the right to discontinue the study at any time for clinical or administrative reasons. The end of the study is defined as the date on which the last patient completes the last visit.

10.10 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the investigator will be responsible for these activities and will determine how the manuscript is written and edited, the number and order of authors, the publication(s) to which it will be submitted, and other related issues according to the Wits RHI publication guidelines.

11 Appendix

11.1: Schedule of Events

(All visits after baseline have a 4-week window on either side of the visit date)

Study Visit	**Screening**	**Baseline**	**Visit 1**	**Follow up Visits: 2, 3, 4, 6, 7, 8**	**Visit 5**	**Visit 9 /EOS**
Study Week	**–**	**0**	**4**	**12, 24, 36, 60, 72, 84**	**48**	**96**
Study Day/Window	**–60 to –1**	**0**	**15-42**		**323–350**	
Informed consent	X					
Demography	X					
Medical history/pre-existing conditions	X	X				
TB symptom screen	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X
Previous/concomitant medications	X	X	X	X	X	X
Height/weight measurement	H/W	W	W	W	W	W
Vital sign measurements	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
Mental health screening		X	X	X	X	X
Sleep questionnaires		X	X	X	X	X
Neuropathy screen		X	X	W12 only	X	
Actigraphy (in subset)	X			W24 only	X	
Adherence questionnaire			X		X	X
Urine pregnancy testing	X	X	X	X	X	X
Urine dipstix		X	X	X	X	X
Hepatitis B antigen		x				
Plasma HIV-1 RNA	X	X	X	X	X	X
CD4 cell count	X			W12 only	X	X
Haematology, biochemistry	X		X	X	X	X
Serum and urine glucose		X	X	X	X	X
Lipid panel		X		W24 only	X	X

Liver function tests		X		W12, 24, 36, 60	X	X
Study Visit	**Screening**	**Baseline**	**Visit 1**	**Follow up Visits: 2, 3, 4, 6, 7, 8**	**Visit 5**	**Visit 9 /EOS**
Study Week	**–**	**0**	**4**	**12, 24, 36, 60, 72, 84**	**48**	**96**
Study Day/Window	**–60 to –1**	**0**	**15-42**		**323–350**	
Measures of renal function		X		X	X	X
Blood for genetic/epigenetic assessment		X	X	W12 and 24 only	X	
Urine for storage		X	X	X	X	X
Plasma preparation and serum cryopreservation		X	X	X	X	X
PBMC preparation and storage		X			X	X
DEXA scans		X			X	X
Inclusion/exclusion criteria	X	X				
Randomisation		X				
Study medications dispensed		X	X	X	X	
Study treatment/medication accountability		X	X	X	X	X

11.2: Schedule of Infant Follow Up

Visit (Infant age)	Birth + 5 days	3 months	6 months	9 months	12 months	15 months	18 months (Final)
Gestational assessment	X	X	X	X	X	X	X
Feeding assessment	X	X	X	X	X	X	X
ART exposure*	X	X	X	X	X	X	X
Anthropometry**	X	X	X	X	X	X	X
Congenital anomalies	X	X	X	X	X	X	X
Developmental screen and assessment	X	X	X	X	X	X	X
Toxicity assessment: CrCl, FBC***	X	X					
DEXA scan			X				

* ART exposure *in utero* and through breastfeeding
**Birth weight and length and head circumferenceWeight, length and weight for length at each study visit (3 monthly)
***CrCl , FBC at birth, 3 monthly

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CLINICAL STUDY PROTOCOL: Final

WRHI 060 (ADVANCE): A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy

PROTOCOL NO. WRHI 060

Sponsor: Wits Reproductive Health and HIV Institute (RHI)

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Version and Date of Protocol: Protocol Version 3.0; 12 December 2017

CONFIDENTIAL

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Contents

Protocol Approval

Study Title	WRHI 060: A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy
Protocol Number	WRHI 060
Study short name	ADVANCE
Protocol Date	Protocol Version 3.0; 12 December 2017

Protocol accepted and approved by:

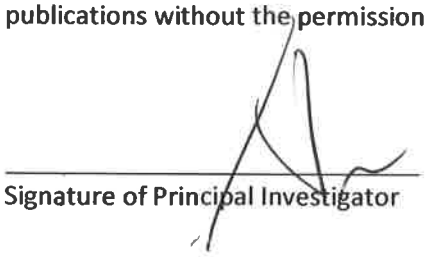
Principal Investigator
Prof WD Francois Venter, FCP (SA)
Deputy Executive Director, Wits RHI
Associate Professor, Department of Medicine
University of the Witwatersrand, Johannesburg, South Africa

Declaration of Investigator

I have read and understand all sections of the protocol entitled "*A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy*" and the accompanying current information for investigators.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 3.0 dated 12 December 2017, the International Conference on Harmonisation harmonised tripartite guideline E6 (R1): Good Clinical Practice, and all applicable government regulations. I will not implement protocol changes without HREC approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorised to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications without the permission of the participant.



Signature of Principal Investigator

12 Dec 2017
Date

Prof. WD Francois Venter

Printed Name of Principal Investigator

List of Abbreviations

Abbreviation	Definition
3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AE	adverse event
API	active pharmaceutical ingredient
ARV	antiretroviral
ART	antiretroviral therapy
Cr	creatinine
CrCl	creatinine clearance
DSMB	data and safety monitoring board
DTG	dolutegravir
EFV	efavirenz
FDC	fixed dose combination
FTC	emtricitabine
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HREC	Human Research Ethics Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
IL-6	interleukin-6
INH	isoniazid
IPT	isoniazid preventive therapy
LMIC	lower and middle-income countries
MCC	Medicines Control Council
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cells
PK	pharmacokinetic
PP	per protocol
QD	once daily
RCT	randomised controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
TAF	tenofovir alafenamide fumarate
TB	tuberculosis
TDF	tenofovir disoproxil fumarate

Abbreviation	Definition
TFV	tenofovir
TFV-DP	tenofovir diphosphate
UACR	urine albumin: creatinine ratio
UCT	University of Cape Town
ULN	upper limit of normal
UPCR	urine protein: creatinine ratio
WHO	World Health Organization
Wits RHI	Wits Reproductive Health and HIV Institute

Protocol Synopsis

Protocol Number: WRHI 060 (ADVANCE)

Title: A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy

Study Phase: Phase 3

Study Sites: 2-4 sites in Johannesburg, South Africa.

Study Objectives: The primary objective of this study is to demonstrate the non-inferiority of dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) when compared with DTG and tenofovir disoproxil fumarate (TDF) plus FTC or compared with efavirenz (EFV) and TDF plus FTC in the first-line treatment of patients infected with human immunodeficiency virus (HIV)-1 as determined by the proportion of patients in each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of each regimen. Pharmacokinetic analyses of DTG, tenofovir (TFV) and tenofovir diphosphate (TFV-DP) concentrations in participants who develop active tuberculosis and in pregnant women will be explored in treatment groups 1 and 2. Pharmacokinetic analyses of EFV and isoniazid (INH) concentrations in participants receiving isoniazid preventive therapy (IPT) will be explored in treatment group 3. Pharmacogenomics and further pharmacokinetic parameters may be explored, contingent on funding.

Patient Population: Patients with HIV-1 infection will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria: Each patient must meet **all** of the following criteria to be enrolled in this study; there is no CD4 threshold entry criterion:

1. Age ≥ 12 years and ≥ 40 kg
2. Documented laboratory diagnosis of infection with HIV-1 (positive enzyme-linked immunosorbent assay HIV-1 antibody test) at screening
3. Plasma HIV-1 RNA (VL) ≥ 500 copies/mL
4. All pre-existing medical or laboratory abnormalities must be deemed to be stable by the investigator prior to study enrolment
5. Calculated creatinine clearance (CrCl) > 60 mL/min (Cockcroft-Gault formula) in > 18 years old OR > 80 mL/min (modified Cockcroft-Gault) in ≤ 18 years old
6. Ability to comprehend the full nature and purpose of the study, in the opinion of the investigator, and to comply with the requirements of the entire study.

Exclusion Criteria: Patients meeting any of the following criteria will be excluded from the study:

1. Previously received more than 30 days of treatment with any form of antiretroviral therapy (ART) or
2. Received any antiretrovirals within the last 6 months
3. Women who are pregnant at the time of the screening or enrolment visits
4. Active tuberculosis and/or are on antituberculous therapy at the time of the screening or enrolment visits
5. Taking and cannot discontinue prohibited concomitant medications listed in 8.3 at least 2 weeks prior to enrolment visit and for the duration of the study period
6. Clinically unstable, in the investigator's opinion

7. Current history of drug or alcohol abuse that, in the opinion of the investigator, may be an impediment to patient adherence to the protocol
8. Patients who participated in a study with an investigational drug within 60 days of screening or who are currently receiving treatment with any other investigational drug or device may be ineligible to participate. This is an investigator decision
9. Have a strong likelihood of relocating far enough to make access to the study site difficult
10. History or presence of allergy to the study drugs or their components
11. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); Child-Pugh C.

Study Design

This is an open label randomised, non-inferiority (10% non-inferiority margin), phase 3 study to assess the efficacy and safety of DTG (50 mg once daily [QD]) administered in combination with TAF (25 mg QD) and FTC (200 mg QD) compared to DTG (50 mg QD) administered in combination with TDF (300 mg QD) and FTC (200 mg QD) and compared to EFV (600 mg QD) administered in combination with TDF (300 mg QD) and FTC (200 mg QD) over 96 weeks in patients with HIV-1 infection eligible for first-line ART.

Approximately 1110 male and female patients infected with HIV-1 who are eligible for first-line ART will be randomly assigned in a 1:1:1 ratio (approximately 370 patients per treatment group) to Treatment Group 1 (DTG + TAF + FTC) or Treatment Group 2 (DTG + TDF + FTC) or Treatment Group 3 (EFV + TDF + FTC). The 12-< 19 year age group will be enrolled and randomised separately; enrolment is estimated at 30-40 per arm (total 90-120). The study includes screening and enrolment visits, 8 study visits from Week 4 to Week 84, and an end-of-study visit at Week 96. Study medication pill counts will be performed at each follow-up visit.

The Data Safety Monitoring Board (DSMB) and South African Medicines Control Council (MCC) independently requested that the 12-< 19 year age group be enrolled separately, as the numbers are likely to be small, using the same criteria as adults, and that the data be analysed separately (the DSMB requested, in addition, for an analysis on the 12-15 year age group).

Screening: Screening will take place between Days –60 and –1, prior to the first study treatment administration. Within the 60-day period, re-screenings may be done to confirm eligibility.

Enrolment: At enrolment (Day 0, Week 0), patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study, given a patient number, randomly assigned to either Treatment Group 1 or Treatment Group 2 or Treatment Group 3, and provided with unblinded study medications.

Follow-up Period: Patients in treatment group 3 will be advised to begin treatment on the evening of Day 0, Week 0, and those in treatment groups 1 and 2 on the morning of Day 1 Week 0. It is also advised that patients in treatment groups 1 and 2 take their study medication in the morning while those in treatment group 3 take their study medication at night. However, the first dose may be delayed up to one week following randomisation. The start date should be noted where possible. Patients will return to the site at pre-defined time intervals for clinical assessments and blood sampling. At all visits patients will be questioned about adverse events (AEs) to assess their wellbeing, and about concomitant medications.

Interim Analyses: To allow early stopping, one interim analysis will be performed on the primary efficacy endpoint, when 400 participants have completed the Week 48 assessments. The interim analysis will test for differences between the study arms, and not for non-inferiority. Unblinded primary efficacy analysis and safety analyses will be provided to the DSMB, which is independent of the study team.

End-of-Study Visit: An end-of-study visit will occur either at the end of the study (Week 96) or earlier if the patient withdraws from the study, fails virologically, or a toxicity occurs that requires a medication change.

Efficacy Assessments: All laboratory endpoints will have a window of 4 weeks before and after the specific visit time point; 48-week data will include any plasma HIV-1 RNA levels done between 44 and 52 weeks; 96-week data will include any data between 92 and 100 weeks.

Primary Efficacy Endpoint: The primary efficacy endpoint is the proportion of patients with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. Patients who do not have an HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are as follows:

- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm
- Proportion of patients on each regimen with plasma HIV-1 RNA levels (< 200 copies/mL) at Week 96
- Time to virologic failure (defined as confirmed HIV-1 RNA levels ≥ 1000 copies/mL at week 12-24 or ≥ 200 copies/mL at or after week 24)
- Change from screening in plasma HIV-1 RNA levels by visit
- Change from screening of CD4 count by visit
- Virological efficacy and tolerability in the 12-< 19 year age group
- Analysis of PK data, virological efficacy and tolerability in those becoming pregnant
- Analysis of PK data, tolerability and virological efficacy in those developing TB
- Analysis of PK interactions between EFV and INH in participants in treatment group 3 receiving IPT
- Analysis of PK interactions between TFV, DTG and INH in participants receiving IPT (contingent on funding)

Safety Assessments: The main safety endpoint is the assessment of the tolerability and safety of the three treatment combinations. Safety analyses will be performed on vital sign measurements; physical examination findings; clinical laboratory analyses, including evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, urine dipstix and creatinine clearance; other investigations (such as DEXA scans); and monitoring AEs and concomitant medications throughout the study.

Throughout the Study:

- TB symptom screen
- Adverse events (AEs) including serious AEs (SAEs)
- Vital sign measurements (blood pressure (BP) and heart rate)
- Targeted physical examination findings
- Mental health assessment (Modified Mini Screen [MMS], Neuropsychiatric Symptom Screen [NSS], International HIV Dementia Scale [IHDS])
- Sleep questionnaires (Sleep Assessment to identify which participants need to complete the Insomnia Severity Scale [ISS])
- Brief pain questionnaire
- Neuropathy screen (adapted from ACTG Brief Peripheral Neuropathy Screening Tool)
- Quality of life questionnaire (Quality of Life Assessment, Lifestyle and Habits) and Adherence questionnaire
- Laboratory analyses (safety and efficacy)

- Other investigations such as DEXA scans

Secondary Safety Endpoints:

- Mental health assessment (MMS, NSS): Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- IHDS: Weeks 0, 24, 48, 72 and 96
- Sleep questionnaires: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Brief pain questionnaire: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Neuropathy screen: Weeks 0, 4, 12, 24 and 48
- Quality of life questionnaire: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Adherence questionnaire: Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in full blood count: Screening, Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in biochemistry: Screening, Weeks4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in serum (fasting) and urine glucose: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in fasting lipids: Weeks 0, 24, 48 and 96
- Changes in liver function tests: Screening, Weeks 12, 24, 36, 48, 60 and 96
- Changes in inflammatory markers
    - D-dimer: Weeks 0, 4, 24 and 96
    - Interleukin-6 (IL-6): Weeks 0, 4, 24 and 96
- Change in measures of renal function
    - Urine dipstix at each visit
    - Creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old) at each visit
    - Urine protein to creatinine ratio (UPCR) at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
    - Urine albumin to creatinine ratio (UACR) at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
    - Retinol-binding protein to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
    - β2 microglobulin to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
    - Fractional excretion of uric acid at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
    - Fractional excretion of phosphate at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in bone mineral density measured by DEXA scans at Weeks 0, 48 and 96
- Women who fall pregnant on study will have plasma DTG trough (total and unbound), plasma tenofovir (TFV) trough, and peripheral blood mononuclear cells (PBMC) tenofovir diphosphate (TFV-DP) concentrations measured at three visits during the pregnancy and at two visits post-partum
- Participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed; at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin.

Investigators will be blinded to inflammatory markers, UPCR, UACR, retinol-binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and fractional excretion of phosphate; PK assessments (these will only be analysed at the end of the study); and DEXA scans. Mental health screening assessments, sleep questionnaires, brief pain questionnaires will also be blinded to the investigators, unless the study nurse or counsellor administering the questionnaire has serious concerns that the patient requires intervention, upon which they should immediately inform the investigator of such concerns.

Special patient populations during study:

Pregnancy: Women will be counselled regarding the unknown risks that could be associated with DTG and TAF exposure to the foetus should they fall pregnant. If they do fall pregnant and elect to stay on the study,

they will be transferred to site 3 (Shandukani) for the duration of the pregnancy and follow up of the infant. Follow up will be as per the protocol-specified clinical and laboratory procedures, including specimens for storage, as well as the Schedule of Evaluations for Pregnant Women, or as needed according to investigator discretion. Infants will be followed 3-monthly after birth for up to 18 months, as per the Schedule of Infant Follow-up, or as needed according to investigator discretion. Study participants in treatment groups 1 and 2 who become pregnant during the study and elect to stay in the study will have plasma DTG trough (total and unbound), plasma TFV trough, and PBMC TFV-DP concentrations measured at three visits during the pregnancy (approximately gestational weeks 20, 28 and 36), and at two visits post-partum (6 weeks and at the time of the three-month infant follow up visit) for PK specimens.

TB: Patients on TB therapy at screening or enrolment visits will be excluded. The management of each arm if the patient develops TB on study drug will be as follows:
Treatment Group 1: (DTG + TAF + FTC) – DTG daily dose will be increased to 50 mg twice daily (12-hourly), until two weeks after TB treatment is completed; TAF will be switched to TDF 300 mg daily, for duration of TB treatment. TAF can be restarted two weeks after completion of TB treatment.
Treatment group 2: (DTG + TDF + FTC) – DTG daily dose will be increased to 50 mg twice daily (12-hourly), until two weeks after TB treatment is completed; for duration of TB treatment.
Treatment group 3: (EFV + TDF + FTC) – no change.

Study participants in treatment groups 1 and 2 who develop TB will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed (DTG dose will be increased to 12-hourly, and those in group 1 will be switched from TAF to TDF); at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin, after daily dosing of DTG has resumed and participants in group 1 have been switched back to TAF.

All PK samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and TFV-DP drug concentrations will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at UCT, where validated TFV assays are run. DTG and TFV-DP assays will be developed and validated before the end of the study. UCT will process and analyse all the pharmacokinetic specimens.

Patients requiring single study drug substitutions: All these patients will be discontinued from the study, except in the case of TB patients as detailed above.

Study Medication
Treatment Group 1: DTG 50 mg + TAF 25 mg + FTC 200 mg administered once daily orally over 96 weeks
Treatment Group 2: DTG 50 mg + TDF 300 mg + FTC 200 mg administered once daily orally over 96 weeks
Treatment Group 3: EFV 600 mg + TDF 300 mg + FTC 200 mg administered once daily orally over 96 weeks.

Sample Size: Approximately 1110 patients randomly assigned in a 1:1:1 ratio (approximately 370 patients per treatment group). The 12-< 19 year age group will be enrolled and randomised separately; enrolment is estimated at 30-40 per arm (total 90-120).

Statistical Methods:
The primary objective of the study is to establish non-inferior efficacy for the DTG + TAF + FTC arm compared with either of the active control arms (EFV + TDF + FTC or DTG + TDF + FTC). Both of these control arms are included in 2015 World Health Organization (WHO) guidelines for first-line treatment. Currently, EFV + TDF + FTC is the preferred regimen for all populations, while DTG + TDF + FTC is an alternative regimen with some restrictions where data are limited (pregnant women; people with TB co-infection). The study will also allow

a comparison of the efficacy of DTG + TDF + FTC versus EFV + TDF + FTC, allowing three treatment comparisons in the study design.

The primary population for analysis will be Intent-to-Treat, including all randomised patients who received at least one dose of study medication.

The primary efficacy parameter will be the percentage of patients who have HIV-1 RNA suppression below 50 copies/mL at Week 48. Patients who either have confirmed HIV-1 RNA levels above 50 copies/mL, or who have missing data for any reason will be considered treatment failures. Patients who have switched off randomised treatment to a different treatment by Week 48 will be considered as treatment successes, provided that the HIV-1 RNA is below 50 copies/mL at Week 48.

In a previous clinical trial conducted at the same investigational centre, the percentage of patients taking first-line antiretroviral treatment who had HIV-1 RNA suppression below 50 copies/mL by Week 48 was 80%.

A sample size of 370 patients per arm (1110 total, including 90-120 in the 12- < 19 age group) will provide at least 80% power to establish non-inferior efficacy for the DTG + TAF + FTC arm, compared to each of the other study arms. A non-inferiority margin of -10% is now the FDA determined standard in the design of phase 3 randomised trials of antiretrovirals. There will also be at least 80% power to establish non-inferior efficacy for the DTG + TDF + FTC arm compared to the EFV + TDF + FTC arm. An overall 1.7% significance level (two one-sided tests) will be used, to adjust for the three treatment comparisons being made.

1.0 Introduction

1.1 Background Information

Significant gains have been made in the last decade in terms of access to antiretroviral (ARV) care within low- and middle-income countries (LMIC) through the support of local governments, international donors, and agencies. However, as the number of patients on antiretroviral treatment (ART) rises, there has been increased attention paid to treatment optimisation, whereby drug dosage and manufacturing, clinical diagnosis and monitoring and health delivery systems are all interrogated for increased efficiencies. Savings from these efforts can be applied to treatment programmes, enabling more patients to receive life-saving therapy.

Since the recent publication of the START and TEMPRANO studies, which demonstrated that ART should be started irrespective of CD4 count,[1, 2] the WHO has announced preliminary guidance recommending everyone infected with HIV should start ART,[3] doubling those eligible for ART, with significant programmatic and financial implications.

Since WHO's 2013 recommendations for a harmonised first-line regimen in adults,[4] effective, more robust, tolerable, and potentially less expensive ARVs have been developed. However, data to recommend using these newer drugs in LMIC are not available. The needs of HIV-positive people are often very different in LMIC: populations include larger proportions of women of childbearing age, children, the severely immunosuppressed and people with TB and other co-infections. Typically, trials for new ARVs by originator manufacturers focus on registration in high-income countries, with data generated on dose selection, comparability and compatibility with other ARVs. Data supporting use in LMIC populations are missing with newer drugs.

Current first-line treatment in LMIC has several challenges:

- **Tolerability** Treatment has side effects, resulting in non-adherence or discontinuation. Better safety profiles would keep people on first-line longer
- **Cost** The cost of ARVs consumes the bulk of LMIC programme budgets. Current first-line cost is unlikely to decrease significantly
- **Robustness/Resistance** First-line is vulnerable to resistance. Finding a first-line regimen that is more robust and durable will limit transition to expensive and less well tolerated second- and third-line regimens
- **Evidence** Generating the evidence level required to change WHO/country guidelines requires large rigorous randomised controlled trials (RCTs), which are lacking for these drugs in LMIC
- **Fixed-dose combinations** New individual drug options for LMIC are held by different originator manufacturers that have prioritised their own fixed-dose combinations (FDCs), which lack the cost benefit of optimised regimens.

New, simpler, safer, more potent and potentially more cost-effective antiretroviral therapy regimens are needed. Decreasing total drug doses of antiretroviral agents represents an untapped possibility for decreasing costs and toxicity, if efficacy can be maintained. Manufacturing costs for originator companies comprise only a fraction of the price of the drug. However, with the rise of generic manufacturers, as well as increased licensing by originator companies to other pharmaceutical companies, the cost of raw materials to manufacture the drugs (active product ingredient, API) has become a more significant component of cost as prices have decreased. Thus, regimens that have an overall lower dose of medications could have a notable impact on the overall cost of ART, as well as often reducing side effects.

1.2 Current Therapy in South Africa

Access to ART has expanded rapidly within South Africa, with over 3 million patients initiated on therapy since 2004,[5] the largest ART programme in the world, with early suggestions of resultant increase in life expectancy[6] and even decreased incidence.[7] South Africa is now the largest procurer of ART generics in the world, along with PEPFAR and the Global Fund. The state programme has, since its inception, used the WHO-recommended combination of two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), a combination that demonstrates excellent virological suppression with good adherence. Current first-line therapy in adults is tenofovir disoproxil fumarate (TDF) and efavirenz (EFV), in combination with emtricitabine (FTC) or lamivudine (3TC), in a single tablet fixed-dose combination,[8] as recommended by WHO.

However, the combination has a low resistance barrier, and poor adherence invariably results in virological failure. Data on the number of first-line failures in South Africa are still elusive but a study looking at several programmes suggested just over 2% of patients migrate across to second-line annually (a larger percentage are lost to follow-up).[9] There is speculation that this percentage will rise, as programmes get larger and adherence counselling is spread across more patients.[10] However, intolerance to boosted protease inhibitors (PIs), the usual third agent of second-line, is well described, and includes gastrointestinal and metabolic concerns. Recently, in response to a growing number of patients failing second-line therapy, genotype resistance testing and third-line drugs including darunavir, raltegravir and etravirine, have been made available within the South African state programme, at considerable expense.[8, 11]

1.3 Rationale for selected study drugs and regimens

We will test two potential new regimens using newly available drugs in combination, both safer and more robust, for effectiveness against the current WHO and South African standard of care (EFV + TDF + FTC), with the express intention of providing adequate 48-week data to alter current first-line recommendations. In parallel to this study, there are protocols dealing with TB, additional studies addressing pregnancy, and studies looking at children below the age of 12 years, all evaluating the safety, dosing and efficacy of these new antiretrovirals. However, none of these address the overall effectiveness of routine use of these combinations in first-line ART, in those over 12 years.

Also in parallel, is a programme to alert generic manufacturers and regulators (such as the South African Medicines Control Council [MCC]) to the potential new regimens, so that registration and manufacturing does not delay the in-country tender process.

This study protocol and set of exclusion criteria reflect the realities of programmatic use of these drugs in LMIC, and will be studied in patients who would be routinely eligible for these regimens. This includes studying the use of the drugs in TB and hepatitis B co-infected patients, adolescents, as well as in women of childbearing age.[12] This will set a new standard for trials intended to demonstrate the benefit of new drugs under real world conditions.

Rationale for the individual drugs to be tested:

The two new drugs are dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) to be used with existing FTC, replacing EFV and TDF in current standard of care, if the study is successful.

- DTG is better tolerated with a greater resistance barrier than currently used EFV
- DTG requires a smaller dose than EFV (50 mg versus both recommended EFV doses (600/400 mg)), lowering manufacturers' costs
- TAF has shown renal and bone benefits over currently used TDF

- TAF requires a smaller dose than TDF (25 mg versus 300 mg), lowering manufacturers' costs
- API requirements will drop; this will reduce the need for investment in additional manufacturing capacity by drug manufacturers
- One major generic manufacturer is willing to guarantee the proposed DTG + TAF + FTC regimen will be at least 20% cheaper than EFV + TDF + FTC
- The better tolerability and higher barrier to resistance of TAF and DTG should result in improved patient outcomes and more durable treatment, with less progression to expensive and more toxic regimens
- Both TAF and DTG are being studied in children less than 12 years, with the possibility of aligning these drugs with adult regimens in future.

A new first-line regimen at 20% less than current regimens and with a higher barrier to failure will result in significant savings of around USD 80 million/year by 2019 for South Africa, with secondary cost savings from reduced movement to second-line and clinical costs of non-adherence.

Rationale for DTG as a replacement for EFV: DTG has shown improved efficacy and safety over EFV in the first-line SINGLE trial, on a backbone of abacavir (ABC) and lamivudine (3TC).[13] DTG appears to have a high resistance barrier, with only a single case of DTG resistance documented in naive patients in high-income countries where the drug has been used for almost three years. The cost of DTG is likely to be the same or less than EFV, at scale, according to the Clinton Health Access Initiative (CHAI) and confirmed by discussions with generic manufacturers. We will use DTG in the study, and compare it with EFV, which is in the current preferred WHO first-line regimen. The soon-to-start NAMSAL study is comparing a lower dose of EFV (EFV 400 mg) to DTG 50 mg, to lower the cost and side-effect profile of EFV; this will not resolve the EFV resistance issue. Adolescents ≥ 12 years, and ≥ 40 kg will be included in the study, as dosing in this group has been studied. DTG dosing for children less than 12 years of age is currently under study, and submitted to the FDA by the originator company at the end of 2015.

Rationale for TAF as a replacement for TDF: Use of DTG with ABC (as used in the originator FDC product) is problematic in LMIC countries because of genetic testing requirement, concerns over risk of cardiac events, lack of available co-formulations, and significant cost over alternatives to ABC. Two potential alternatives are TDF 300 mg once daily, which is widely available, or TAF, 25 mg once daily. TAF, which is a prodrug of tenofovir has demonstrated lower renal and bone toxicity compared to TDF. Results from SPRING2 and Flamingo study showed high efficacy of DTG when combined with TDF/FTC.[13, 14] However, there are still limited data using TAF with DTG.[15] Clinical trials to study TAF dosing and safety in children are only just getting underway. TAF is being studied as part of an FDC with elvitegravir + cobicistat + FTC in children 6-12 years weighing > 25 kg using the adult tablet. A trial to study TAF + FTC dosing and safety in adolescents 12-<19 years and 6-12 years olds weighing > 25 kg started in early 2015 and is expected to be completed in mid-2018.

Rationale for the regimen DTG + TAF + FTC: The combination DTG 50 mg with FTC 200 mg and TAF 25 mg would give a total once-daily dose of 275 mg – a significant improvement on pill size when compared with current standard of care, TDF 300 mg, FTC 200 mg [or 3TC 300 mg] and EFV 600 mg, totalling 1100 mg [1200 mg] daily. At the time this protocol was developed, there were no RCTs evaluating TAF 25 mg + FTC as first-line treatment in any form, including in combination with DTG. Subsequently, TAF 25 mg + FTC has been studied in combination with another integrase inhibitor, bictegravir, as part of a three-drug fixed dose combination (compared to DTG 50 mg with a fixed dose combination of TAF/FTC 25/200 mg, and compared to fixed dose combination DTG/ABC/3TC 50/600/300 mg), showing non-inferiority at 48 weeks. TAF 25 mg + FTC is being evaluated in switching studies that provide only limited evidence for efficacy in first-line treatment. To justify scale-up of manufacture of this combination, it would be important to have WHO recommendation, based on clinical trial data. Most of the phase 2 and phase 3 clinical development of TAF thus far has been based on clinical trials comparing TAF 10 mg with TDF 300 mg, both with FTC and elvitegravir boosted by cobicistat, which cannot be used in TB, and where data on pregnant women are limited. The FDC tablet will be

substantially smaller than the current regimen (comparable in size to a multivitamin supplement) and will have an impact on patient and programme convenience. Alternative integrase inhibitors are either not suitable for LMIC, or only in earlier stages of development.

Rationale for the regimen DTG + TDF + FTC: TAF drives the cost reduction of the new regimen; however, having data to support DTG use with TDF would guarantee that the study would deliver at least a benefit in terms of robustness and toxicity reduction over current standard of care, with at least crude price parity. Currently, TDF has only been tested with DTG in around 400 patients in clinical trials, although the combination is used commonly in high-income countries, despite the lack of evidence. For WHO to recommend this as the preferred new initiation ART regimen, while switching millions of people to this combination from the current standard of care, requires robust evidence. This combination is being tested in the event that TAF, which has potentially important drug interactions with rifampicin, an altered side effect profile, and also has not been studied as extensively in children or pregnant women, proves not to be non-inferior in this study.

Rationale for using EFV + TDF + FTC: This is the current standard of care in first-line in all LMIC (FTC and 3TC are interchangeable in almost all guidelines; FTC is currently the preferred agent in South Africa in the state programme). We have consulted with WHO and multiple other stakeholder and donors. For countries to move away from this current regimen, which has performed well in the field and which now has a large evidence base, would require the new regimens to be compared head-to-head, even though EFV and TDF are likely to fall away from high-income country guidelines. WHO has recommended that we therefore include this study arm. Using this process, future regimens will be required to be tested against a standard of care.

2.0 Study Objectives

2.1 Primary Objective

The primary objective of this study is to demonstrate the non-inferiority of DTG and TAF plus FTC when compared with DTG and TDF plus FTC or compared with EFV and TDF plus FTC in the first-line treatment of patients infected with HIV-1 as determined by the proportion of patients in each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of each regimen. Pharmacokinetic analyses of DTG, tenofovir (TFV) and tenofovir diphosphate (TFV-DP) concentrations in participants who develop active tuberculosis and in pregnant women will be explored in treatment groups 1 and 2. Pharmacokinetic analyses of EFV and isoniazid (INH) concentrations in participants receiving isoniazid preventive therapy (IPT) will be explored in treatment group 3.

3.0 Study Design

This is an open label, randomised, phase 3, three-arm, study, conducted over 96 weeks. *(See figure 1).*

The study includes a screening period (Days –60 to –1), enrolment visit (Week 0), and a 96-week treatment (follow-up) period.

Approximately 1110 male and female patients infected with HIV-1 eligible for first-line therapy, will be randomly assigned in a 1:1:1 ratio (approximately 370 patients per treatment group) to either Treatment Group 1 (DTG + TAF + FTC) or Treatment Group 2 (DTG + TDF + FTC) or Treatment Group 3 (EFV + TDF + FTC).

To ensure adequate representation of 12-<19 year olds in any treatment group, 12-< 19 year old participants will be randomised separately, with an anticipated 30-40 in each arm in this age group, and will be enrolled and followed up at the Shandukani (site 3). The randomisation will be electronically generated. All patients will be assigned a unique patient number by the randomisation system. After a patient number has been assigned, the number will not be reused even if the patient withdraws before receiving any study medication. All medications will be administered in an open label design.

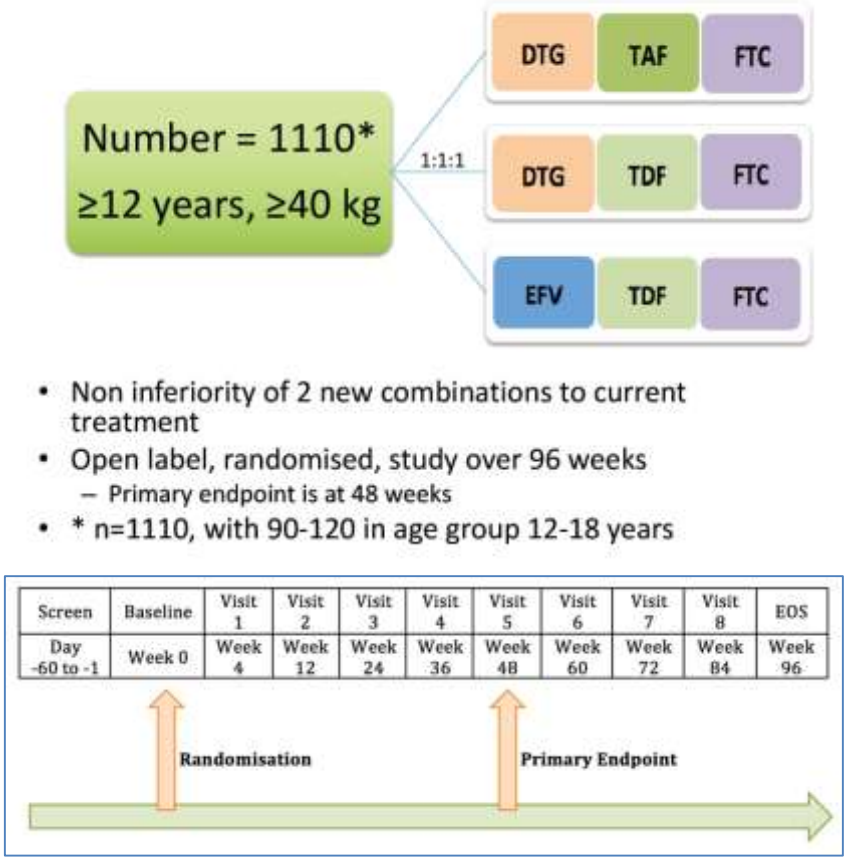


Figure 1: Study design

Table 1: Treatment Regimen

Study Medications	Tablet/Capsule Strength	Dosage Regimen
Treatment Group 1[a] (2 tablets)		
DTG	50 mg	Once daily
TAF	25 mg	Once daily
FTC	200 mg	Once daily
Treatment Group 2[b] (2 tablets)		
DTG	50 mg	Once daily
TDF	300 mg	Once daily
FTC	200 mg	Once daily
Treatment Group 3[c] (1 tablet)		
EFV	600 mg	Once daily
TDF	300 mg	Once daily
FTC	200 mg	Once daily

Abbreviations: DTG, dolutegravir; TAF, tenofovir alafenamide fumarate; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; EFV, efavirenz.
[a] TAF and FTC combined as a single tablet
[b] TDF/FTC combined as a single tablet
[c] TDF/FTC/EFV combined as a single tablet

4.0 Study Sites

ADVANCE will be conducted at four sites in Johannesburg.
Site 1: Wits RHI Yeoville Research Centre, Wits RHI Yeoville Clinic, 35 Bedford, Cnr Dunbar Street, Yeoville
Site 2: HIV/AIDS Adult Clinic Area 556, Adult HIV/AIDS Clinic Area 556, Charlotte Maxeke Johannesburg Academic Hospital, Jubilee Road, Johannesburg, 2193
Site 3: Wits RHI Shandukani Hillbrow Johannesburg, Hillbrow Health Precinct, 22 Esselen Street, Hillbrow, Johannesburg, 2001
Site 4: Wits RHI Research Centre, 7 Esselen Street, Hillbrow, Johannesburg, 2001

Participants 12-< 19 years will be enrolled and followed up at site 3. Participants 19 years and older will be enrolled and followed up at sites 1, 2 and 4.
Women who become pregnant and elect to continue participation in the study will be transferred to site 3 as per Participant Transfer SOP. 12-< 19 year old participants who become pregnant will continue to be managed at site 3.

5.0 Selection of Study Population

Approximately 1110 patients infected with HIV-1 who are eligible for first-line antiretroviral therapy will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria. Of the 1110 study participants, 90-120 are planned to be in the 12-< 19 year age group.

There is no CD4 threshold for this study, in keeping with WHO guidelines, as well as the South African government guidelines, which removed CD4 count thresholds as from September 2016.

Before performing any study procedures, all potential participants or their parents/legal guardians will provide written informed consent, and will sign an informed consent form (ICF). Assent will also be obtained,

where applicable. Potential participants will have the opportunity to have any questions answered before and after signing the ICF. The informed consent process and all questions raised will be documented. The study staff who conduct the informed consent process will also sign the ICF.

5.1 Inclusion Criteria

Each patient must meet **all** of the following criteria to be enrolled in this study; there is no CD4 threshold entry criterion:

1. Age ≥ 12 years and ≥ 40 kg
2. Documented laboratory diagnosis of infection with HIV-1 (positive enzyme-linked immunosorbent assay HIV-1 antibody test) at screening
3. Plasma HIV-1 RNA (VL) ≥ 500 copies/mL
4. All pre-existing medical or laboratory abnormalities must be deemed to be stable by the investigator prior to study enrolment
5. Calculated creatinine clearance (CrCl) > 60 mL/min (Cockcroft-Gault formula) in > 18 years old OR > 80 mL/min (modified Cockcroft-Gault) in ≤ 18 years old
6. Ability to comprehend the full nature and purpose of the study, in the opinion of the investigator, and to comply with the requirements of the entire study.

5.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Previously received more than 30 days of treatment with any form of antiretroviral therapy (ART) or
2. Received any antiretrovirals within the last 6 months
3. Women who are pregnant at the time of the screening or enrolment visits
4. Active tuberculosis and/or are on antituberculous therapy at the time of the screening or enrolment visits
5. Taking and cannot discontinue prohibited concomitant medications listed in 8.3 at least 2 weeks prior to enrolment visit and for the duration of the study period
6. Clinically unstable, in the investigator's opinion
7. Current history of drug or alcohol abuse that, in the opinion of the investigator, may be an impediment to patient adherence to the protocol
8. Patients who participated in a study with an investigational drug within 60 days of screening or who are currently receiving treatment with any other investigational drug or device may be ineligible to participate. This is an investigator decision
9. Have a strong likelihood of relocating far enough to make access to the study site difficult
10. History or presence of allergy to the study drugs or their components
11. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); Child-Pugh C.

6.0 Study Procedures

6.1 Screening

1. Informed consent/assent process
2. Inclusion/exclusion criteria (eligibility) determination
3. Demographic data
4. Pre-existing medical condition(s)
5. TB symptom screen
6. Concomitant medications
7. Physical examination, height, weight and vital sign measurements (BP, pulse rate and temperature)
8. Urine pregnancy test, for women of child bearing potential

9. Clinical laboratory testing:
    - Haematology, biochemistry, liver function tests
    - Confirm HIV-1 status with laboratory ELISA test
    - Plasma HIV-1 RNA
    - CD4 cell count
    - Creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old) and urine dipstix

Rescreening (Days -60 to -1)
During the 60-day screening period, a patient may be rescreened to determine eligibility. Rescreening will involve retesting of subsequent biological samples, and/or reassessment of any inclusion and exclusion criteria that previously failed the patient. If more than 60 days have elapsed, the patient will need to be fully rescreened under a new screening number.

6.2 Enrolment

1. Review inclusion/exclusion criteria
2. Review pre-existing medical condition(s)
3. Review concomitant medications
4. Symptom-led physical examination, weight, blood pressure and pulse rate
5. TB symptom screen
6. Mental health assessment (MMS, NSS and IHDS)
7. Sleep questionnaires
8. Brief pain questionnaire
9. Neuropathy screen
10. Quality of life questionnaire
11. Urine pregnancy test, for women of child bearing potential
12. Clinical laboratory testing
    - Hepatitis B surface antigen test (HBsAg)
    - Lipid panel (fasting)
    - Serum (fasting) and urine glucose
    - Inflammatory markers
        - D-dimer
        - IL-6
    - Measures of renal function
        - Urine protein to creatinine ratio (UPCR)
        - Urine albumin to creatinine ratio (UACR)
        - Retinol-binding protein to creatinine ratio
        - β2 microglobulin to creatinine ratio
        - Fractional excretion of uric acid
        - Fractional excretion of phosphate
    - Urine, serum, plasma and PBMCs for storage
    - Neuropathy genetic/epigenetic blood specimen in a subset of 110 consecutively-enrolled participants ≥ 19 years of age.
13. DEXA scan
14. Randomisation
15. Study medications dispensing, patient education on adherence and accountability

6.3 Follow-up Visit Procedures

1. Assess adverse events

2. Concomitant medications
3. Symptom-led physical examination, weight, blood pressure and pulse rate
4. TB symptom screen
5. Mental health assessment (MMS, NSS at all visits; IHDS only at Weeks 24, 48 and 72)
6. Sleep questionnaires
7. Brief pain questionnaire
8. Neuropathy screen (Weeks 4, 12, 24 and 48)
9. Quality of life questionnaire
10. Adherence questionnaire
11. Urine pregnancy test (unless pregnancy has already been confirmed)
12. Clinical laboratory testing:
    - Plasma HIV-1 RNA
    - CD4 count (Weeks 24 and 48)
    - Haematology
    - Biochemistry
    - Serum (fasting) and urine glucose
    - Lipids (fasting) (Week 24 and 48)
    - Liver function tests (Weeks 12, 24, 36, 48 and 60)
    - Inflammatory markers
        - D-dimer: Weeks 4 and 24
        - IL-6: Weeks 4 and 24
    - Measures of renal function
        - Urine dipstix
        - Creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old)
        - Urine protein to creatinine ratio (UPCR) at Weeks 12, 24, 36, 48, 60, 72 and 84
        - Urine albumin to creatinine ratio (UACR) at Weeks 12, 24, 36, 48, 60, 72 and 84
        - Retinol-binding protein to creatinine ratio at Weeks 12, 24, 36, 48, 60, 72 and 84
        - β2 microglobulin to creatinine ratio at Weeks 12, 24, 36, 48, 60, 72 and 84
        - Fractional excretion of uric acid at Weeks 12, 24, 36, 48, 60, 72 and 84
        - Fractional excretion of phosphate at Weeks 12, 24, 36, 48, 60, 72 and 84
    - Urine, serum, and plasma for storage
    - PBMCs for storage at Week 48
    - Neuropathy genetic/epigenetic blood specimen at Weeks 24 and 48 (in a subset of 110 consecutively-enrolled participants, ≥ 19 years of age
    - PK specimens all participants to be stored at Weeks 24 and 48
    - PK specimens for pregnant women, and patients on TB treatment (as per appendices 3 and 5)
    - Pharmacogenomics at Week 36 (whole blood)
13. Other investigations
    - DEXA scans at Week 48 (except in pregnant participants)
14. Study medications dispensing, patient education and accountability

6.4 Physical Examination and Vital Sign Measurements

Vital sign measurements (temperature, pulse rate, systolic and diastolic blood pressure) will be collected at screening. At all other study visits only blood pressure and pulse rate will be routinely measured, and other vital signs only if indicated clinically. Temperature is routinely measured in paediatric and pregnant participants, and therefore will be done at each scheduled visit for adolescents (12-< 19 years) and pregnant women at Site 3.

A full physical examination will be performed at screening and last study visit (early withdrawal/Week 96), and a targeted symptom directed physical examination where clinically indicated at all other visits. Height and weight will be recorded at the screening visit and weight will be measured at all scheduled study visits from enrolment to the last study visit in participants ≥19 years. Height will be measured for adolescents (12-< 19 years) at each scheduled visit.

6.5 Efficacy Assessments

Efficacy will be assessed by the evaluation of plasma HIV-1 RNA level. The primary efficacy endpoint will be the proportion of participants with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. Participants who do not have a HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

Participants with detectable HIV-1 RNA (≥ 50 copies/mL) will receive adherence counselling, with a repeat test using the same HIV RNA PCR assay at least one month after counselling. The result of the repeat test will be used for the primary analysis of efficacy. This is to prevent patients being classified as treatment failures if their HIV RNA result is marginally above the limit of assay quantification from testing error. There is high variability in measurement of HIV RNA at the lower limit of quantification of the HIV RNA PCR assays. In previous studies, 60-70% of patients with HIV RNA results in the range of 50-199 copies/mL on first test, had a subsequent HIV RNA result < 50 copies/mL on retesting of the same sample.

The following algorithm will be used in efficacy assessments:

1. Patients with HIV RNA levels 50-199 copies/mL after Week 24

Participants with detectable HIV-1 RNA (≥ 50 copies/mL) will receive adherence counselling, with a repeat test using the same HIV RNA PCR assay at least one month after counselling. If the repeat VL is < 200 copies/mL, the participant will receive additional adherence counselling and the VL load will be repeated at the next scheduled study visit. If the repeat VL is ≥ 200 copies/mL, it will be managed as appropriate (see Patients with HIV RNA levels 200-999 copies/mL after Week 24 or Patients with HIV RNA levels ≥ 1000 copies/mL after Week 24, as applicable).

2. Patients with HIV RNA levels 200-999 copies/mL after Week 24If there are two consecutive detectable HIV RNA results of 200-999 copies/mL at any time after Week 24 of the study, the patient will be further counselled on treatment adherence and viral load repeated. If the third HIV RNA result is still within 200–999 copies/mL, the patient will be switched to a second-line treatment with two nucleoside reverse transcriptase inhibitors plus a protease inhibitor and followed up in the study. If the subsequent HIV RNA result returns to below 200 copies/mL within 4 weeks, the patient will continue in the study on their original randomised treatment. .

3. Patients with HIV RNA levels ≥ 1000 copies/mL after Week 24

If there are two HIV-1 RNA results of at least 1000 copies/mL at any time after Week 24 of the study, a resistance test will be performed.

"Significant resistance" will be defined as a score above 30 in the Stanford algorithm to any of the three antiretrovirals the patient has been randomised to receive. If significant resistance is present, the participant will be switched to a second-line treatment with two nucleoside reverse transcriptase inhibitors and a protease inhibitor and followed up within the study.

If significant drug resistance is not present, the patient will be counselled on treatment adherence. If the subsequent HIV RNA test returns to < 50 copies/mL within 4 weeks, the patient can continue on their original

randomised treatment. If the subsequent HIV RNA test after adherence counselling still shows HIV RNA levels ≥ 1000 copies/mL, the patient will be switched to two nucleoside reverse transcriptase inhibitors plus a boosted protease inhibitor and followed up within the study.

In instances where HIV-1 RNA copies cannot be amplified, investigator's discretion will apply.

4. Patients with treatment-limiting toxicity.

Patients who develop treatment-limiting adverse events on EFV can be switched to receive DTG if this is judged to be appropriate by the investigator. Similarly, patients who develop treatment-limiting adverse events on DTG can be switched to EFV if this is judged to be appropriate. Patients who develop treatment-limiting adverse events related to tenofovir (either TDF or TAF) can be switched to zidovudine (AZT). Patients can also be switched onto alternative antiretrovirals if this is judged to be appropriate, but patients should all receive at least three antiretrovirals as part of their ongoing treatment.

In all cases, patients should be followed up as part of the main ADVANCE trial protocol if feasible. If this is not possible, there should be follow up visits every 6 months to monitor HIV RNA levels, confirm what ARVs they are taking and document any other clinical outcomes including that they are still alive.

6.6 Pharmacokinetics and pharmacogenetics

With the exception of the DTG and TFV PK in participants who develop TB or become pregnant and elect to continue participating in ADVANCE, and the EFV/isoniazid PK described below, additional PK and pharmacogenomic (PG) work is contingent upon additional funding.

Pharmacokinetic data from ADVANCE will be used to address the four aims listed below.

1. Describing antiretroviral exposure
There are currently no pharmacokinetic (PK) data from Africa on exposure to dolutegravir and TAF; and there are limited data on TDF exposure. Understanding factors associated with exposure (e.g. age, sex, weight, renal function) in an African population is important before scaling up the next generation of antiretrovirals to the population most affected by HIV. The average of three trough concentrations of DTG and tenofovir (both TDF and TAF are converted to tenofovir in plasma) will be used to describe exposure. These trough concentrations will be measured on all participants receiving DTG (treatment groups 1 and 2) and all participants receiving TAF (treatment group 2) at weeks 24, 48 and 96.

In order to better define DTG, TAF and TDF pharmacokinetics, intensive PK sampling will be performed in a subset of 40 participants (≥ 19 years), 20 in treatment groups 1 and 2 respectively. Intensive sampling data will be used together with sparse sampling data to develop a population PK model, from which AUC will be estimated for each participant. All participants (≥ 19 years) in treatment groups 1 and 2 who have reached Week 24 will be approached for their willingness to participate in the intensive PK sampling until we have reached 20 participants in each group (however the intensive PK visit will not take place on the same day as the week 24 visit as it will require the participant to arrive early in the morning and to remain at the site all day). Participants will be requested to omit their morning dose of study medication on the morning of the intensive PK visit. They will be observed taking their study medication with a snack. An intravenous cannula will be inserted and will remain *in situ* for serial sampling. Sampling will be performed at 0 (pre-dose), 1, 2, 4, 6, 8, 10 and 24 hours post dosing. Participants who are < 19 years old, or who are pregnant or who are taking rifampicin-containing TB treatment will not take part in the intensive PK sampling.

All PK samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. As the PK specimens will only be analysed in several batches, DTG and TFV drug concentrations will not

be made available to the study clinician. UCT will set up the relevant laboratory assays and will process and analyse all the pharmacokinetic specimens.

2. Pharmacokinetic-pharmacodynamic (PK-PD) analyses

PK-PD analyses will be used to evaluate associations between drug exposure and efficacy. There are limited data showing an association between efavirenz exposure and efficacy, but there is controversy about the minimal effective concentration. There are also limited data suggesting that DTG concentrations are not associated with efficacy. Because virologic failure/non-suppression events are likely to be uncommon, a nested case control study design will be used matching one case to four randomly selected controls, matched for ART duration. Participants with undetectable antiretroviral drug concentrations at the time of viral load measurements showing failure/non-suppression will be deemed to be non-adherent. It is well known that there is no association between plasma concentrations of nucleoside/nucleotide reverse transcriptase inhibitors and efficacy, but undetectable tenofovir concentrations in participants with detectable DTG will indicate non-adherence.

There are limited African data on PK-PD analyses for antiretroviral toxicity. There are some data on associations between efavirenz concentrations and early neuropsychiatric toxicity, and one study from our group showing associations between efavirenz concentrations and lipids and glucose. However, that was a cross-sectional study so confirming the findings of associations between efavirenz exposure and metabolic toxicity in a prospective study will have important implications for ongoing efavirenz use. There are no African data on associations between TAF and TDF exposure and renal tubular and bone toxicity. There are limited data that failed to show an association between DTG exposure and toxicity, but recent observational data showing more toxicity in women (who have higher DTG exposure than men) suggests that there is an association, which may have been missed as there was a predominantly male population in the registration trials.

3. Pharmacogenomic analyses
African populations have the highest genetic diversity, but are the least studied. Novel polymorphisms in genes involved in the absorption, distribution, metabolism, and excretion (ADME) are more likely to be found in African populations because of their high genetic diversity. There have been a number of pharmacogenomic studies of efavirenz exposure in African populations, but none of DTG, TAF and TDF. Genomic sampling will be performed at week 36 in all participants who consent (separate consent for genetic sampling will be obtained). Whole blood (10 mL) will be stored at -80◦C at Sydney Brenner Institute for Molecular Biosciences (SBIMB), University of the Witwatersrand, for DNA extraction in a batch at the end of the study. Genotyping will then be done with the H3Africa Consortium Array, which was designed using 3500 whole genome sequences from African individuals and includes 2.5 million single nucleotide polymorphisms (SNPs). Analysis of genomic factors associated with antiretroviral drug exposures will initially focus on known functional SNPs of the relevant genes involved in the absorption, distribution, metabolism and elimination of DTG, TAF and TDF. The full dataset, including additional imputed SNPs using an African reference panel will be used for subsequent genome-wide association analysis for factors associated with exposure to and toxicity from DTG, TAF and TDF.

4. Drug-drug interactions between antiretrovirals and isoniazid
Isoniazid preventive therapy (IPT) will be given for 12 months to eligible participants in ADVANCE. Isoniazid (INH) is known to inhibit a number of cytochrome P450 enzymes, which are involved in the metabolism of DTG, TAF (CYP3A4) and efavirenz (CYP2A6). Concentrations of EFV, DTG and tenofovir (in participants on TAF) will be compared **on and off** INH prophylaxis to determine the effect, if any, of co-administered isoniazid on drug exposure. DTG (treatment groups 1 and 2), TFV (treatment group 2) and EFV (treatment group 2) concentrations will be measured in all participants at weeks 24, 48 and 96. All PK samples will be centrifuged,

and plasma will be stored at -80◦C for analysis in a batch at the end of the study. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at University of Cape Town, where validated efavirenz and tenofovir assays are run. Dolutegravir assays will be developed and validated before the end of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and EFV drug concentrations will not be made available to the study clinician.

6.7 Additional Assessments

TB symptom screen

At every visit, every participant will be screened for tuberculosis using the TB symptom screen, as is standard of care within the national treatment guidelines. Those who screen positive on the TB symptom screen will be investigated as per site-specific procedures or relevant guidelines, and if active TB is diagnosed, referred for initiation of TB treatment. If TB is diagnosed at screening or enrolment, the participant will not be eligible to participate in the study. Their study medications will be adjusted as per section 7.6 of the protocol.

Mental health assessment

There is a complex association between HIV and mental illness. As is the case with the general population, individuals with any type of mental illness are at risk of acquiring HIV, and individuals with HIV (and other chronic illnesses) are at risk of developing most forms of mental illnesses (anxiety; acute and post traumatic; stress disorders; depression; bipolar disorder; psychotic disorders; neurocognitive disorders). This is compounded by the fact that some ARVs, such as EFV are known to cause neuropsychiatric side effects. In addition, recent emerging cohort data suggest that DTG may also be associated with neuropsychiatric side effects, which was not seen in DTG registrational studies. ADVANCE provides an opportunity to look at this in the context of a more real world randomised study. Symptoms associated with DTG use in cohorts which are not already being captured in various tools being used in ADVANCE are included in the Neuropsychiatric Symptom Screen.

Unfortunately, no single tool is effective in screening for all mental health problems, and many have not been validated in LMIC study populations such as that of ADVANCE, although many are used in both research and to monitor treatment response. ADVANCE will use the Modified Mini Screen, which screens for depression, anxiety and psychosis to screen all participants at every visit from the enrolment visit onwards. The screen will be performed by study nurses, and the investigators will be blinded to the MMS. Where study nurse is concerned about the participant's mental status based on the outcome of the MMS, the participant will be referred to a study doctor to be assessed independently and referred to the appropriate mental health services if necessary.

In addition, neurocognitive screening using the International HIV Dementia Scale will be assessed providing ADVANCE study site staff have capacity to implement the screening tool adequately.

Pain

The burden of pain in HIV-positive populations is high. Pain is common (50-75% of individuals report a painful condition), is most frequently experienced as moderate to severe in intensity and patients often report more than one pain site. This pain burden is associated with reduced quality of life. Certain painful conditions, such as HIV-associated sensory neuropathy, are more prevalent on some drug regimens and warrant monitoring. Incidence, intensity and interference caused by pain will be measured by patient self-report, using a focussed brief pain questionnaire. Psychosocial factors, including depression, catastrophising and perceived HIV stigma may influence intensity of pain and activity in people living with HIV. These study questions have been incorporated into a substudy in order to reduce consultation time and questionnaire burden on participants in the primary study. Inclusion in the substudy is not required as part of the ADVANCE study and will only be for those patients willing to take part in addition to involvement in the ADVANCE study. Ethical approval for the substudy will be obtained separately from the main ADVANCE study.

Neuropathy screen

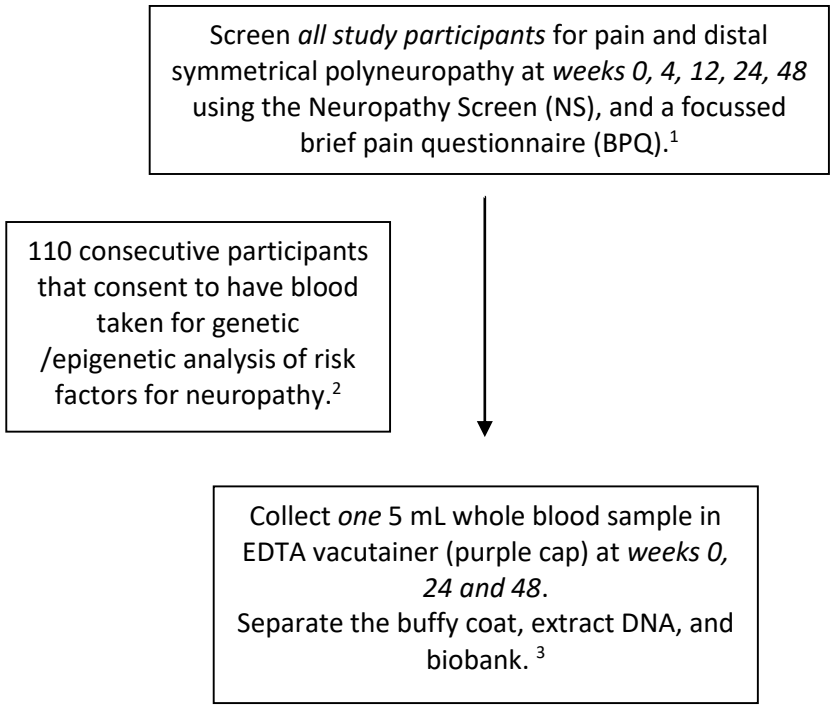
HIV-associated sensory neuropathy (HIV-SN) is a common neurological complication of HIV and its treatment, with a prevalence of over 50% in a similar Johannesburg cohort. Incidence of HIV-SN is higher on some ARV regimens than others, and perception of pain may be altered by others, and so screening for HIV-SN will allow for comparison of neurotoxicity of the drug regimens. HIV-SN is frequently painful and treatments often ineffective. Genetic and epigenetic studies are important to help elucidate the pathogenesis of HIV-SN and the associated pain, and also to help determine potential drug targets. Such studies will be possible with screening for HIV-SN and extraction of DNA from patient blood samples.

Participants will be assessed for the presence of neuropathy using an adapted version of the validated AIDS Clinical Trials Group (ACTG) Brief Peripheral Neuropathy Screening tool (referred to as "Neuropathy screen" throughout this protocol). This validated tool is widely used in clinical trials and encompasses assessment of both clinical signs (vibration sense, pin-prick detection, ankle-jerk reflexes) and symptoms (pain, numbness, paraesthesia), which if both are present are indicative of sensory neuropathy. The screening takes about 10 minutes per patient to complete, and is incorporated into the physical examination. Assessment will be made at weeks 0, 4, 12, 24 and 48. These data will be used to assess the incidence of HIV-SN (asymptomatic and painful) in patients on modern treatment regimens and risk factors for the development of the neuropathy. These data will be compared to historical data from patients on neurotoxic stavudine-based regimens.

Bloods for assessing epigenetic changes

At Weeks 0, 24 and 48, 5 mL of blood will be taken to assess both for genetic and epigenetic associations with development of neuropathy and the pain associated with it. The extracted DNA will be analysed at the Sydney Brenner Institute for Molecular Biosciences (SBIMB), University of the Witwatersrand, Johannesburg, South Africa for the duration of the research study and biobanked for future use. The genetic/epigenetic component will only be assessed in a subset of 110 consecutively-enrolled participants (≥ 19 years of age) who consent to have blood taken for genetic and epigenetic analysis. The data will be analysed as a case-control study targeting polymorphisms / methylation sites we have identified as being good candidates in other cohorts on stavudine-based treatment regimens. The sample size is based on the number of targets and the estimated effect-size of genetic and epigenetic influences. The figure below outlines the design of this substudy.

Protocol for pain and neuropathy substudy



[1] These two questionnaires are already included in the main study protocol.
[2] DNA will be collected and stored only for the 110 participants (≥ 19 years of age) consented to the neuropathy genetics substudy. *Post hoc*, participants will be separated into case-control super groups (painful neuropathy vs neuropathy vs neuropathy-free) based on the outcomes of the phenotyping that takes place at each visit.
[3] Extraction and quality control procedures will take place at the internationally accredited biobank facilities of the Sydney Brenner Institute for Molecular Biosciences (SBIMB), University of the Witwatersrand.

Sleep
Sleep disturbances are common in individuals with chronic diseases. However, little work has been done to understand the effect of HIV infection on sleep in sub-Saharan Africa. Sleep disturbances are also a common side effect of some ARVs, including DTG and EFV. Poor sleep quality and quantity affect (amongst other factors) quality of life, immunity and cognitive function; of particular importance in HIV-positive populations.

The ADVANCE study offers a unique opportunity to investigate this. At all study visits from enrolment, we shall assess sleep using a brief screening sleep questionnaire, followed by the validated Insomnia Severity Scale in those in whom the screening questionnaire identifies a problem.

Quality of life (QoL)
Both HIV infection and ART can impact on the QoL of people living with HIV, negatively and positively. We will assess QoL in all participants in all arms of ADVANCE at each visit from enrolment until the end of study, using a Quality of life questionnaire.

Novel Viral Load Testing Technologies
HIV viral load (VL) testing is the accepted standard for monitoring of patients on antiretroviral therapy (ART). Many countries, including South Africa, have adopted the test and treat strategy for HIV ART initiation, thereby increasing the number of VL tests required. VL testing capacity has been scaled up significantly, but problems remain in the transport arena, particularly shipping of specimens from remote regions. We will evaluate improved transport and storage options using dried blood spots (DBS) and dried plasma spots (DPS), and evaluate these on novel technologies. We will also perform laboratory-based evaluations of point-of-care VL monitoring technologies using whole blood.

DBS have long been used to transport specimens in a safe format and at room temperature. We wish to perform a longitudinal evaluation of the FVE extraction method for the Cobas TaqMan VL assay on the Cobas 8800 (Roche Diagnostics, Rotkreuz, Switzerland) and compare this to the Abbott RealTi*m*e HIV-1 (Abbott, Des Plaines, IL, USA) assay, both using a single DBS.

It is well documented that cell associated nucleic acids can affect the reliability of the VL result from a DBS. A number of novel storage materials which separate the plasma from the blood cells are entering the market and these need evaluation as a stable, safe and simple manner of specimen transport as DPS from remote areas, while maintaining the VL test on plasma.

Decentralisation of VL monitoring is an option for remote regions, but platforms used in these regions must be proven fit-for-purpose before they can be used for VL monitoring. We will evaluate point-of-care technologies for longitudinal VL monitoring in the laboratory using whole blood.

We will request an extra 10 mL (2x5 mL EDTA tubes) of blood when participants report for VL testing during the study. No additional visits will be required and the blood will be collected while the routine study bloods are being drawn. These blood specimens will be collected from the study sites and couriered to the CLS

laboratory where DBS and DPS will be prepared. Whole blood testing will be performed and the remaining specimen will be centrifuged and the plasma tested using the Xpert HIV-1 VL (Cepheid, Sunnyvale, CA, USA) assay. Any remaining plasma will be stored at -80^{o}C for further evaluations. The DBS and DPS will be stored at room temperature for one week, eluted as per manufacturer instructions and tested using the same assay. These results can also be compared to study VL results.

6.8 End of Study/Early Withdrawal Visit

An end-of-study visit will occur either at the end of the study (Week 96) or earlier if the patient withdraws from the study, fails virologically, or a toxicity occurs that requires a medication change that is not permitted within the protocol. The following procedures will be performed at the end of study/early withdrawal visit:

1. Assess adverse events
2. Concomitant medications
3. Physical examination, weight, blood pressure and pulse rate
4. TB symptom screen
5. Mental health assessment (MMS, NSS, IHDS)
6. Sleep questionnaires
7. Brief pain questionnaire
8. Quality of life questionnaire
9. Adherence questionnaire
10. Urine pregnancy test
11. Clinical laboratory testing:
    - Plasma HIV-1 RNA
    - CD4 count
    - Haematology
    - Biochemistry
    - Serum (fasting) and urine glucose
    - Lipids (fasting)
    - Liver function tests
    - Inflammatory markers
        - D-dimer
        - IL-6
    - Measures of renal function
        - Urine dipstix
        - Creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old)
        - Urine protein to creatinine ratio (UPCR)
        - Urine albumin to creatinine ratio (UACR)
        - Retinol-binding protein to creatinine ratio
        - β2 microglobulin to creatinine ratio
        - Fractional excretion of uric acid
        - Fractional excretion of phosphate
    - Urine, serum, and plasma for storage
    - PBMCs for storage
12. Other investigations
    - DEXA scan (except in pregnant participants). For EW, perform only if not done in the last 9 months
13. Study medications accountability

6.9 Early Withdrawal

Patients are free to withdraw from the study at any time for any reason. If a patient withdraws from the study early, all procedures for the end-of-study visit should be conducted, unless they were last performed within 2 weeks of the withdrawal/EOS visit. The investigator may also withdraw the patient at any time in the interest of patient safety, for virological failure or if the study is terminated. The primary reason for withdrawal must be recorded in the source document.

Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. Patients who miss any study visits will be followed up according to study site SOP "Participant recruitment and retention". At least 2 attempts (by telephone, personal visit or email) will be made before the patient is considered lost to follow-up. All follow-up attempts (method, date, and time) will be documented in the source document.

The investigator may withdraw a patient from the study, ideally after discussion with the principal investigator, if the patient:

- Is in violation of the protocol
- Experiences a serious or intolerable AE which interferes with study procedures
- Has laboratory safety assessments that reveal clinically significant changes from the screening/enrolment values, and which are likely due to study drugs
- Experiences virological failure, as described above
- Requires a medication that is prohibited by the protocol
- Is non-adherent to study protocol requirements and/or medication
- Withdraws consent or refuses to continue participation and/or procedures/observations.

A patient can also be withdrawn at the discretion of the investigator.

6.10 Split visit

A split visit may be conducted within the visit window of a scheduled visit in which certain visit procedures have not been completed. Reasons for split visits may include but are not limited to: participant leaving the clinic before all of the visit procedures could be completed, or the procedure was omitted during the scheduled visit or the participant returned for management of safety events. Where this occurs, data collected at the split visit will be analysed as part of the scheduled visit data.

6.11 Unscheduled visit

An unscheduled visit may be initiated by a participant reporting safety events, or collecting additional study medications outside the scheduled visit date. The investigator may conduct unscheduled visits for management of safety events and other study procedures.

6.12 Replacements

Patients who discontinue participation in the study for any reason after randomisation will not be replaced.

7.0 Safety Considerations

Safety analyses will be performed on vital sign measurements; physical examination findings; clinical laboratory analyses, including evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, urine dipstix and creatinine clearance; other investigations (such as DEXA scans); and monitoring AEs and concomitant medications throughout the study. All laboratory endpoints will have a window of 4 weeks before and after the specific visit time point. DEXA scans should be done within

one month of enrolment; subsequent DEXA scans should occur within the window for the scheduled study visit.

Investigators will be blinded to measures of UPCR, UACR, retinol binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and fractional excretion of phosphate; PK assessments (these will only be analysed at the end of the study); and DEXA scans. Mental health screening assessments, sleep questionnaires, brief pain questionnaire results will also be blinded to the investigators, unless the study nurse or counsellor administering the questionnaire has serious concerns that the patient requires intervention, upon which they should immediately inform the investigator of such concerns.

Safety issues will be discussed in detail among study doctors and with the patient before taking any decisions as to study continuation.

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient in a clinical investigation with a medicinal product regardless of its causal relationship to study medication. Patients will be instructed to contact the principal investigator or designee at any time after randomisation if any symptoms develop.

A treatment-emergent AE is defined as any event, including laboratory abnormalities, not present before exposure to study medication or any event already present that worsens in either intensity or frequency after exposure to study medication.

An AE is also any of the following occurring after study randomisation:

- Complications that occur as a result of a protocol-mandated procedure after randomisation to study medications
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of the study after randomisation to study medications
- Reasons for and complications arising from a termination of pregnancy due to medical and/or surgical reasons.

An AE does not include the following:

- Medical or surgical procedures performed. However, the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before screening visit that do not get worse
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalisation for elective surgery)
- Overdose of study medication without clinical sequelae
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason.

Adverse events will be assessed (reported and/or observed) and documented from enrolment once the patient is randomised to study medications, until exit from the study (i.e. early withdrawal or end-of-study visit at week 96). Any medical conditions observed at screening and which do not exclude the patient from the study will be documented as pre-existing medical conditions. All AEs will be followed to adequate resolution. Any ongoing AE at early withdrawal or the end-of-study visit will be further followed until satisfactory resolution or until the investigator deems the event to be chronic or the patient to be stable, up to a maximum of 30 days after the last visit.

All AEs regardless of the grade will be documented in chart notes and entered into an AE log. AEs of grade 3 and 4 and unexpected adverse drug events (meeting SAE criteria) will be entered into the RAE case report form (CRF) for reporting purposes. Grade 1 and 2 AEs will not be entered in AE case report form.

AEs occurring in infants born to study participants
All infant AEs, regardless of the grade and relationship to the mother's ARVs, will be documented in chart notes and entered into an AE log. Only Grade 3 or 4 AEs that have been determined to be either related or possibly related to the mother's ARVs, as well as the reportable AEs (RAEs) as described below will be entered in the AE case report form.

Infant AEs that are required to be reported on the Reportable Adverse Event form are as follows:

	Up to and including the 6 month visit	After the 6 month visit through study exit	Study drugs for which RAE reporting is required
TG 1	SAEs	SUSARS	DTG, TAF, FTC
TG 2	SAEs	SUSARS	DTG, TDF, FTC
TG 3	SUSARS	SUSARS	EFV, TDF, FTC

All suspected congenital anomalies must also be reported on the RAE form, regardless of grade and relationship to the mother's ARVs. However, clinically insignificant physical findings at birth (e.g. polydactyly etc.), including those regarded as normal variants (e.g. umbilical hernia), do not need to be reported.

In addition to the above, the following must also be reported for mothers in Treatment Group 1 or Treatment Group 2:
- Pregnancy complications that result in medically indicated and/or elective termination of the pregnancy
- Spontaneous abortions and foetal deaths, including any chromosomal analysis done on foetuses in these situations.

7.2 Serious Adverse Events (SAE)

An SAE is defined as any AE that:
- Results in death
- Is immediately life threatening (includes events which put patients at risk of death at the time of the event but not events which may have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Of clinical significance in the opinion of the investigator.

Any SAE must be documented in an SAE CRF. All SAEs and unexpected ADRs will be reported to the medical monitor and Wits RHI Safety Committee (WSC), by email, within 24 hours from the time site personnel first learn of the event. All SAEs will be reviewed and adjudicated with regard to causality assessment by the CEC.

7.3 Assessment of AEs

The severity or intensity of an AE refers to the extent to which an AE affects daily activities. The severity of all AEs, including laboratory abnormalities, will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1, July 2017).

The relationship or association of the study medication in causing or contributing to the AE will be characterised using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study medication and the reported event.
Possibly related:	This relationship suggests that a potential causal relationship exists between drug administration and the AE, with a reasonable time relationship to drug intake, but could also be explained by other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction).
Related:	This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

All SAEs that occur during the study (regardless of relationship to study medication) must be reported in detail and followed until the events resolve, stabilise, or become non-serious. All SAEs will be reported to the Human Research Ethics Committee (HREC) according to HREC requirements. Medical and scientific judgement should be exercised in deciding whether an AE, which does not meet the routine definition of an SAE but is important from a safety perspective and may jeopardise the patient or require intervention to prevent one of the other outcomes listed in the definition of serious, should be considered as serious.

7.4 Immune Reconstitution Inflammatory Syndrome (IRIS)

Approximately 10-20% of patients who start ART with advanced immunosuppression experience clinical deterioration during the first months due to IRIS and is most frequently described in association with TB and CM. Skin conditions such as molluscum contagiosum and Kaposi's sarcoma may also worsen due to IRIS. The diagnosis of IRIS can be difficult, mainly because there is no confirmatory diagnostic test. IRIS is seen more frequently in patients treated with integrase inhibitor-based ART[16, 17]. It will be important to ascertain whether AEs and SAEs occurring in ADVANCE are IRIS events. Investigators will assess all AEs for the possibility of IRIS and categorise according to the IRIS definitions as IRIS/probable IRIS/not IRIS. All IRIS/probable IRIS will be entered into the CRF. IRIS definitions are described in the site Clinical Assessments SOP. All IRIS events will be reviewed by the CEC.

7.5 Management of Pregnancy

DTG Preclinical toxicity studies for DTG in pregnancy did not reveal any significant concerns, and DTG was classified as FDA pregnancy category B, prior to the removal of this classification from use. In registration trials and Compassionate Use programmes, among 38 pregnancies, 1 congenital anomaly, 18 live births without any anomalies, 9 elective terminations without any anomalies, 13 spontaneous abortions without any anomalies, and 3 ectopic pregnancies were described. In post marketing surveillance, 74 pregnancies were reported as of 16 January 2016, with 18 live births without any anomalies, 2 live births with congenital anomalies, 4 spontaneous abortions without anomaly, 1 spontaneous abortion with anomaly, 1 stillbirth without anomaly and 39 pregnancies ongoing or lost to follow-up. According to the Antiretroviral pregnancy registry (APR), with first trimester DTG exposure, there were two defects seen in 77 live births, and two defects noted in 56 live births with second and third trimester exposure (it is likely that the pregnancies reported to the APR overlap with those described above).[18] Recent data from CROI from IMPAACT 1026 in 30 mother-infant pairs, had four varied congenital anomalies reported, and the researchers are still collecting data on these cases.[15] Data presented at IAS 2017 from Botswana which introduced DTG as first-line ART in May 2016 showed that the risk of adverse birth outcomes was similar for DTG-based and EFV-based ART. This study included 845 women who received a DTG-based regimen during pregnancy.[19] Data from a smaller European cohort reported at the IAS 2017 were also reassuring.[20]

TAF Preclinical toxicity studies for TAF did not reveal any significant concerns. TDF is used as a proxy for TAF

carcinogenicity and peri-postnatal studies. According to the APR, with first trimester exposure to any TDF-containing regimen, 2.2% (61/2779) of live births had birth defects, and 2.0% (27/1321) of live births with second and third trimester exposure.

Other studies Several other clinical studies using DTG and/or TAF in pregnant women are underway, which will include pregnant women receiving DTG and/or TAF. ARIA is a phase 3b study comparing DTG + ABC + 3TC to ATV/r + TDF + FTC in ARV naïve women (n=474). Women in the DTG arm who become pregnant on the study will roll over into a single-arm PK and safety study. It is anticipated that this study should recruit approximately 25 women. DOLphin is a small study that will randomise late presenting pregnant women to received either DTG or EFV-based regimens. It will look at PK in late pregnancy, post-partum and during breastfeeding, and will be followed up by a larger study, DOLphin 2. IMPAACT 1026s and PANNA will enrol women who become pregnant whilst using DTG or TAF into PK studies. The NAMSAL study comparing DTG to EFV 400mg will continue women who become pregnant on their assigned study drug. WAVES, a phase 3 study of EVG + COBI + FTC + TDF versus ATV/r + FTC + TDF in women, has an open label extension with EVG + COBI + FTC + TAF. Those randomised to EVG + COBI + FTC + TDF will continue on this arm, while those on ATV/r + FTC + TDF will be re-randomised to continue ATV/r + FTC + TDF, or to receive EVG + COBI + FTC + TAF. Women who fall pregnant on the open label study will be allowed to continue on their randomised regimen in the study. Other studies to evaluate DTG and/or TAF in pregnancy are still in planning stages, including IMPAACT 2010, which has a similar design to this study in terms of study drugs, but only enrolling pregnant women. More data will also continue to accumulate from continued clinical use of DTG in countries where it is licensed and easily available.

This study All eligible women of childbearing potential (and where possible their partners) will be counselled about the potential risks associated with pregnancy during the trial and the uncertainty of long-term effects of antiretroviral therapy on infant outcome.

Women will be encouraged not to fall pregnant during their study participation. They will receive counselling and be provided with condoms and appropriate contraception (oral or injectable hormonal contraception). They will be advised to report to the study site staff as soon as possible if pregnancy is suspected.

Urine pregnancy tests will be performed in all female patients of childbearing potential at every visit from screening to the end-of-study (Week 96) or early withdrawal visit, and as required during the study according to local standard practice for clinical care or according to the investigator's discretion, where pregnancy may be suspected.

If a female patient becomes pregnant during the study and consents to further participation, they may elect to remain in the study. They will be transferred to site 3 (Shandukani) for the duration of the pregnancy and follow up of the infant. Follow up will be as per the protocol-specified clinical and laboratory procedures, including specimens for storage, as well as the Schedule of Evaluations for Pregnant Women, or as needed according to investigator discretion. No DEXA scans will be done during pregnancy. In addition, a viral load will be done at diagnosis of pregnancy, and additional viral load monitoring will be allowed according to the investigator's discretion. A foetal ultrasound scan will be done at the time of diagnosis of pregnancy to assess gestational age. A further foetal ultrasound for foetal anomalies will be done at gestational week 24. If any anomalies are detected, the participant will be counselled and appropriately referred for further care. All other study procedures will continue as per protocol, and the additional antenatal visits will be scheduled where possible to coincide with scheduled protocol visits.

Study participants in treatment groups 1 and 2 who become pregnant during the study and elect to stay in the study will have plasma DTG trough (total and unbound), plasma tenofovir (TFV) trough, and PBMC TFV-DP concentrations measured at three visits during the pregnancy (approximately gestational weeks 20, 28 and 36), and at two visits post-partum (6 weeks and at the time of the three-month infant follow up visit) for

pharmacokinetic (PK) specimens. All PK visits during pregnancy and post-partum are planned to coincide with scheduled visits as per the SoE as much as possible. See appendix 12.3: Schedule of PK Assessments for Pregnant Women.

All PK samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and TFV-DP drug concentrations will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at UCT, where validated TFV assays are run. DTG and TFV-DP assays will be developed and validated before the end of the study. UCT will process and analyse all the pharmacokinetic specimens.

All pregnancies will be reported to the appropriate pregnancy ART exposure registers, as well as to Gilead and ViiV.

Infants born to study participants
Infants will be followed 3-monthly after birth for up to 18 months, as per the Schedule of Infant Follow-up, or as needed according to investigator discretion. They will be assessed for congenital anomalies; potential toxicities due to ART exposure *in utero* and throughout breastfeeding; growth and development.
HIV testing for infants will not be performed as part of the study, but will be done as per National Guidelines and standard of care. Testing will be done through NHLS at scheduled study visits, if appropriate; or at any time during study follow-up at the discretion of the investigators.

The following will be conducted at 3-monthly visits (birth + 5 days; 3 months, 6 months, 9 months, 12 months, 15 months, 18 months; see appendix 12.4: Schedule of Infant Follow-up):

- Gestational assessment (at birth)
- Infant Feeding Questionnaires
- Infant/child ART exposure (maternal ART or infant prophylaxis)
- Anthropometry:
    - Birth weight and length and head circumference
    - Weight, length, head circumference and weight for length at each study visit (3-monthly)
- Congenital anomalies assessment
- Developmental screen and assessment (IGMST) from 6 months of life
- Standard of care HIV testing (when appropriate)
- Toxicity assessment: ALT, creatinine clearance, FBC at birth and 3 months, and every 3 months during breastfeeding. NOTE: Date of complete cessation of breastfeeding is taken as 6 weeks from date of last exposure to breast milk)
- DEXA scan: 6 months

Children will be referred as necessary, if any abnormality is suspected.

Developmental Screen of Infants
For the purposes of this study, we will use the Infant Gross Motor Screening tool (IGMST). This tool has been validated in HIV-infected infants and we anticipate that < 2% of HIV-exposed infants in this study will be HIV-infected. A simple tool, which is easy to use and easy to score in our clinical setting is necessary, and therefore IGMST will be used as a screening tool. The IGMST can be used in infants from 6 months until 18 months, and assesses gross motor development at each age, according to a checklist. The child's age needs to be accurately calculated and each milestone achieved receives a score. Development is evaluated to be either "satisfactory", requiring no further intervention, or "at risk", requiring further assessment and management. IGMST will be administered 3-monthly from the age of 6 months to 18 months (see appendix 12.4: Schedule

of Infant Follow-up). Any infants identified to be “at risk” will be referred to Charlotte Maxeke Johannesburg Academic Hospital or another suitable facility for further evaluation and management.

7.6 Management of TB

DTG: DTG is currently being studied in patients on TB treatment in a separate study, comparing a DTG-based regimen versus EFV-based treatment, and this study should be completed in 2016. Additional PK studies in patients with TB are in progress or planned. Current recommendations are that DTG be dosed twice daily if given with rifampicin (RIF).

TAF: Currently there are no data on interactions between TAF and RIF, but a significant interaction is predicted based on modelling from PK interactions between TAF and carbamazepine. A study in healthy volunteers is currently planned, which will examine the interaction between TAF and RIF, followed by a study in patients with TB.

This study: Active TB is an exclusion criterion for entry to this study. At the screening visit, those who screen TB-negative and are eligible for isoniazid preventive therapy (IPT), as per national guidelines, will be offered IPT and initiated on IPT. At every visit, every participant will be screened for tuberculosis using the TB symptom screen, as is standard of care within the national treatment guidelines. Those who screen positive on the TB symptom screen will be investigated as per site Clinical Assessments SOP, and if active TB is diagnosed, referred for initiation of TB treatment.

The management of each arm if the patient develops TB on study drug will be as follows:
Treatment Group 1: (DTG + TAF + FTC) – DTG daily dose will be increased to 50 mg twice daily (12-hourly), until two weeks after TB treatment is completed; TAF will be switched to TDF 300 mg daily, for duration of TB treatment. TAF can be restarted two weeks after completion of TB treatment.
Treatment group 2: (DTG + TDF + FTC) – DTG daily dose will be increased to 50 mg twice daily (12-hourly), until two weeks after TB treatment is completed; for duration of TB treatment.
Treatment group 3: (EFV + TDF + FTC) – no change.

Study participants in treatment groups 1 and 2 who develop TB will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed (DTG dose will be increased to 12-hourly, and those in group 1 will be switched from TAF to TDF); at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin, after daily dosing of DTG has resumed and participants in group 1 have been switched back to TAF. All PK visits should coincide with scheduled visits as per the SoE as much as possible. See appendix 12.5: Schedule of PK Assessments in Participants with TB.

All PK samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and TFV-DP drug concentrations will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at UCT, where validated TFV assays are run. DTG and TFV-DP assays will be developed and validated before the end of the study. UCT will process and analyse all the pharmacokinetic specimens.

Studies looking at PK of both DTG and TAF in the presence of RIF are underway; data from these studies will be evaluated by the scientific protocol committee, to see whether these changes in dose and drug are still necessary. If not, treatment will be continued at initiation dose.

7.7 Management of single drug substitutions

For participants in Treatment Groups 1 and 2 who develop TB during the study, study medication must be modified as described in section 7.6. Other permitted substitutions are described in section 6.5. Any allergic reaction that is felt to be study drug-related, will be assessed and drug interrupted as felt necessary by the investigator; grade 3 or 4 reactions that are deemed to be related to any study medication will lead to immediate and permanent discontinuation.

7.8 Management of liver dysfunction while on study

If the following occurs after initiation of study regimen, the investigator will call the patient to inform them to stop taking study medication and arrange for an additional visit, and clinically assess, treat any condition and repeat laboratory tests as needed:

- ALT ≥ 8x upper limit of normal (ULN);
- ALT ≥ 3x ULN (if enrolment ALT is < 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 ≥ 3x enrolment ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥ 5x ULN and < 8x ULN that persists > 2 weeks (with bilirubin < 2x ULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥ 5x ULN but < 8x ULN and cannot be monitored weekly for > 2 weeks;
- Subjects who develop ALT ≥ 5x ULN should be followed weekly until resolution or stabilisation (ALT < 5x ULN on 2 consecutive evaluations).

Restarting study drug: If a causal relationship between the liver event and DTG cannot be ruled out, then DTG must be permanently discontinued and the subject not rechallenged.

Drug restart following transient resolving liver events not related to study drug: Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT < 3x ULN where:

- Liver chemistries have a clear underlying cause other than drug-induced liver injury (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury
- The subject is receiving compelling benefit and benefit of drug restart exceeds risk
- Approval from the Principal Investigator for the drug restart has been obtained
- The subject has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death
- The subject has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file
- Following drug restart, the participant will return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

7.9 Safety of patients in the study

To ensure safety of patients, this study will be conducted to standards of ICH-GCP, South African GCP, Good Participatory Practice and other applicable regulatory and ethical standards. In addition, there will be a DSMB to oversee the safety aspects of the clinical trial. The DSMB is run by the NIH, with international representation, and comprises members who are independent of the study site and staff.

There will be a Scientific Advisory Committee, including the PI and other stakeholders, which will oversee the conduct of the study, and ensure continual updates concerning the study implementation.

In addition, a Clinical Endpoint Committee (CEC), also known as an Endpoint Adjudication Committee (EAC), will be established. This is an independent group of experts that reviews the clinical trial data in order to give expert opinions about clinical events of interest, such as clinical endpoints or IRIS events. The endpoint review committee will have at least the following members: two to four members comprising of an independent chair; an expert in the disease being studied; and a member of the trial management or steering committee.

Patients will have access, via the sponsor, to post trial treatment, through the state sector, with expanded access to DTG for those patients benefitting from it, if non-inferiority is confirmed.

8.0 Study Medication

Patients in treatment group 3 will be advised to begin treatment on the evening of Day 0, Week 0, and those in treatment groups 1 and 2 on the morning of Day 1 Week 0. It is also advised that patients in treatment groups 1 and 2 take their study medication in the morning while those in treatment group 3 take their study medication at night. This is important for minimising treatment related side effects and for the pharmacokinetic assessments. However, the first dose may be delayed up to one week following randomisation. The start date should be noted. All study medications are to be orally self-administered as directed according to the package insert. Open label study medication will be supplied to the patient at enrolment and Weeks 4-84. All medications used in this study will be provided as open label medications. Patients will be instructed to bring all used and unused study medication bottles with them to each study visit.

Table 2: Study Medication Supplies

Product	Formulation	Manufacturer
Dolutegravir	50 mg tablets	ViiV Healthcare
Tenofovir disoproxil fumarate plus emtricitabine (FDC)	300/200 mg tablets	Gilead Sciences or generic manufacturer, to be determined
Tenofovir alafenamide fumarate plus emtricitabine (FDC)	25/200 mg tablets	Gilead Sciences
Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC)	600/300/200 mg tablets	MSD or generic manufacturer, to be determined
Abbreviations: FDC, fixed-dose combination		

Currently, it is anticipated the originator companies will donate study drugs. If this does not occur, alternative supplies are available, including from generic manufacturers; however, colour and size of the medication may change from that detailed below. Regulators will be advised accordingly, if this is the case.

Dolutegravir

Each tablet contains dolutegravir sodium equivalent to 50 mg of DTG. The tablet, if supplied by ViiV Healthcare, is a yellow, round biconvex shape, film coated tablet about 9 mm diameter, de-bossed with “SV 572” on one side and “50” on the reverse side. The tablets will be stored at 15-30 ^{0}C.

Tenofovir disoproxil fumarate plus emtricitabine (FDC)
Tenofovir disoproxil fumarate plus emtricitabine (FDC) is a co-formulation of TDF 300 mg and FTC 200 mg as a film-coated tablet. The medication, if supplied by Gilead Sciences, is packed in a white plastic bottle of 30 tablets, and will be stored at room temperature (below 30 ^{0}C).

Tenofovir alafenamide fumarate plus emtricitabine (FDC)
Tenofovir alafenamide fumarate plus emtricitabine (FDC) is a co-formulation of TAF 25 mg and FTC 200 mg as a film-coated tablet. The medication, if supplied by Gilead Sciences is packed in a white plastic bottle of 30 tablets, and will be stored at room temperature (below 30 ^{0}C).

Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC)
Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC) is a co-formulation of TDF 300 mg, FTC 200 mg and EFV 600 mg as a film-coated tablet. The medication, if supplied by MSD is packed in a white plastic bottle of 30 tablets, and will be stored at room temperature (below 30 ^{0}C).

All study medications will be stored per manufacturers' specifications in the package insert.

8.1 Medication Supplies

The study site will acquire study medication from multiple sources, including the originator companies and generic manufacturers. All study medications will be administered in an unblinded fashion and supplied as commercial drug, over-labelled for clinical trial use in accordance with local regulatory requirements.

At the site, all study medications must be kept in a secure cabinet or room with access restricted to only necessary study site personnel. Storage instructions for site personnel and patients will be provided on the label. Study medication labels will contain information to meet the applicable regulatory requirements.

8.2 Study Medication Accountability

The investigator will maintain accurate records of receipt of all study medications, including dates of receipt. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study medications will be reconciled and retained or destroyed according to applicable regulations. Patient compliance will be evaluated through review of drug dispensing and administration records.

8.3 Prior, Concomitant and Subsequent Therapy

DTG As DTG is neither an inducer nor inhibitor of CYP3A, there are no significant interactions with hormonal contraceptives. However, as an *in vitro* inhibitor of OCT-2 (organic cation transporter), DTG increases metformin concentrations and dose adjustment of metformin should be considered when starting and stopping co-administration of DTG with metformin. Metformin intake is not a contraindication to study participation. Renal function should be monitored as per protocol. Antacids containing magnesium or aluminium, as well as calcium, iron, zinc and multivitamin supplements should be dosed at least 2 hours after or 6 hours before DTG dosing, due to complex binding to polyvalent cations.

TAF TAF is transported by P-gp and BCRP. Medicinal products that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption. *In vitro* and clinical PK drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving TAF with other medicinal products is low. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is not an inhibitor of CYP3A4 *in vivo*. TAF is a substrate of OATP *in vitro*.

The following medications should not be in use at screening; during the course of the study, if required, the investigator must review whether the patient is on the EFV or DTG arm, and decide whether the new medication can be used safely:

- Investigational drug within 2 weeks of the first study drug dose (enrolment)
- Anticonvulsants
    - Carbamazepine
    - Oxcarbazepine
    - Phenobarbital
    - Phenytoin
- Midazolam
- Triazolam
- Pimozide
- Ergot alkaloids
    - Ergotamine
- Herbal products
    - St. John's Wort
- Probenicid

Drugs with nephrotoxic potential should be used with care.

9.0 Statistical Methods

All plasma HIV-1 RNA levels end points will have a window of 4 weeks before and after that time point; 48-week data will include any plasma HIV-1 RNA levels done between 44 and 52 weeks; 96-week data will include any data between 92 and 100 weeks. As required by the DSMB and MCC, separate analyses will be undertaken for the 12-< 19 year age group.

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. Patients who do not have an HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

9.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm (the FDA regards substitutions within the first month on the grounds of intolerance or toxicity and then only to a drug of the same class, as a success; this would mean that patients moved from TAF to TDF would not be classified as a success)
- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (< 200 copies/mL) at Week 96
- Time to virologic failure (defined as confirmed HIV-1 RNA levels ≥ 1000 copies/mL at week 12-24 or ≥ 200 copies/mL at or after week 24)
- Change from screening in plasma HIV-1 RNA levels by visit
- Change from screening of CD4 count by visit
- Virological efficacy and tolerability in the 12-<19 year age group
- Analysis of PK data, virological efficacy and tolerability in those becoming pregnant
- Analysis of PK data, tolerability and virological efficacy in those developing TB
- Analysis of PK interactions between EFV and INH in participants in treatment group 3 receiving IPT

- Analysis of PK interactions between TFV, DTG and INH in participants receiving IPT (contingent on funding)

9.3 Safety Endpoints

Safety Assessments: The main safety endpoint is the assessment of the tolerability and safety of the three treatment combinations. Safety analyses will be performed on vital sign measurements; physical examination findings; clinical laboratory analyses, including evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, inflammatory markers, measures of renal function, urine dipstix and creatinine clearance; other investigations (such as DEXA scans); and monitoring AEs and concomitant medications throughout the study. All laboratory endpoints will have a window of 4 weeks before and after the specific visit time point. DEXA scans should be done within one month of enrolment; subsequent DEXA scans should occur within the window for the scheduled study visit.

Throughout the Study:

- TB symptom screen
- Adverse events (AEs) including serious AEs (SAEs)
- Vital sign measurements (blood pressure (BP) and heart rate)
- Targeted physical examination findings
- Mental health assessment (Modified Mini Screen [MMS], Neuropsychiatric Symptom Screen [NSS], International HIV Dementia Scale [IHDS])
- Sleep questionnaires (Sleep Assessment to identify which participants need to complete the Insomnia Severity Scale [ISS])
- Brief pain questionnaire
- Neuropathy screen (adapted from ACTG Brief Peripheral Neuropathy Screening Tool)
- Quality of life questionnaire (Quality of Life Assessment, Lifestyle and Habits) and Adherence questionnaire
- Laboratory analyses (safety and efficacy)
- Other investigations such as DEXA scans

Secondary Safety Endpoints:

- Mental health assessment (MMS, NSS): Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- IHDS: Weeks 0, 24, 48, 72 and 96
- Sleep questionnaires: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Brief pain questionnaire: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Neuropathy screen: Weeks 0, 4, 12, 24 and 48
- Quality of life questionnaire: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Adherence questionnaire: Weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in full blood count: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in biochemistry: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in serum (fasting) and urine glucose: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in fasting lipids: Weeks 0, 24, 48 and 96
- Changes in liver function tests: Screening, Weeks 12, 24, 36, 48, 60 and 96
- Changes in inflammatory markers
    - D-dimer: Weeks 0, 4, 24 and 96
    - Interleukin-6 (IL-6): Weeks 0, 4, 24 and 96
- Change in measures of renal function
    - Urine dipstix at each visit

  - Creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old) at each visit
  - Urine protein to creatinine ratio (UPCR) at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
  - Urine albumin to creatinine ratio (UACR) at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
  - Retinol-binding protein to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
  - β2 microglobulin to creatinine ratio at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
  - Fractional excretion of uric acid at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
  - Fractional excretion of phosphate at Weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96
- Change in bone mineral density measured by DEXA scans at Weeks 0, 48 and 96
- Women who fall pregnant on study will have plasma DTG trough (total and unbound), plasma tenofovir (TFV) trough, and peripheral blood mononuclear cells (PBMC) tenofovir diphosphate (TFV-DP) concentrations measured at three visits during the pregnancy and at two visits post-partum
- Participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed; at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin.

Investigators will be blinded to measures of UPCR, UACR, retinol-binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and fractional excretion of phosphate; PK assessments (these will only be analysed at the end of the study); and DEXA scans. Inflammatory markers (d-dimer and IL-6 will be measured on stored plasma as post hoc analyses. Mental health screening assessments, sleep questionnaires, brief pain questionnaires will also be blinded to the investigators, unless the study nurse or counsellor administering the questionnaire has serious concerns that the patient requires intervention, upon which they should immediately inform the investigator of such concerns.

9.4 Sample Size

In a previous clinical trial conducted at the same investigational centre, the percentage of patients taking first-line antiretroviral treatment who had HIV-1 RNA suppression below 50 copies/mL by Week 48 was 80%. Registration studies of both DTG and TAF support this threshold.

A sample size of 370 patients per arm (1110 total) will provide at least 80% power to establish non-inferior efficacy for the DTG + TAF + FTC arm, compared to each of the other study arms. A non-inferiority margin of -10% is now the FDA determined standard in the design of pivotal phase 3 randomised trials of antiretrovirals. There will also be at least 80% power to establish non-inferior efficacy for the DTG + TDF + FTC arm compared to the EFV + TDF + FTC arm. An overall 1.7% significance level (two one-sided tests) will be used, to adjust for the three treatment comparisons being made. The 12-<19 age group will be analysed separately.

9.5 Analysis Sets

The following analysis sets will be used in the statistical analyses:

All-randomised set: The all-randomised set will consist of all randomised patients, regardless of whether or not any study treatment dosing was completed. Patients will be analysed according to the treatment they were randomly assigned to.

Intent to treat (ITT) set: The ITT set will consist of all randomised patients who received at least one dose of study medications.

Per-protocol set: The PP set will consist of all randomised patients who fully comply with the inclusion and exclusion criteria, have received at least 80% of all doses of study treatment up to Week 48, and have an

evaluable plasma HIV-1 RNA level assessment at Week 48. Criteria will be defined in more detail in the statistical analysis plan (SAP). Patients will be analysed according to the treatment they received.

Safety set: The safety set will consist of all patients who receive at least one dose of randomly assigned study treatments. All safety analyses will be performed using the safety set. Patients will be analysed according to the treatment they received.

All efficacy analyses will be performed using the all-randomised, ITT and PP sets. All safety analyses will be performed using the safety set.

9.6 Statistical Analysis

The primary objective of the study is to establish non-inferior efficacy for the DTG + TAF + FTC arm compared with either of the control arms (DTG + TDF + FTC or EFV + TDF + FTC). Both of these treatments are included in current World Health Organization for first-line treatment. Currently, EFV + TDF + FTC is most widely recommended, while DTG + TDF + FTC is listed as an alternative treatment. The study will also allow a comparison of the efficacy of DTG + TDF + FTC versus EFV + TDF + FTC. Hence there are three treatment comparisons included in the study design.

The primary population for analysis will be Intent-to-Treat, including all randomised patients who received at least one dose of study medication.

The primary efficacy parameter will be the percentage of patients who have HIV-1 RNA suppression below 50 copies/mL at Week 48. Patients either who have HIV-1 RNA levels above 50 copies/mL, or who have missing data for any reason will be considered treatment failures. Patients who have switched off randomised treatment to a different treatment by Week 48 will be considered as treatment successes, if the HIV-1 RNA is below 50 copies/mL at Week 48.

The treatment arms will be compared in the following sequence, using the fallback procedure to control the familywise error rate:

1. Treatment group 1 versus treatment group 3
2. Treatment group 1 versus treatment group 3
3. Treatment group 1 versus treatment group 2

The fallback procedure will be used to control the overall type I error rate among the three primary treatment comparisons. With this procedure, the three primary treatment comparison hypotheses are tested according to the predefined sequence above. Each hypothesis is assigned an initial significance level (alpha) of 0.017 and with each rejection of hypothesis, the significance level used for testing the next hypothesis accumulates. For example, if the first test for non-inferiority is significant at the p=0.017 level, the second test will use a p-value of 0.034. If the second test is significant at the p=0.034 level, the third test will use a p-value of 0.05. Whenever a hypothesis is not rejected, the next hypothesis in the sequence will be tested at the initially allocated p=0.017 level. [21] Non-inferiority will be evaluated using a one-sided test.

Additional details will be provided in the statistical analysis plan.

9.7 Primary Efficacy Analysis

The primary endpoint is the proportion of patients with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. The difference in proportions of patients who achieve the primary endpoint across the 3 treatment groups will be analysed. This variable will also be tabulated, displaying the proportions of

patients with undetectable plasma HIV-1 RNA levels (with 95% CI) by treatment group, the estimate (with 95% CI) for the difference in proportion across all three treatment groups, and the corresponding non-inferiority test p-values.

The consistency of the treatment effect across subgroups will be investigated. All efficacy analyses will be performed using the all-randomised, ITT and PP sets.

9.8 Safety Analyses

Treatment-emergent AEs will be tabulated by treatment, system organ class, preferred term, seriousness, severity, and relationship to treatment. Tabulations will contain the number and percentage of patients with an event as well as the number of events. All AEs will be listed.

Shift tables (change from screening/enrolment value to on-treatment values) based on laboratory normal ranges will be presented for each laboratory measurement at each assessment time. In addition, laboratory parameters will be summarised by descriptive statistics.

Changes in vital sign measurements, physical examination data, previous and concomitant treatments, medical history, mental health, sleep, neuropathy screen and quality of life questionnaires, urine dipstix, clinical laboratory parameters, lipids, creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old), inflammatory markers, measures of renal function, pharmacokinetic parameters and DEXA will be summarised by treatment group and visit, where relevant.

9.9 Interim Analyses

A data safety monitoring board (DSMB) will monitor the study in order to ensure that harm is minimised and benefits maximised for the study patients. Membership of the DSMB will be completely independent of the study staff. The NIH has agreed to use its existing International DSMB to oversee the study.

To allow early stopping, one interim analysis will be performed on the primary efficacy endpoint, when 400 participants have completed the Week 48 assessments. The interim analysis will test for differences between the study arms, and not for non-inferiority. Unblinded primary efficacy analysis and safety analyses will be provided to the DSMB that is independent of the study team. The study drug allocation will be unblinded to investigators and patients throughout the study to Week 96. The DSMB will issue recommendations concerning trial continuation.

Stopping rules:

This study is designed to impact guidelines and change clinical practice and therefore it is important to ensure that the study is terminated appropriately if any treatment group shows clear benefit, rendering it unethical to retain participants on other treatment groups. A stopping rule will be applied if an extreme level of significance ($p < 0.001$ [Peto rule]) is reached between the study arms at the time of the interim analysis.

No formal stopping rules will be used by the DSMB for safety outcomes.

See WRHI 060 Statistical Analysis Plan (SAP) for more details.

10.0 Data Management

At every visit, patients' information will be recorded in source documents including chart notes/worksheets and laboratory test results. Data from CRFs/worksheets and other data sources will be entered into an

electronic data capturing system (EDC, to be provided by a Contract Research Organisation) and as specified in the study Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the database.

Each person involved with the study will have an individual logon and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

11.0 Other Study Activities

11.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the regulatory authorities or the Human Research Ethics Committee (HREC).

The principal investigator or designee and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. All computers are password-protected and records can only be accessed by authorised study staff.

11.2 Reporting

The protocol and relevant supporting documents will be submitted to the Medicine Control Council (MCC) and HREC for approval. The study protocol will be registered with the South African National Clinical Trial Registry (www.sanctr.gov.za) / National Human Research Ethics Committee (www.ethicsapp.co.za) and www.ClinicalTrial.gov. Six-monthly progress reports will be submitted to MCC and HREC for the duration of the study, and as requested. Upon completion or premature termination of the study, the investigator will provide HREC and the regulatory authorities with a summary of the study's outcome, and any reports required.

11.3 Investigator Documentation

Prior to beginning the study, the principal investigator will be asked to comply with ICH E6(R1) 8.2 by providing the following essential documents, including but not limited to:

- An original investigator-signed investigator agreement page of the protocol
- An HREC-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patients
- HREC approval
- *Curriculum vitae* for the principal investigator and each investigator. Current licensure must be noted on the *curriculum vitae*. They will be signed and dated by each investigator at study start-up, indicating that they are accurate and current
- Laboratory certifications and normal ranges for any laboratories used by the site.

11.4 Monitoring of the Study

The study monitor has the obligation to follow the study closely. In doing so, the monitor will visit the study facility at periodic intervals, in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the principal investigator and study

staff. All aspects of the study will be carefully monitored for compliance with applicable government regulation with respect to current ICH GCP guidelines and current standard operating procedures.

11.5 Protocol Amendments

Amendments to the protocol must be submitted in writing to the MCC and HREC for approval before patients are enrolled into an amended version of the protocol, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. This should be fully documented and where possible notify the relevant regulatory authorities.

11.6 Protocol Violations and Deviations

The principal investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The principal investigator or designee may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to trial patients without prior HREC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the HREC for review and approval and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the HREC and agreed to by the principal investigator or designee. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion, exclusion or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient, when the patient or principal investigator or designee has failed to adhere to significant protocol requirements (inclusion and exclusion criteria) and the patient was enrolled without prior approval, or when there is non-adherence to regulations or some ICH GCP guidelines.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigator or designees will be notified in writing by the monitor of violations and deviations. The HREC should be notified of all protocol violations and deviations in a timely manner.

11.7 Inspection of Records

Principal investigator or designee and institutions involved in the study will permit trial-related monitoring, audits, HREC review, and regulatory inspections by providing direct access to all study records.

11.8 Records Retention

All correspondence (e.g. with HREC, or MCC) relating to this clinical study should be kept in appropriate study folders. Records of patients, source documents, CRFs, and drug inventory sheet pertaining to the study must be kept on file. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, if required by the applicable regulatory requirements. If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who is willing to accept the responsibility.

11.9 Study Termination

Although Wits RHI has every intention of completing the study, Wits RHI reserves the right to discontinue the study at any time for clinical or administrative reasons. The end of the study is defined as the date on which the last patient completes the last visit.

11.10 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the investigator will be responsible for these activities and will determine how the manuscript is written and edited, the number and order of authors, the publication(s) to which it will be submitted, and other related issues according to the Wits RHI publication guidelines.

12.0 Appendix

12.1. Schedule of Events

Study Visit	Baseline		Visit 1	Follow-up Visits: 2, 3, 4, 6, 7, 8	Endpoints	
	Screening	Enrolment			Visit 5	Visit 9 /EOS
Study Week	**–**	**0**	**4**	**12[a], 24, 36, 60, 72, 84**	**48**	**96**
Study Window (days)	**–60 to –1**	**0**	**-13/ +28**	**-41/+42**	**-41/+42**	**-41/+42**
Informed consent	X					
Demography	X					
Medical history/pre-existing conditions	X	X				
TB symptom screen	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X
Previous/concomitant medications	X	X	X	X	X	X
Height[b]/weight measurement	H/W	W	W	W	W	W
Vital signs[c] and temperature[d] measurements)	X	X	X	X	X	X
Physical examination	X	X[e]	X[e]	X[e]	X[e]	X
Mental health screening (MMS, NSS)		X	X	X	X	X
IHDS		X		W24 and 72 only	X	X
Sleep questionnaires		X	X	X	X	X
Brief pain questionnaire		X	X	X	X	X
Neuropathy screen[f]		X	X	W12 and 24 only	X	
Adherence questionnaire			X	X	X	X
Quality of life questionnaire		X	X	X	X	X
Urine pregnancy testing	X	X	X	X	X	X
Hepatitis B antigen		X				
Haematology, biochemistry	X		X	X	X	X
Confirm HIV-1 status with ELISA	X					
Plasma HIV-1 RNA	X[i]		X	X	X	X
DBS, DPS and Point-of-care VL	X		X	X	X	X
CD4 cell count	X			W24 only	X	X
Creatinine clearance (Cockcroft-Gault) and urine dipstix	X		X	X	X	X

Study Visit	Baseline		Visit 1	Follow-up Visits: 2, 3, 4, 6, 7, 8	Endpoints	
	Screening	Enrolment			Visit 5	Visit 9 /EOS
Study Week	**–**	**0**	**4**	**12[a], 24, 36, 60, 72, 84**	**48**	**96**
Study Window (days)	**–60 to –1**	**0**	**-13/ +28**	**-41/+42**	**-41/+42**	**-41/+42**
Serum (fasting) and urine glucose		X	X	X	X	X
Lipid panel (fasting)		X		W24 only	X	X
Liver function tests	X			W12, 24, 36, 60	X	X
Inflammatory markers		X	X	W24 only		X
Measures of renal function		X		X	X	X
Blood for genetic/epigenetic assessment[g]		X		W24	X	
Urine for storage		X	X	X	X	X
Plasma preparation and serum cryopreservation		X	X	X	X	X
PBMC preparation and storage		X			X	X
PK levels (TFV, DTG, EFV)				24	X	X
Pharmacogenomic specimen (whole blood)				36		
DEXA scans[h]		X Window 1 month			X	X
Inclusion/exclusion criteria	X	X				
Randomisation		X				
Study medications dispensed		X	X	X	X	
Study treatment/medication accountability		X	X	X	X	X

[a] Week 12 visit window is -27/+42 days
[b] Height will be measured for adolescents at each scheduled visit
[c] BP, pulse rate, respiration rate will be performed at all scheduled visits
Only at screening and symptom-led at other visits.
[d] Temperature is routinely measured in paediatric and pregnant participants at each visit
[e] Symptom-led physical examination
[f] Adapted from ACTG Brief peripheral neuropathy screening tool
[g] Bloods for epigenetic assessment will be taken on a subset of 110 consecutively enrolled participants ≥19 years old.
[h] DEXA scans will NOT be performed in participants who become pregnant and elect to stay in the study (for the duration of the pregnancy).
[i] DBS sample will be stored for efavirenz drug level testing at screening visits for selected participants.

12.2. Schedule of Evaluations for Pregnant Women

Visit[a]	Pregnancy confirmation[b]	GW 20[c]	GW 24[c]	Follow-up Visits[c]: GW 28, 32, 36, 40	Delivery
Study Visit Window	**+ 3 weeks**	**+/- 2 weeks**	**+/- 2 weeks**	**+/- 2 weeks**	**+ 2 weeks**
Informed consent[d]	X				
TB symptom screen	X	X	X	X	X
Adverse event monitoring		X	X	X	X
Previous/concomitant medications	X	X	X	X	X
Weight measurement	X	X	X	X	X
Vital sign measurements	X	X	X	X	X
Physical examination (targeted)	X	X	X	X	X
Plasma HIV-1 RNA	X				
Urine and blood pregnancy testing	X				
Urine dipstix	X	X	X	X	X
Foetal ultrasound	X[e]		X[f]		

[a] All other study procedures will be as for non-pregnant participants

[b] If scheduled study visit occurs within two weeks of pregnancy confirmation visit, do not repeat procedures already performed

[c] GW = gestational week; Where possible, visits will be aligned with scheduled protocol visits

[d] Sign informed consent for pregnant women to continue in ADVANCE

[e] Gestational age scan should occur within 4 weeks from pregnancy confirmation date

[f] Foetal anomaly scan

12.3. Schedule of PK Assessments for Pregnant Women

	GW 20 [a]	GW 28 [a]	GW 36 [a]	6 weeks PP [b]	3 months PP [b]
Study Visit Window	**+/- 4 weeks**	**+/- 4 weeks**	**+/- 4 weeks**	**+/- 2 weeks**	**+/- 4 weeks**
Plasma DTG trough (total and unbound); plasma TFV[c] trough; PBMC TFV-DP [d] concentrations	X	X	X	X	X

[a] GW = gestational week; Where possible, visits will be aligned with scheduled protocol visits

[b] PP = post partum

[c] TFV = tenofovir

[d] TFV-DP = tenofovir diphosphate

12.4. Schedule of Infant Follow-up

Visit (Infant age)	Birth	3 months	6 months	9 months	12 months	15 months	18 months (Final)
Study Visit Window	+ 7 days[a]	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks
Gestational assessment	X						
ART exposure[b]	X	X	X	X	X	X	X
Anthropometry[c]	X	X	X	X	X	X	X
Vitals (respiration rate, pulse rate, temperature)	X	X	X	X	X	X	X
Physical examination	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Congenital anomalies	X	X	X	X	X	X	X
Infant Feeding Questionnaire	X	X	X	X	X	X	X
Developmental screen and assessment (IGMST[e])			X	X	X	X	X
HIV testing[f]	X	X	X	X	X	X	X
Toxicity assessment: ALT, CrCl, FBC[g]	X	X	X	X	X	X	X
DEXA scan			X				

[a] Birth Visit window = +3 days if co-enrolled on P1026s

[b] ART exposure *in utero* and throughout breastfeeding

[c] Weight, length, head circumference and weight for length

[d] Symptom-led physical examination

[e] Infant Gross Motor Screening Tool from 6 months of life

[f] HIV testing will be done through NHLS (if and when appropriate) as per National Guidelines and standard of care; or at any time at the investigator's discretion

[g] ALT, CrCl, FBC at birth and 3 months, and every 3 months during breastfeeding (NOTE: Date of complete cessation of breastfeeding is taken as 6 weeks from date of last exposure to breast milk)

12.5. Schedule of PK Assessments in Participants with TB

	Confirmation of TB diagnosis [a]	Next 2 visits per study SoE	Post TB treatment [b]
Study Visit Window	**+/- 0 weeks [c]**	**+/- 6 weeks**	**+ 4 weeks**
Plasma DTG trough (total); plasma TFV[d] trough; PBMC TFV-DP [e] concentrations (only participants in treatment groups 1 and 2)	X	X	X

[a] At this visit, DTG will be increased to 50 mg 12-hourly, and those in TG-1 will be switched from TAF to TDF

[b] 4 weeks after completion of TB treatment (after daily dosing of DTG resumed and participants in TG switched back to TAF)

[c] PK assessments must be done on the day that treatment changes are made

[d] TFV = tenofovir

[e] TFV-DP = tenofovir diphosphate

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PROTOCOL AMENDMENT #1

PROTOCOL #: WRHI 060

STUDY NAME: ADVANCE

PROTOCOL TITLE

A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy

Version 1.0; 29 April 2016

Amended to

Version 2.0; 08 November 2016

WRHI 060 Summary of Changes:

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 7: Study site.	1-2 sites in Johannesburg, South Africa	2-3 sites in Johannesburg, South Africa
Page 7, 8, 18: Inclusion and exclusion criteria	**Inclusion #5** Calculated creatinine clearance (CrCl) > 60 mL/min (MDRD formula) **Exclusion #11: no old text**	**Inclusion #5** Calculated creatinine clearance (CrCl) > 60 mL/min (Cockcroft-Gault formula) in > 18 years old OR > 80 mL/min (modified Cockcroft-Gault) in ≤ 18 years old **Exclusion #11: new texts added** Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); Child-Pugh C.

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 8: Study design	To ensure adequate representation of adolescents in any treatment group randomisation will be stratified according to age greater or less than 18 years.	The 12-18 year age group will be enrolled and randomised separately; enrolment is estimated at 30-40 per arm (total 90-120). The Data Safety Monitoring Board (DSMB) and South African Medicines Control Council (MCC) independently requested that the 12-18 year age group be enrolled separately, as the numbers are likely to be small, using the same criteria as adults, and that the data be analysed separately (the DSMB requested, in addition, for an analysis on the 12-15 year age group)
Page 9, Secondary Efficacy Endpoints		• Analysis of pharmacokinetic (PK) data, virological efficacy and tolerability in those developing TB • Analysis of PK data, virological efficacy and tolerability in those becoming pregnant • Virological efficacy and tolerability in the 12-18 year age group.
Page 10: Secondary Safety Endpoints	Changes in endpoint measurements	**Added:** • Participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough levels measured at three visits.
Page 10: Special patients populations	• Management of TB co-infection Studies looking at PK of both DTG and TAF in the presence of rifampicin are underway; data from these studies will be evaluated by the scientific protocol committee, to see whether these changes in dose and	• Management of TB co-infection expanded The management of each arm if the patient develops TB on study drug will be as follows: Treatment Group 1: (DTG + TAF + FTC) – DTG daily dose will be increased to 50 mg twice daily, until two weeks after TB treatment is completed; TAF will be

	drug are still necessary, during the course of the study. If not, treatment will be continued at initiation dose. PK levels of TDF, TAF and DTG will be performed at TB diagnosis in Treatment Group 1 and 2 (according to which drug they are taking), as well as during and after TB treatment (if still on study), to assess changes in therapeutic levels with the changes.	switched to TDF 300 mg daily, for duration of TB treatment. TAF can be restarted two weeks after completion of TB treatment. Treatment group 2: (DTG + TDF + FTC) – DTG daily dose will be increased to 50 mg twice daily, until two weeks after TB treatment is completed; for duration of TB treatment. Treatment group 3: (EFV + TDF + FTC) – no change. Some patients may have TB diagnosed at other healthcare facilities. Where this happens, we will also measure TAF levels (trough if time of last TAF dose known; otherwise 3 random levels over a period of 3-4 hours) in those who are in treatment group 2 when they present to the research center where they will be switched to TDF at that visit. TAF levels will be measured again one month after stopping rifampicin, after the patient has been switched back to TAF. All study participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough levels measured at five visits: prior to increasing the DTG dosing to twice daily, three additional trough levels (these should be drawn at scheduled study visits where possible) and a final trough level one month after stopping rifampicin, after daily dosing of DTG has resumed. Trough levels will also be measured in control subjects (without TB coinfection) in a 3:1 ratio. Samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. UCT is setting up DTG and TAF laboratory assays and will process all the pharmacokinetic specimens

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 11: Sample size	• 1050 (350 per arm)	• 1110 (370 per arm)
Page 20: Study procedures (Follow up)	• Adherence questionnaire at Weeks 4, 48 and 96. • PK specimens not in version 1.0	• Adherence questionnaire at each study visit after initiation of study medication **Added** • PK specimens for adolescents, pregnant women, and patients on TB treatment
Page 20: Efficacy Assessments	• within 2 months of the date of counseling	• All patients with detectable HIV-1 RNA (> 50 copies/mL) will receive adherence counselling, with a repeat test at least one month after counselling.
Page 22: Sleep	• At all study visits, we shall assess sleep using two standardised sleep questionnaires which have been validated and previously used in South African cohorts. The faces sleepiness scale is a pictorial measure of sleepiness, which consists of cartoon faces showing various degrees of eye closure, yawning, a hand rubbing an eye, and a person asleep. The faces scale is therefore a particularly useful tool for individuals who are not fluent in English or those not proficient in reading. A further screening questionnaire will be used to identify patients with insomnia, who will then complete the insomnia severity scale. The questionnaires will	• Sleep disturbances are common in individuals with chronic diseases. However, little work has been done to understand the effect of HIV infection on sleep in sub-Saharan Africa. The Advance study offers a unique opportunity to investigate this. At all study visits from enrolment, we shall assess sleep using a brief screening questionnaire, followed by the validated Insomnia Severity Scale in those in whom the screening questionnaire identifies a problem.

Page and Section of Protocol	Old text (version 1)	New text (version 2)
	take approximately 10-15 minutes to administer, in total.	
Page 24: Assessment of AEs	• Possibly related criteria not in version 1.0.	• Possibly related: This relationship suggests that a potential causal relationship exists between drug administration and the AE, with a reasonable time relationship to drug intake, but could also be explained by other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction).
Page 25-26: Management of Pregnancy	• there was one defect seen in 10 live births, and one defect was noted in 18 live births with second and third trimester exposure • According to the APR, with first trimester exposure to any TDF-containing regimen, 2.3% of 10 live births had birth defects, and 2.1% of live births with second and third trimester exposure. • They will receive counselling and be provided with condoms and appropriate contraception. • Women who become pregnant on DTG arms and elect to stay in the study will have their DTG levels taken monthly. Those on the DTG + TAF + FTC arm who become pregnant will have monthly TAF levels in addition to DTG levels.	• there was one defect seen in 22 live births, and one defect was noted in 29 live births with second and third trimester exposure • According to the APR, with first trimester exposure to any TDF-containing regimen, 2.2% (61/2779) of live births had birth defects, and 2.0% (27/1321) of live births with second and third trimester exposure. • They will receive counselling and be provided with condoms and appropriate contraception (oral or injectable hormonal contraception). • If a female patient becomes pregnant during the study and consents to further participation, they may elect to remain in the study. They will continue to be followed up according the protocol-specified clinical and laboratory procedures, including specimens for storage. No DEXA scans will be

Page and Section of Protocol	Old text (version 1)	New text (version 2)
		done during pregnancy. In addition, a viral load will be done at diagnosis of pregnancy, and additional viral load monitoring will be allowed according to the investigators discretion. From gestational week 20, pregnant women will have monthly study visits as per standard of care during the antenatal period (see Appendix 2: Schedule of Evaluations for Pregnant Women). A foetal ultrasound scan will be done at the time of diagnosis of pregnancy to assess gestational age. A further foetal ultrasound for foetal anomalies will be done at gestational week 24. If any anomalies are detected, the participant will be counselled and appropriately referred for further care. All other study procedures will continue as per protocol, and these additional antenatal visits will be scheduled where possible to coincide with scheduled protocol visits. All study participants in treatment groups 1 and 2 who become pregnant during the study and elect to stay in the study will have DTG and TAF (according to regimen) trough levels measured monthly. Trough levels will also be measured in control subjects (non-pregnant) in a 3:1 ratio. DTG and TAF drug levels will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. UCT is setting up DTG and TAF laboratory assays and will

Page and Section of Protocol	Old text (version 1)	New text (version 2)
	• Developmental Screen of Infants – not in version 1.0.	process all the pharmacokinetic samples. All pregnancies will be reported to the appropriate pregnancy ART exposure registers, as well as to Gilead and ViiV. • Developmental Screen of Infants For the purposes of this study, we will use the Infant Gross Motor Screening tool (IGMST). This tool has been validated in HIV-infected infants and we anticipate that < 2% of HIV-exposed infants in this study will be HIV-infected. A simple tool, which is easy to use and easy to score in our clinical setting is necessary, and therefore IGMST will be used as a screening tool. The IGMST can be used in infants from 6 months until 18 months, and assesses gross motor development at each age, according to a checklist. The child's age needs to be accurately calculated and each milestone achieved receives a score. Development is evaluated to be either "satisfactory", requiring no further intervention, or "at risk", requiring further assessment and management. IGMST will be administered 3-monthly from the age of 6 months to 18 months (see Appendix 3: Schedule of Infant Follow-up). Any infants identified to be "at risk" will be referred to Charlotte Maxeke Johannesburg Academic Hospital or another suitable facility for further evaluation and management.

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 27: Management of TB	• PK levels of TDF, TAF and DTG will be performed at TB diagnosis in Treatment Group 1 and 2 (according to which drug they are taking), as well as during and after TB treatment (if still on study), to assess changes in therapeutic levels with the changes.	• Some patients may have TB diagnosed at other healthcare facilities. Where this happens, we will also measure TAF levels (trough if time of last TAF dose known; otherwise 3 random levels over a period of 3-4 hours) in those who are in treatment group 2 when they present to the research center where they will be switched to TDF at that visit. TAF levels will be measured again one month after stopping rifampicin, after the patient has been switched back to TAF. All study participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough levels measured at five visits: prior to increasing the DTG dosing to twice daily, three additional trough levels (these should be drawn at scheduled study visits where possible) and a final trough level one month after stopping rifampicin, after daily dosing of DTG has resumed. Trough levels will also be measured in control subjects (without TB coinfection) in a 3:1 ratio. Samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end of the study. UCT is setting up DTG and TAF laboratory assays and will process all the pharmacokinetic specimens.

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 27: Management of single drug substitutions	• Any modification of the antiretroviral regimen will result in patient exclusion, except in TB, in the manner described above.	• Any modification of the antiretroviral regimen will result in patient exclusion, except in TB, in the manner described above. Any allergic reaction that is felt to be study drug-related, will be assessed and drug interrupted as felt necessary by the investigator; grade 3 or 4 reactions will lead to immediate and permanent discontinuation.
Page 28: Management of liver dysfunction while on study	• Management of liver dysfunction while on study – not in version 1.0.	If the following occurs after initiation of study regimen, the investigators will call the patient to inform them to stop taking study medication and arrange for an additional visit, and clinically assess, treat any condition and repeat laboratory tests as needed: • ALT ≥ 8x upper limit of normal (ULN); • ALT ≥ 3x ULN (if baseline ALT is < 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 ≥ 3x baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia; • ALT ≥ 5x ULN and < 8x ULN that persists > 2 weeks (with bilirubin < 2x ULN and no signs or symptoms of acute hepatitis or hypersensitivity); • ALT ≥ 5x ULN but < 8x ULN and cannot be monitored weekly for > 2 weeks;

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 28: Management of liver dysfunction while on study		• Subjects who develop ALT ≥ 5x ULN should be followed weekly until resolution or stabilisation (ALT < 5x ULN on 2 consecutive evaluations). **Restarting study drug**: If a causal relationship between the liver event and DTG cannot be ruled out, then DTG must be permanently discontinued and the subject not rechallenged. **Drug restart following transient resolving liver events not related to study drug**: Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT < 3x ULN) where: • Liver chemistries have a clear underlying cause other than drug-induced liver injury (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury • The subject is receiving compelling benefit and benefit of drug restart exceeds risk • Approval from the Principal Investigator for the drug restart has been obtained • The subject has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 28: Management of liver dysfunction while on study		• The subject has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file • Following drug restart, the participant will return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.
Page 29: Safety of patients in the study	• New texts added	• Patients will have access, via the sponsor, to post trial treatment, through the state sector, with expanded access to DTG for those patients benefitting from it, if non-inferiority is confirmed.

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 29-30: Study Treatments	• New texts added	• Those on the two DTG-containing arms will be requested NOT to take their medication on the morning of their study visits.
Dolutegravir	• The tablets do not require any special storage conditions.	• The tablets will be stored at 15-30 C.
Tenofovir disoproxil fumarate plus emtricitabine (FDC)	• The medication, if supplied by Gilead Sciences, is packed in a white plastic bottle of 112 tablets, and will be stored at room temperature (below 30 0C).	• The medication, if supplied by Gilead Sciences, is packed in a white plastic bottle of 30 tablets, and will be stored at room temperature (below 30 ^{0}C).
Tenofovir alafenamide fumarate plus emtricitabine (FDC)	• The medication, if supplied by Gilead Sciences is packed in a white plastic bottle of 112 tablets, and will be stored at room temperature (below 30 ^{0}C).	• The medication, if supplied by Gilead Sciences is packed in a white plastic bottle of 30 tablets, and will be stored at room temperature (below 30 ^{0}C).
Efavirenz plus tenofovir disoproxil fumarate plus emtricitabine (FDC)	• The medication, if supplied by MSD is packed in a white plastic bottle of 112 tablets, and will be stored at room temperature (below 30 ^{0}C).	• The medication, if supplied by MSD is packed in a white plastic bottle of 30 tablets, and will be stored at room temperature (below 30 ^{0}C).
Page 31: Prior, Concomitant and Subsequent Therapy	• The following medications are not to be used during the course of the study.	• The following medications should not be in use at screening; during the course of the study, if required, the investigator must review whether the patient is on the EFV or DTG arm, and decide whether the new medication can be used safely:

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 31. Statistical Analysis Plans	• Added text	• As required by the DSMB and MCC, separate analyses will be undertaken for the 12-18 year age group.
Page 31-32. Secondary Efficacy Endpoints	• Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm	• Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm (the FDA regards substitutions within the first month on the grounds of intolerance or toxicity and then only to a drug of the same class, as a success; this would mean that patients moved from TAF to TDF would not be classified as a success) • Analysis of PK data, virological efficacy and tolerability in those becoming pregnant • Analysis of PK data, tolerability and virological efficacy in those developing TB
Page 32. Sample size	• In a previous clinical trial conducted at the same investigational centre, the percentage of patients taking first-line antiretroviral treatment who had HIV-1 RNA suppression below 50 copies/mL by Week 48 was 80%.	• In a previous clinical trial conducted at the same investigational centre, the percentage of patients taking first-line antiretroviral treatment who had HIV-1 RNA suppression below 50 copies/mL by Week 48 was 80%. Registration studies of both DTG and TAF support this threshold. • The 12-18 age group will be analysed separately.
Page 32. Analysis Sets	•	• Intent to treat (ITT) set: The ITT set will consist of all randomised patients who received at least one dose of study medications.

Page and Section of Protocol	Old text (version 1)	New text (version 2)
Page 33: Statistical Analysis	• .New texts.	• The treatment arms will be compared in the following sequence, using the fall-back procedure to control the family-wise error rate: 1.Treatment group 1 versus treatment group 3 2.Treatment group 1 versus treatment group 3 3.Treatment group 1 versus treatment group 2 The fallback procedure will be used to control the overall type I error rate among the three primary treatment comparisons. With this procedure, the three primary treatment comparison hypotheses are tested according to the predefined sequence above. Each hypothesis is assigned an initial significance level (alpha) of 0.017 and with each rejection of hypothesis, the significance level used for testing the next hypothesis accumulates. For example, if the first test for non-inferiority is significant at the p=0.017 level, the second test will use a p-value of 0.034. If the second test is significant at the p=0.034 level, the third test will use a p-value of 0.05. Whenever a hypothesis is not rejected, the next hypothesis in the sequence will be tested at the initially allocated p=0.017 level. Non-inferiority will be evaluated using a one-sided test. Additional details will be provided in the statistical

Page and Section of Protocol	Old text (version 1)	New text (version 2)
		analysis plan.
Page 34: Stopping rule	• The Peto rule will be used to adjust the p-value of the final analysis for the two interim analyses. The study would only be stopped for efficacy reasons if the efficacy of one arm (using the primary efficacy endpoint) was significantly worse than either of the two other treatment arms, with a p-value <0.001	• This study is designed to impact guidelines and change clinical practice and therefore it is important to ensure that the study is terminated appropriately if any treatment group shows clear benefit, rendering it unethical to retain participants on other treatment groups. A stopping rule will be applied if an extreme level of significance ($p < 0.001$ [Peto rule]) is reached between the study arms at the time of the interim analysis.
Page 34. Data Management		• data capturing system (EDC, to be provided by a Contract Research Organisation
Page 40: appendix	• A new appendix added	• Appendix 2: Schedule of Evaluations for Pregnant Women

PROTOCOL AMENDMENT #2

PROTOCOL #: WRHI 060

STUDY NAME: ADVANCE

PROTOCOL TITLE

A 96-week Randomised, Phase 3 Non-inferiority Study of DTG + TAF + FTC Compared with DTG + TDF + FTC and EFV + TDF + FTC in Patients Infected with HIV-1 Starting First-line Antiretroviral Therapy

Version 2.0; 08 November 2016

Amended to

Version 3.0; 12 December 2017

WRHI060 SUMMARY OF CHANGES PRTOCOL V2 TO V3

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
Throughout the protocol	Age of adolescent 12 -18 years	Age of adolescent 12 < 19 years
Page 9	**Study Sites:** 2-3 sites in Johannesburg, South Africa	**Study Sites**: 2-4 sites in Johannesburg, South Africa
	The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of each regimen.	The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of each regimen. Pharmacokinetic analyses of DTG, tenofovir (TFV) and tenofovir diphosphate (TFV-DP) concentrations in participants who develop active tuberculosis and in pregnant women will be explored in treatment groups 1 and 2. Pharmacokinetic analyses of EFV and isoniazid (INH) concentrations in participants receiving isoniazid preventive therapy (IPT) will be explored in treatment group 3. Pharmacogenomics and further pharmacokinetic parameters may be explored, contingent on funding.
Page 10, 39	**Follow-up Period:** Patients will begin treatment on the evening of Day 0, Week 0. However, the first dose may be delayed up to one week following	**Follow-up Period:** Patients in treatment group 3 will be advised to begin treatment on the evening of Day 0, Week 0, and those in treatment groups 1 and 2 on the morning of Day 1 Week 0. It is also advised that patients in treatment groups 1 and 2 take their study medication in the morning while those in treatment group 3 take their study medication at

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	randomisation.	night. However, the first dose may be delayed up to one week following randomisation. The start date should be noted where possible.
Page 11, 46	**Interim Analyses:** To allow early stopping, 2 interim analyses will be performed on the primary efficacy endpoint: the first when approximately one-third of all patients have completed the Week 48 assessments and the second after approximately two-thirds of patients have completed the Week 48 assessments.	**Interim Analyses:** To allow early stopping, one interim analysis will be performed on the primary efficacy endpoint, when 400 participants have completed the Week 48 assessments. The interim analysis will test for differences between the study arms, and not for non-inferiority.
	Safety Assessments: Safety analyses will be performed on physical examination findings, vital sign measurements, clinical laboratory analyses, other investigations (such as DEXA scans) and monitoring AEs and concomitant medications throughout the study.	The main safety endpoint is the assessment of the tolerability and safety of the three treatment combinations. Safety analyses will be performed on vital sign measurements; physical examination findings; clinical laboratory analyses, including evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, urine dipstix and creatinine clearance;
	Throughout the Study: • Adverse events (AEs) including serious AEs (SAEs) • Vital sign measurements (blood pressure (BP) and heart rate) • Targeted physical examination findings • Mental health screening	**Throughout the Study:** • TB symptom screen • Adverse events (AEs) including serious AEs (SAEs) • Vital sign measurements (blood pressure (BP) and heart rate) • Targeted physical examination findings • Mental health assessment (Modified Mini Screen [MMS], Neuropsychiatric Symptom Screen [NSS], International HIV Dementia Scale [IHDS]) • Sleep questionnaires (Sleep Assessment to identify which participants need to complete the Insomnia Severity Scale [ISS]) • Brief pain questionnaire

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	• Sleep questionnaires • Neuropathy screen • Quality of life questionnaire • Actigraphy (in a subset of patients) • Laboratory analyses	• Neuropathy screen (adapted from ACTG Brief Peripheral Neuropathy Screening Tool) • Quality of life questionnaire (Quality of Life Assessment, Lifestyle and Habits) and Adherence questionnaire • Laboratory analyses (safety and efficacy)

Page 12, 43, 44	**Secondary Safety Endpoints:**
	• Mental health screening: Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
	• Women who fall pregnant on study will have monthly TAF, TDF and DTG levels done, and active follow-up and evaluation of their infants
	• Participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough levels measured at three visits.
	Clinicians will be blinded to screening and laboratory values that are not part of standard of care, unless assessed as severe (grade 3 and 4).
		Secondary Safety Endpoints:
		• Mental health assessment (MMS, NSS): Weeks 0, 4, 12, 24, 36, 48, 60, 72, 84 and 96
		• IHDS: Weeks 0, 24, 48, 72 and 96
		• Changes in inflammatory markers
		  ○ D-dimer: Weeks 0, 4, 24 and 96
		  ○ Interleukin-6 (IL-6): Weeks 0, 4, 24 and 96
		• Women who fall pregnant on study will have plasma DTG trough (total and unbound), plasma tenofovir (TFV) trough, and peripheral blood mononuclear cells (PBMC) tenofovir diphosphate (TFV-DP) concentrations measured at three visits during the pregnancy and at two visits post-partum
		• Participants in treatment groups 1 and 2 who develop TB during the study will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed; at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin.

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
		Investigators will be blinded to inflammatory markers, UPCR, UACR, retinol-binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and fractional excretion of phosphate; PK assessments (these will only be analysed at the end of the study); and DEXA scans. Mental health screening assessments, sleep questionnaires, brief pain questionnaires will also be blinded to the investigators, unless the study nurse or counsellor administering the questionnaire has serious concerns that the patient requires intervention, upon which they should immediately inform the investigator of such concerns.
Page 13	**Special patient populations during study:** **Pregnancy:** Women will be counselled regarding the unknown risks that could be associated with DTG and TAF exposure to the foetus should they fall pregnant, but if they do fall pregnant and elect to stay on the study, they will be offered additional study visits (monthly). Infants will be followed post partum for up to 18 months. Pharmacokinetic (PK) levels of TAF, TDF and DTG will be done at diagnosis of pregnancy in Treatment Groups 1 and 2 (according to which drug they are taking), and at monthly study visits pre- and post partum.	**Special patient populations during study:** **Pregnancy:** Women will be counselled regarding the unknown risks that could be associated with DTG and TAF exposure to the foetus should they fall pregnant. If they do fall pregnant and elect to stay on the study, they will be transferred to site 3 (Shandukani) for the duration of the pregnancy and follow up of the infant. Follow up will be as per the protocol-specified clinical and laboratory procedures, including specimens for storage, as well as the Schedule of Evaluations for Pregnant Women, or as needed according to investigator discretion. Infants will be followed 3-monthly after birth for up to 18 months, as per the Schedule of Infant Follow-up, or as needed according to investigator discretion. Study participants in treatment groups 1 and 2 who become pregnant during the study and elect to stay in the study will have plasma DTG trough (total and unbound), plasma TFV trough, and PBMC TFV-DP concentrations measured at three visits during the pregnancy (approximately gestational weeks 20, 28 and 36), and at two visits post-partum (6 weeks and at the time of the three-month infant follow up visit) for PK specimens.
Page 13	**TB:** All study participants in treatment groups 1 and 2 who develop TB during the study will have DTG	**TB:** Study participants in treatment groups 1 and 2 who develop TB will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed (DTG dose will be increased to 12-hourly, and those in group 1 will be switched from TAF to

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	trough levels measured at five visits: prior to increasing the DTG dosing to twice daily, three additional trough levels (these should be drawn at scheduled study visits where possible) and a final trough level one month after stopping rifampicin, after daily dosing of DTG has resumed. Trough levels will also be measured in control subjects (without TB co-infection) in a 3:1 ratio. Samples will be centrifuged, and plasma will be stored at -80∘C for analysis in a batch at the end of the study. UCT is setting up DTG and TAF laboratory assays and will process all the pharmacokinetic specimens.	TDF); at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin, after daily dosing of DTG has resumed and participants in group 1 have been switched back to TAF. All PK samples will be centrifuged, and plasma will be stored at -80∘C for analysis in a batch at the end of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and TFV-DP drug concentrations will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at UCT, where validated TFV assays are run. DTG and TFV-DP assays will be developed and validated before the end of the study. UCT will process and analyse all the pharmacokinetic specimens.
Page 17	**Rationale for the regimen DTG + TAF + FTC:** Additional information not in version 2.0	**Rationale for the regimen DTG + TAF + FTC:** At the time this protocol was developed, there were no RCTs evaluating TAF 25 mg + FTC as first-line treatment in any form, including in combination with DTG. Subsequently, TAF 25 mg + FTC has been studied in combination with another integrase inhibitor, bictegravir, as part of a three-drug fixed dose combination (compared to DTG 50 mg with a fixed dose combination of TAF/FTC 25/200 mg, and compared to fixed dose combination DTG/ABC/3TC 50/600/300 mg), showing non-inferiority at 48 weeks.
Page 18	**2.2 Secondary Objectives** The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of DTG and TAF	**2.2 Secondary Objectives** The secondary objectives of this study are to evaluate the 96-week viral suppression, CD4 count changes, tolerability, overall safety, and efficacy of each regimen. Pharmacokinetic analyses of DTG, tenofovir (TFV) and tenofovir diphosphate (TFV-DP) concentrations in participants who develop active tuberculosis and in pregnant women will be explored in treatment groups 1 and 2.

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	plus FTC when compared with DTG and TDF plus FTC or EFV and TDF plus FTC in each regimen.	Pharmacokinetic analyses of EFV and isoniazid (INH) concentrations in participants receiving isoniazid preventive therapy (IPT) will be explored in treatment group 3.
Page 19	**3.0 Study Design** To ensure adequate representation of adolescents in any treatment group, randomisation will be stratified according to age greater or less than 18 years, with an anticipated 30-40 in each arm in this age group. The randomisation will be electronically generated.	**3.0 Study Design** Group 1 (DTG + TAF + FTC) or Treatment Group 2 (DTG + TDF + FTC) or Treatment Group 3 (EFV + TDF + FTC). To ensure adequate representation of 12-<19 year olds in any treatment group, 12-< 19 year old participants will be randomised separately, with an anticipated 30-40 in each arm in this age group, and will be enrolled and followed up at the Shandukani (site 3).
Page 20	**4.0 Study Sites –** not in version 2.0	**4.0 Study Sites** ADVANCE will be conducted at four sites in Johannesburg. Site 1: Wits RHI Yeoville Research Centre, Wits RHI Yeoville Clinic, 35 Bedford, Cnr Dunbar Street, Yeoville Site 2: HIV/AIDS Adult Clinic Area 556, Adult HIV/AIDS Clinic Area 556, Charlotte Maxeke Johannesburg Academic Hospital, Jubilee Road, Johannesburg, 2193 Site 3: Wits RHI Shandukani Hillbrow Johannesburg, Hillbrow Health Precinct, 22 Esselen Street, Hillbrow, Johannesburg, 2001 Site 4: Wits RHI Research Centre, 7 Esselen Street, Hillbrow, Johannesburg, 2001 Participants 12-< 19 years will be enrolled and followed up at site 3. Participants 19 years and older will be enrolled and followed up at sites 1, 2 and 4. Women who become pregnant and elect to continue participation in the study will be transferred to site 3 as per Participant Transfer SOP. 12-< 19 year old participants who become pregnant will continue to be managed at site 3.
Page 21	**5.1 Screening** • Haematology, biochemistry	**6.1 Screening** • Haematology, biochemistry, liver function tests

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
Page 22	*Re-Screening (Days -60 to -1)* During the 60-day screening period, a patient may be re-screened to determine eligibility. Re-screening will involve retesting of subsequent biological samples, and/or re-assessment of any inclusion and exclusion criteria that previously failed the patient.	*Rescreening (Days -60 to -1)* During the 60-day screening period, a patient may be rescreened to determine eligibility. Rescreening will involve retesting of subsequent biological samples, and/or reassessment of any inclusion and exclusion criteria that previously failed the patient. If more than 60 days have elapsed, the patient will need to be fully rescreened under a new screening number.
Page 22	**5.2 Enrollment:** • Mental health screen • Clinical laboratory testing • Lipid panel (fasting) • Serum (fasting) and urine glucose • Liver function tests Neuropathy genetic/epigenetic blood specimen	**6.2 Enrollment:** 5 TB symptom screen • Mental health assessment (MMS, NSS and IHDS) 12 Clinical laboratory testing • Hepatitis B surface antigen test (HBsAg) • Lipid panel (fasting) • Serum (fasting) and urine glucose • Inflammatory markers ○ D-dimer ○ IL-6 Neuropathy genetic/epigenetic blood specimen in a subset of 110 consecutively-enrolled participants ≥ 19 years of age.
	5.3 Follow-up Visit Procedures 3 Mental health screen	**6.3 Follow-up Visit Procedures** 4. TB symptom screen 5. Mental health assessment (MMS, NSS at all visits; IHDS only at Weeks 24, 48 and 72) 11. Urine pregnancy test (unless pregnancy has already been confirmed)
Page 23	11 Clinical laboratory testing: • Lipids (Week 24, 48 and 96) • Neuropathy genetic/epigenetic blood specimen at Weeks 4, 12, 24 and 48	12.Clinical laboratory testing: • Lipids (fasting) (Week 24 and 48) • Inflammatory markers ○ D-dimer: Weeks 4 and 24 ○ IL-6: Weeks 4 and 24 • Neuropathy genetic/epigenetic blood specimen at Weeks 24 and 48 (in a subset of 110 consecutively-enrolled participants, ≥ 19 years of age

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	• PK specimens for adolescents, pregnant women, and patients on TB treatment 12. Other investigations • DEXA scans at Weeks 48 and 96 13. Study medications dispensing and patient education	• PK specimens all participants to be stored at Weeks 24 and 48 • PK specimens for pregnant women, and patients on TB treatment (as per appendices 3 and 5) • Pharmacogenomics at Week 36 (whole blood) 13. Other investigations • DEXA scans at Week 48 (except in pregnant participants) 14. Study medications dispensing, patient education and accountability
Page 25	**5.4 Physical Examination and Vital Sign Measurements** A full physical examination will be performed at screening, and a targeted symptom directed physical examination where clinically indicated thereafter. Height and weight will be recorded at the screening visit and weight will be measured at all scheduled study visits from enrolment to the last study visit. Vital sign measurements (temperature, pulse rate, systolic and diastolic blood pressure) will be collected at screening. At all other study visits only blood pressure and pulse rate will be routinely measured, and other vital signs only if indicated clinically.	**6.4 Physical Examination and Vital Sign Measurements** Vital sign measurements (temperature, pulse rate, systolic and diastolic blood pressure) will be collected at screening. At all other study visits only blood pressure and pulse rate will be routinely measured, and other vital signs only if indicated clinically. Temperature is routinely measured in paediatric and pregnant participants, and therefore will be done at each scheduled visit for adolescents (12-< 19 years) and pregnant women at Site 3. A full physical examination will be performed at screening and last study visit (early withdrawal/Week 96), and a targeted symptom directed physical examination where clinically indicated at all other visits. Height and weight will be recorded at the screening visit and weight will be measured at all scheduled study visits from enrolment to the last study visit in participants ≥19 years. Height will be measured for adolescents (12-< 19 years) at each scheduled visit.
Page 24 - 25	**5.5 Efficacy Assessments**	**6.5 Efficacy Assessments**

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	Efficacy will be assessed by the evaluation of plasma HIV-1 RNA level. The primary efficacy endpoint will be the proportion of patients with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. Patients who do not have a HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. All patients with detectable HIV-1 RNA (> 50 copies/mL) will receive adherence counselling, with a repeat test at least one month after counselling. If repeated HIV-1 RNA ≥ 1000 copies/mL, a resistance test will be performed, and the patient terminated from the study. In instances where HIV-1 RNA copies cannot be amplified, investigator's discretion will apply. In patients who continue to have 50-1000 copies/mL, adherence intensification and repeat testing will continue until suppression below 50 copies/mL, upon which study monitoring will occur as per protocol, or when persistently above 1000 copies/mL (2 measures), upon which the patient will be	Participants with detectable HIV-1 RNA (≥ 50 copies/mL) will receive adherence counselling, with a repeat test using the same HIV RNA PCR assay at least one month after counselling. The result of the repeat test will be used for the primary analysis of efficacy. This is to prevent patients being classified as treatment failures if their HIV RNA result is marginally above the limit of assay quantification from testing error. There is high variability in measurement of HIV RNA at the lower limit of quantification of the HIV RNA PCR assays. In previous studies, 60-70% of patients with HIV RNA results in the range of 50-199 copies/mL on first test, had a subsequent HIV RNA result < 50 copies/mL on retesting of the same sample. The following algorithm will be used in efficacy assessments: (details in the protocol): 1. Patients with HIV RNA levels 50-199 copies/mL after Week 24 2. Patients with HIV RNA levels 200-999 copies/mL after Week 24If there are two consecutive detectable HIV RNA results of 200-999 copies/mL at any time after Week 24 of the study 3. Patients with HIV RNA levels ≥ 1000 copies/mL after Week 24 4. Patients with treatment-limiting toxicity In all cases, patients should be followed up as part of the main ADVANCE trial protocol if feasible. If this is not possible, there should be follow up visits every 6 months to monitor HIV RNA levels, confirm what ARVs they are taking and document any other clinical outcomes including that they are still alive.

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	terminated from the study.	
Page 25 - 27	Pharmacokinetics and pharmacogenetics Was not in version 2.0	**6.6 Pharmacokinetics and pharmacogenetics** Pharmacokinetic data from ADVANCE will be used to address the four aims listed below. *1. Describing antiretroviral exposure* *2. Pharmacokinetic-pharmacodynamic (PK-PD) analyses* *3. Pharmacogenomic analyses* *4. Drug-drug interactions between antiretrovirals and isoniazid* See details in the protocol
Page 27 - 30	**5.6 Additional Assessments** **Actigraphy has been removed**	**6.7 Additional Assessments** **TB symptom screen** **Mental health assessment** **Pain** **Bloods for assessing epigenetic changes** **Quality of life (QoL)** **Novel Viral Load Testing Technologies** See details in the protocol
Page 30	**6.8 End of Study/Early Withdrawal Visit** Procedures was not detailed in version 2.0.	**6.8 End of Study/Early Withdrawal Visit** Procedures now detailed in version 3.0.
Page 31	**6.10 Split visit** Not in version 2.0	**6.10 Split visit** A split visit may be conducted within the visit window of a scheduled visit in which certain visit procedures have not been completed. Reasons for split visits may include but are not limited to: participant leaving the clinic before all of the visit procedures could be completed, or the procedure was omitted during the scheduled visit or the participant returned for management of safety events. Where this occurs, data collected at the split visit will be analysed as part of the scheduled visit data.
Page 32	**6.11 Unscheduled visit** Not in version 2.0	**6.11 Unscheduled visit** An unscheduled visit may be initiated by a participant reporting safety events, or collecting additional study medications outside the scheduled visit date. The investigator may conduct unscheduled visits for management of safety events and other study procedures.

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
Page 32	**6.0 Safety Assessments** Safety evaluations will include the monitoring of AEs and concomitant medications, clinical laboratory assessments, physical examinations, vital sign measurements, and evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, urine dipstix and creatinine clearance.	**7.0 Safety Considerations** Safety analyses will be performed on vital sign measurements; physical examination findings; clinical laboratory analyses, including evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, urine dipstix and creatinine clearance; other investigations (such as DEXA scans); and monitoring AEs and concomitant medications throughout the study. All laboratory endpoints will have a window of 4 weeks before and after the specific visit time point. DEXA scans should be done within one month of enrolment; subsequent DEXA scans should occur within the window for the scheduled study visit. Investigators will be blinded to measures of UPCR, UACR, retinol binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and fractional excretion of phosphate; PK assessments (these will only be analysed at the end of the study); and DEXA scans. Mental health screening assessments,, sleep questionnaires, brief pain questionnaire results will also be blinded to the investigators, unless the study nurse or counsellor administering the questionnaire has serious concerns that the patient requires intervention, upon which they should immediately inform the investigator of such concerns.
Page 33	**AEs occurring in infants born to study participants** **Not in version 2.0**	**AEs occurring in infants born to study participants** New addition
	6.3 Assessment of AEs The severity or intensity of an AE refers to the extent to which an AE affects daily activities. The severity of all AEs, including laboratory abnormalities, will be graded according to the Division of AIDS grading table (version 2.0, November 2014).	**7.3 Assessment of AEs** The severity or intensity of an AE refers to the extent to which an AE affects daily activities. The severity of all AEs, including laboratory abnormalities, will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1, July 2017).

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	Immune Reconstitution Inflammatory Syndrome (IRIS) **Not in version 2.0**	**7.4 Immune Reconstitution Inflammatory Syndrome (IRIS)** Approximately 10-20% of patients who start ART with advanced immunosuppression experience clinical deterioration during the first months due to IRIS and is most frequently described in association with TB and CM. Skin conditions such as molluscum contagiosum and Kaposi's sarcoma may also worsen due to IRIS. The diagnosis of IRIS can be difficult, mainly because there is no confirmatory diagnostic test. IRIS is seen more frequently in patients treated with integrase inhibitor-based ART[16, 17]. It will be important to ascertain whether AEs and SAEs occurring in ADVANCE are IRIS events. Investigators will assess all AEs for the possibility of IRIS and categorise according to the IRIS definitions as IRIS/probable IRIS/not IRIS. All IRIS/probable IRIS will be entered into the CRF. IRIS definitions are described in the site Clinical Assessments SOP. All IRIS events will be reviewed by the CEC.
Page 35		**7.5 Management of Pregnancy** [15] Data presented at IAS 2017 from Botswana which introduced DTG as first-line ART in May 2016 showed that the risk of adverse birth outcomes was similar for DTG-based and EFV-based ART. This study included 845 women who received a DTG-based regimen during pregnancy.[19] Data from a smaller European cohort reported at the IAS 2017 were also reassuring.[20]
		If a female patient becomes pregnant during the study and consents to further participation, they may elect to remain in the study. They will be transferred to site 3 (Shandukani) for the duration of the pregnancy and follow up of the infant. Follow up will be as per the protocol-specified clinical and laboratory procedures, including specimens for storage, as well as the Schedule of Evaluations for Pregnant Women, or as needed according to investigator discretion. No DEXA scans will be done during pregnancy.
Page 36		Study participants in treatment groups 1 and 2 who become pregnant during the study and elect to stay in the study will have plasma DTG trough (total and unbound), plasma tenofovir (TFV) trough, and

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
		PBMC TFV-DP concentrations measured at three visits during the pregnancy (approximately gestational weeks 20, 28 and 36), and at two visits post-partum (6 weeks and at the time of the three-month infant follow up visit) for pharmacokinetic (PK) specimens. All PK visits during pregnancy and post-partum are planned to coincide with scheduled visits as per the SoE as much as possible. See appendix 12.3: Schedule of PK Assessments for Pregnant Women. All PK samples will be centrifuged, and plasma will be stored at -80∘C for analysis in a batch at the end of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and TFV-DP drug concentrations will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at UCT, where validated TFV assays are run. DTG and TFV-DP assays will be developed and validated before the end of the study. UCT will process and analyse all the pharmacokinetic specimens
Page 36-37	**Children born to study participants** Children will be followed up to 18 months, and assessments regarding congenital anomalies, potential toxicities due to ART exposure *in utero* and throughout breastfeeding, growth and development will be assessed.	**Infants born to study participants** Infants will be followed 3-monthly after birth for up to 18 months, as per the Schedule of Infant Follow-up, or as needed according to investigator discretion. They will be assessed for congenital anomalies; potential toxicities due to ART exposure *in utero* and throughout breastfeeding; growth and development. HIV testing for infants will not be performed as part of the study, but will be done as per National Guidelines and standard of care. Testing will be done through NHLS at scheduled study visits, if appropriate; or at any time during study follow-up at the discretion of the investigators. • Gestational assessment (at birth) • Infant Feeding Questionnaires • Infant/child ART exposure (maternal ART or infant prophylaxis) • Anthropometry: ○ Birth weight and length and head circumference

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
		○ Weight, length, head circumference and weight for length at each study visit (3-monthly) • Congenital anomalies assessment • Developmental screen and assessment (IGMST) from 6 months of life • Standard of care HIV testing (when appropriate) • Toxicity assessment: ALT, creatinine clearance, FBC at birth and 3 months, and every 3 months during breastfeeding. NOTE: Date of complete cessation of breastfeeding is taken as 6 weeks from date of last exposure to breast milk) • DEXA scan: 6 months
Page 37-38	**This study** Active TB is an exclusion criterion for entry to this study. Patients will be screened for active TB at every visit, using the 4-question screening tool in the South African guidelines. Those screening positive will be investigated and managed in accordance with the TB guidelines.	**This study:** Active TB is an exclusion criterion for entry to this study. At the screening visit, those who screen TB-negative and are eligible for isoniazid preventive therapy (IPT), as per national guidelines, will be offered IPT and initiated on IPT. At every visit, every participant will be screened for tuberculosis using the TB symptom screen, as is standard of care within the national treatment guidelines. Those who screen positive on the TB symptom screen will be investigated as per site Clinical Assessments SOP, and if active TB is diagnosed, referred for initiation of TB treatment.
		Study participants in treatment groups 1 and 2 who develop TB will have DTG trough, plasma TFV trough, and PBMC TFV-DP concentrations measured at four visits: when TB diagnosis is confirmed (DTG dose will be increased to 12-hourly, and those in group 1 will be switched from TAF to TDF); at the next two scheduled study visits; and a final PK visit 4-8 weeks after stopping rifampicin, after daily dosing of DTG has resumed and participants in group 1 have been switched back to TAF. All PK visits should coincide with scheduled visits as per the SoE as much as possible. See appendix 12.5: Schedule of PK Assessments in Participants with TB. All PK samples will be centrifuged, and plasma will be stored at -80◦C for analysis in a batch at the end

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
		of the study. As the PK specimens will only be analysed at the end of the study, DTG, TFV and TFV-DP drug concentrations will not be made available to the study clinician, who will rely on viral load monitoring data to make clinical decisions. Batch analyses of all the PK samples will be done at the accredited pharmacology laboratory at UCT, where validated TFV assays are run. DTG and TFV-DP assays will be developed and validated before the end of the study. UCT will process and analyse all the pharmacokinetic specimens.
Page 38	**6.6 Management of single drug substitutions** Any modification of the antiretroviral regimen will result in patient exclusion, except in TB, in the manner described above. Any allergic reaction that is felt to be study drug-related, will be assessed and drug interrupted as felt necessary by the investigator; grade 3 or 4 reactions will lead to immediate and permanent discontinuation.	**7.7 Management of single drug substitutions** For participants in Treatment Groups 1 and 2 who develop TB during the study, study medication must be modified as described in section 7.6. Other permitted substitutions are described in section 6.5. Any allergic reaction that is felt to be study drug-related, will be assessed and drug interrupted as felt necessary by the investigator; grade 3 or 4 reactions that are deemed to be related to any study medication will lead to immediate and permanent discontinuation.
Page 39	**7.0 Study Treatments** All study medications are to be orally self-administered as directed according to the package insert. Open label study medication will be supplied to the patient at enrolmment and Week 4-84. All medications used in this study will be provided as open label medications. Patients will be instructed to bring all used and unused study medication bottles with	**8.0 Study Medication** Patients in treatment group 3 will be advised to begin treatment on the evening of Day 0, Week 0, and those in treatment groups 1 and 2 on the morning of Day 1 Week 0. It is also advised that patients in treatment groups 1 and 2 take their study medication in the morning while those in treatment group 3 take their study medication at night. This is important for minimising treatment related side effects and for the pharmacokinetic assessments. However, the first dose may be delayed up to one week following randomisation. The start date should be noted.

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
	them to each study visit. Those on the two DTG-containing arms will be requested NOT to take their medication on the morning of their study visits	
Page 42	**8.2 Secondary Efficacy Endpoints** • Change from baseline in plasma HIV-1 RNA levels by visit • Change from baseline of CD4 count by visit • Analysis of PK data, virological efficacy and tolerability in those becoming pregnant • Analysis of PK data, tolerability and virological efficacy in those developing TB	**9.2 Secondary Efficacy Endpoints** • Virological efficacy and tolerability in the 12-<19 year age group • Analysis of PK data, virological efficacy and tolerability in those becoming pregnant • Analysis of PK data, tolerability and virological efficacy in those developing TB • Analysis of PK interactions between EFV and INH in participants in treatment group 3 receiving IPT • Analysis of PK interactions between TFV, DTG and INH in participants receiving IPT (contingent on funding)
Page 42	**8.3 Safety Endpoints** The main safety endpoint is the assessment of the tolerability and safety of the three treatment combinations as measured by the nature and frequency of AEs and changes in questionnaires, vital sign measurements, physical examination findings, clinical laboratory analyses and concomitant medications.	**9.3 Safety Endpoints** **Safety Assessments:** The main safety endpoint is the assessment of the tolerability and safety of the three treatment combinations. Safety analyses will be performed on vital sign measurements; physical examination findings; clinical laboratory analyses, including evaluation of changes in full blood count, biochemistry, serum and urine glucose, lipids, liver function tests, inflammatory markers, measures of renal function, urine dipstix and creatinine clearance; other investigations (such as DEXA scans); and monitoring AEs and concomitant medications throughout the study. All laboratory endpoints will have a window of 4 weeks before and after the specific visit time point. DEXA scans should be done within one month of enrolment; subsequent DEXA scans should occur within the window for the scheduled study visit
Page 53	**Schedule of PK Assessments for Pregnant Women** Not in version 2.0	**12.3. Schedule of PK Assessments for Pregnant Women** New table

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
Page 55	**. Schedule of PK Assessments in Participants with TB** Not in version 2.0	**12.5. Schedule of PK Assessments in Participants with TB** New table
Page 57		15. Sax P et al. Phase 3 randomized, controlled clinical trial of bictegravir coformulated with FTC/TAF in a fixed-dose combination (B/F/TAF) vs dolutegravir (DTG) + F/TAF in treatment-naïve HIV-1 positive adults: week 48 results. IAS 2017, Paris. Late breaker poster abstract TUPDB0201LB. 16. Wijting I et al. Integrase inhibitors are an independent risk factor for IRIS: an ATHENA cohort study. CROI 2017. February 13-16, 2017. Seattle. Poster abstract 731. http://www.croiconference.org/sessions/integrase-inhibitors-are-independent-risk-factor-iris-athena-cohort-study (Abstract and poster link) 17. Dutertre M et al. Initiation of art based on integrase inhibitors increases the risk of IRIS. CROI 2017. February 13-16, 2017. Seattle. Poster abstract 732. http://www.croiconference.org/sessions/initiation-art-based-integrase-inhibitors-increases-risk-iris (Abstract and poster) 18. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2017. http://www.apregistry.com/forms/interim_report.pdf (PDF) 19. Zash R et al. Dolutegravir / tenofovir / emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. IAS 2017. 23-26 July 2017. Paris, France. Abstract MOAX0202LB 20. Thorne C et al. Pregnancy and neonatal outcomes following prenatal exposure to

Page and section of protocol	Old Text (Version 2)	New Text (Version 3)
		dolutegravir. IAS 2017. 23-26 July 2017. Paris, France. Abstract MOPEC0609 New references added in version 3.0

STATISTICAL ANALYSIS PLAN

Protocol title: A 96-week randomised, phase 3 non-inferiority Study of DTG+TAF+FTC compared with DTG+TDF+FTC and EFV+TDF+FTC in patients Infected with HIV-1 starting first-line antiretroviral therapy.	
Protocol number: WRHI 060	**Applicable Protocol Version :** Version 3, 12 December 2017
Author: Dr Andrew Hill Protocol statistician	**Sponsor representative(s):** Prof WD Francois Venter Global PI: ADVANCE Study Dr M Moorhouse Co-PI: ADVANCE Study C M Serenata Technical Head: OPTIMIZE G Akpomiemie Research Operations Manager WITS RHI
	Date: 01-Mar-2019
Revision history: Draft 3	

The layout of this document is based on the Guideline on the International Conference of Harmonization (ICH E9).

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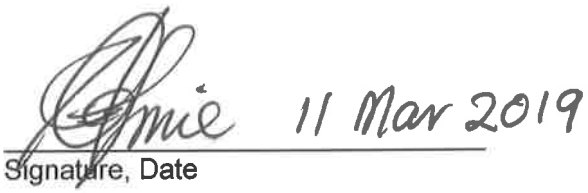

11 Mar 2019

Signature, Date

Glossary of abbreviations and definitions

AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
ATC	Anatomical therapeutic chemical
AUC_{0-inf}	Area under the plasma concentration vs. time curve, from 0 to infinity
AUC_{0-t}	Area under the plasma concentration vs. time curve, from 0 to last observed concentration
BMI	Body Mass Index
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration (at steady state)
CL_{ss}/F	Apparent clearance at steady state
%CV	Percentage coefficient of variation
DEXA	Dual Energy X-ray Absorptiometry
DSMB	Data safety monitoring board
DTG	Dolutegravir
EFV	Efavirenz
FDA	Food and Drug Administration
FTC	Emtricitabine
HIV	Human immunodeficiency virus
HBsAG	Hepatitis B surface antigen
HREC	Wits Human Research Ethics Committee
ICH	International Conference on Harmonisation
IMP	Investigation medicinal product
INSTI	Integrase strand transfer inhibitor
ITT	Intention to treat
MCC	Medicines Control Council
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of observations
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PK	Pharmacokinetics
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
$T_{½}$	Terminal elimination phase half-life
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil
TB	Tuberculosis
T_{max}	Time of maximum observed concentration, relative to last dose
UACR	Ratio of urine albumin to creatinine
ULN	Upper limit of normal

UPCR	Ratio of urine protein to creatinine
V_z/F	Apparent volume of distribution
WHO	World Health Organisation
WHODD	WHO Drug Dictionary
Wits RHI	Wits Reproductive Health and HIV Institute
WSC	Wits RHI Safety Committee
λ_z	Elimination rate constant

General

The Statistical Analysis Plan (SAP) provides details regarding the statistical methods to be used in analysing trial data and defines the statistical programming specifications and proposed tables and listings. It defines the variables and the different study populations and additional details of the analyses not provided in the clinical protocol.

The SAP is based on the final clinical protocol, dated 08 November 2016.

The SAP will be finalised prior to database lock. Any deviations from the SAP will be described in the clinical study report.

Overview of trial

Decreasing total drug doses of antiretroviral agents represents an untapped possibility for decreasing costs and toxicity, if efficacy can be maintained. Manufacturing costs for originator companies comprise only a fraction of the price of the drug. However, with the rise of generic manufacturers, as well as increased licensing by originator companies to other pharmaceutical companies, the cost of raw materials to manufacture the drugs (active product ingredient, API) has become a more significant component of cost as prices have decreased. Thus, regimens that have an overall lower dose of medications could have a notable impact on the overall cost of ART, as well as often reducing side effects.

Trial Objective

The primary objective of this study is to demonstrate the non-inferiority of dolutegravir (DTG) and tenofovir alafenamide fumarate (TAF) plus emtricitabine (FTC) when compared with DTG and tenofovir disoproxil fumarate (TDF) plus FTC or compared with efavirenz (EFV) and TDF plus FTC in the first-line treatment of patients infected with human immunodeficiency virus (HIV)-1 as determined by the proportion of patients in each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

Efficacy endpoints

Primary efficacy endpoint

The primary efficacy endpoint is the proportion of patients with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48. Patients who do not have an HIV-1 RNA sample taken at Week 48 will be considered as not having achieved undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Week 48.

Secondary efficacy endpoints

- Proportion of patients on each regimen with undetectable plasma HIV-1 RNA levels (< 50 copies/mL) at Weeks 48 and 96, using the standardised FDA Snapshot algorithm.
- Proportion of patients with plasma HIV-1 RNA levels < 200 copies/mL at Week 96.
- Time to virologic failure (defined as confirmed HIV-1 RNA levels ≥ 1000 copies/mL at Week 12-24 or ≥ 200 copies/mL at or after Week 24).
- Change from screening in plasma HIV-1 RNA levels at each visit.
- Change from screening in plasma CD4 levels at each visit.
- Analysis of pharmacokinetic (PK) data, virological efficacy and tolerability in those developing TB.
- Analysis of PK data, virological efficacy and tolerability in those becoming pregnant.
- Analysis of DEXA scans and BMI data collected from participants from Week 4-48
- Change in weight from screening at each visit

Safety Assessments

Safety analyses are to be performed on physical examination findings, vital sign measurements, clinical laboratory analyses, other investigations (such as DEXA scans) and monitoring AEs and concomitant medications throughout the study.

Study Design

This is an open label randomised, non-inferiority (10% non-inferiority margin), phase 3 study to assess the efficacy and safety of DTG (50 mg once daily [QD]) administered in combination with TAF (25 mg QD) and FTC (200 mg QD) compared to DTG (50 mg QD) administered in combination with TDF (300 mg QD) and FTC (200 mg QD) and compared to EFV (600 mg QD) administered in combination with TDF (300 mg QD) and FTC (200 mg QD) over 96 weeks in patients with HIV-1 infection eligible for first-line ART.

1053 male and female patients aged 12 and older infected with HIV-1 who are eligible for first-line ART were randomly assigned in a 1:1:1 ratio (351 patients per treatment group) to Treatment Group 1 (DTG + TAF + FTC) or Treatment Group 2 (DTG + TDF + FTC) or Treatment Group 3 (EFV + TDF + FTC). The 12-18 year age group was enrolled and randomised separately; enrolment was estimated at 30-40 per arm (total 90-120)[1]. The study included screening and enrolment visits, 8 study visits from Week 4 to Week 84, and an end-of-study visit at Week 96. Study medication pill counts were performed at each follow-up visit.

On request of the Data Safety Monitoring Board (DSMB) and South African Medicines Control Council (MCC), the 12-18 year age group was enrolled separately and this group will be analysed separately.

[1] These are a subset of the total n of 1110

The DSMB also requested separate analyses on the 12-15 year age group.

Schedule of events

The schedule of events is presented in Protocol V2.

Study Visit	Baseline		Visit 1	Follow-up Visits: 2, 3, 4, 6, 7, 8	Endpoints	
	Screening	Enrolment			Visit 5	Visit 9 /EOS
Study Week	–	0	4	12[a], 24, 36, 60, 72, 84	48	96
Study Window (days)	-60 to -1	0	-13/+28	-41/+42	-41/+42	-41/+42
Informed consent	X					
Demography	X					
Medical history/pre-existing conditions	X	X				
TB symptom screen	X	X	X	X	X	X
Adverse event monitoring		X	X	X	X	X
Previous/concomitant medications	X	X	X	X	X	X
Height/weight measurement	H/W	W	W	W	W	W
Vital sign measurements (BP, pulse rate, temperature[b])	X	X	X	X	X	X
Physical examination	X	X[c]	X[c]	X[c]	X[c]	X[c]
Mental health screening		X	X	X	X	X
Sleep questionnaires		X	X	X	X	X
Neuropathy screen		X	X	W12 and 24 only	X	
Actigraphy (in subset)		X		W24 only	X	
Adherence questionnaire			X	X	X	X
Quality of life questionnaire		X	X	X	X	X
Urine pregnancy testing	X	X	X	X	X	X
Hepatitis B antigen		X				
Haematology, biochemistry	X		X	X	X	X
Confirm HIV-1 status with ELISA	X					
Plasma HIV-1 RNA	X		X	X	X	X
CD4 cell count	X			W24 only	X	X
Creatinine clearance (Cockcroft-Gault) and urine dipstix	X		X	X	X	X
Serum (fasting) and urine glucose		X	X	X	X	X
Lipid panel (fasting)		X		W24 only	X	X

Study Visit	Baseline		Visit 1	Follow-up Visits: 2, 3, 4, 6, 7, 8	Endpoints	
	Screening	Enrolment			Visit 5	Visit 9 /EOS
Study Week	–	0	4	12[a], 24, 36, 60, 72, 84	48	96
Study Window (days)	–60 to –1	0	-13/+28	-41/+42	-41/+42	-41/+42
Liver function tests		X		W12, 24, 36, 60	X	X
Measures of renal function		X		X	X	X
Blood for genetic/epigenetic assessment		X	X	W12 and 24	X	
Urine for storage		X	X	X	X	X
Plasma preparation and serum cryopreservation		X	X	X	X	X
PBMC preparation and storage		X			X	X
PK specimens for adolescents, pregnant women, and patients on TB treatment			X	X	X	X
DEXA scans*		X			X	X
Inclusion/exclusion criteria	X	X				
Randomisation		X				
Study medications dispensed		X	X	X	X	
Study treatment/medication accountability		X	X	X	X	X

* DEXA scans will not be performed in participants who become pregnant and elect to stay in the study (for the duration of the pregnancy)

[a] – Week 12 visit window is -27/+42 days

[b] – Only at screening and Symptom-led at other visits

[c] – Symptom-led physical examination

Table 1: Schedule of events

Visit[a]	Pregnancy confirmation	GW 20[b]	GW 24[b]	Follow-up Visits[b]: GW 28, 32, 36, 40	Delivery
Study Visit Window	+ 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks
Informed consent[c]	X				
TB symptom screen	X	X	X	X	X
Adverse event monitoring		X	X	X	X
Previous/concomitant medications	X	X	X	X	X
Weight measurement	X	X	X	X	X
Vital sign measurements	X	X	X	X	X
Physical examination (targeted)	X	X	X	X	X
Urine and blood pregnancy testing	X				
Urine dipstix	X	X	X	X	X
Foetal ultrasound	X[d]		X[e]		

[a] All other study procedures will be as for non-pregnant participants

[b] GW = gestational week; Where possible, visits will be aligned with scheduled protocol visits

[c] Sign informed consent for pregnant women to continue in Advance

[d] Gestational age scan

[e] Foetal anomaly scan

Protocol V2: Schedule of events for pregnant women

Treatment period

Patients began treatment on the evening of Day 0, Week 0. Patients returned to the site at pre-defined time intervals for clinical assessments and blood sampling. At all visits patients were questioned about adverse events (AEs) to assess their wellbeing, and to verify concomitant medications.

Study medication

Treatment Group 1: DTG 50 mg + TAF 25 mg + FTC 200 mg administered once daily orally over 96 weeks.

Treatment Group 2: DTG 50 mg + TDF 300 mg + FTC 200 mg administered once daily orally over 96 weeks.

Treatment Group 3: EFV 600 mg + TDF 300 mg + FTC 200 mg administered once daily orally over 96 weeks.

Details of the study medication are available in Table .

Study Medications	Tablet/Capsule Strength	Dosage Regimen
Treatment Group 1a (2 tablets)		
DTG	50 mg	Once daily
TAF	25 mg	Once daily
FTC	200 mg	Once daily
Treatment Group 2b (2 tablets)		
DTG	50 mg	Once daily
TDF	300 mg	Once daily
FTC	200 mg	Once daily
Treatment Group 3c (1 tablet)		
EFV	600 mg	Once daily
TDF	300 mg	Once daily
FTC	200 mg	Once daily

Abbreviations: DTG, dolutegravir; TAF, tenofovir alafenamide fumarate; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; EFV, efavirenz.

a TAF and FTC combined as a single tablet
b TDF/FTC combined as a single tablet
c TDF/FTC/EFV combined as a single tablet

Table 3: Study medication

Sample size justification

A sample size of 351 patients per arm (1053 total, including 90-120 in the 12-18 year age group) provides at least 80% power to establish non-inferior efficacy for the DTG + TAF + FTC arm, compared to each of the other study arms. A non-inferiority margin of -10% is now standard in the design of phase 3 randomised trials of antiretrovirals for treatment naïve patients. The power to establish non-inferior efficacy for the DTG + TDF + FTC arm compared to the EFV + TDF + FTC arm was set to 80%.

The 1053 patients were randomly assigned in a 1:1:1 ratio (351 patients per treatment group). The 12-18 year age group was enrolled and randomised separately; 30-40 per arm (total 90-120).

Replacements

Patients who discontinue participation in the study for any reason after randomisation were not replaced.

Study population

The study population consisted of patients infected with HIV-1. No CD4 threshold was taken into consideration for the selection of study patients. The inclusion and exclusion criteria are listed in the Study Protocol dated 08 November 2016 (section 4).

Study procedures

The Study Procedures are listed in the Study Protocol dated 08 November 2016 (section 5) in conjunction with the schedule of events listed in the appendices to the study protocol.

Statistical Analysis Conventions

All continuous variables and changes from baseline will, where applicable, be analysed descriptively, citing the mean, standard deviation (SD), median, minimum, maximum and number of observations (n). Categorical variables will, where applicable, be summarised by means of frequency tables.

Demographic and Background Variables

Screening

- Demographic: age, sex, race, marital status, weight, height, BMI
- TB symptom screen
- Physical examination
- Vital signs: Systolic and diastolic blood pressure, pulse rate, temperature
- Urine pregnancy test (if applicable)
- Clinical laboratory: haematology, biochemistry, plasma HIV-1 RNA, Mean CD4 count, creatinine clearance

Enrolment

- Symptom-led physical examination
- Sleep questionnaire
- Neuropathy screen
- Country of Origin

- Quality of life questionnaire
- Urine pregnancy test (if applicable)
- HBsAg
- Clinical laboratory: UPCR, UACR, retinol binding protein to creatinine ratio, β2 microglobulin to creatinine ratio, fractional excretion of uric acid and phosphate
- DEXA scan to determine bone density as well as body fat percentage and whole body lean mass

Medical history

Medical history was obtained at the screening and enrolment visits prior to the participant commencing study drug administration, including both past and present medical conditions. The following was recorded in the CRF:

- Details of disease/procedure
- Start date
- Stop date (or ongoing if applicable)

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1.

Safety variables (see schedule of events under study design for collection times)

Adverse events

An AE is defined as any untoward medical occurrence in a patient in a clinical investigation with a medicinal product regardless of its causal relationship to study medication. Patients were instructed to contact the principal investigator or designee at any time after randomisation if any symptoms developed.

A treatment-emergent AE is defined as any event, including laboratory abnormalities, not present before exposure to study medication or any event already present that worsens in either intensity or frequency after exposure to study medication.

An AE is also any of the following occurring after study randomisation:

- Complications that occur as a result of a protocol-mandated procedure after randomisation to study medications.
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of the study after randomisation to study medications.
- Reasons for and complications arising from a termination of pregnancy due to medical and/or surgical reasons.

An AE did not include the following:

- Medical or surgical procedures performed. However, the condition that led to the procedure was deemed an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before screening visit that did not worsen.
- Situations where an untoward medical occurrence had not occurred (e.g., hospitalisation for elective surgery).
- Overdose of study medication without clinical sequelae.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

Adverse events were assessed (reported and/or observed) and documented from enrolment once the patient was randomised to study medications, until exit from the study (i.e. early withdrawal or end-of-study visit at week 96). Any medical conditions observed at screening and which did not exclude the patient from the study were documented as pre-existing medical conditions. All AEs were followed to adequate resolution. Any ongoing AE at early withdrawal or the end-of-study visit was followed-up until satisfactory resolution or until the investigator deemed the event to be chronic or the patient to be stable, up to a maximum of 30 days after the last visit.

AEs were documented in chart notes and those of grade 3 and 4 and unexpected adverse drug events were entered into the AE case report form (CRF). The grading of AEs was according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.0 November 2014 (see Appendix 1). In the case where grading for some laboratory toxicities require upper limits of normal (ULN), the BARC Global Central Laboratory chemistry and haematology reference ranges will be used to identify appropriate ULNs based on the patient's age and sex. (See Appendix 2).

Serious Adverse Events (SAE)

An SAE was defined as any AE that:

- Resulted in death
- Was immediately life threatening (including events which put patients at risk of death at the time of the event but not events which might have caused death if more severe)
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly or birth defect
- Of clinical significance in the opinion of the investigator

Any SAE should have been documented in an SAE CRF. All SAEs and unexpected ADRs were reported to the Wits RHI Safety Committee (WSC), by email, within 24 hours from the time site personnel first learn of the event.

Assessment of AEs

The severity or intensity of an AE refers to the extent to which an AE affects daily activities. The severity of all AEs, including laboratory abnormalities, was graded according to the Division of AIDS grading table (version 2.0, November 2014).

The relationship or association of the study medication in causing or contributing to the AE will be characterised using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study medication and the reported event.
Possibly related:	This relationship suggests that a potential causal relationship exists between drug administration and the AE, with a reasonable time relationship to drug intake, but could also be explained by other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction).
Related:	This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

All SAEs that occur during the study (regardless of relationship to study medication) were reported in detail and followed-up until the events resolved, stabilised, or became non-serious. All SAEs were reported to the Human Research Ethics Committee (HREC) according to HREC requirements. Medical and scientific judgement were exercised in deciding whether an AE, which did not meet the routine definition of an SAE but was important from a safety perspective and might have jeopardise the patient or required intervention to prevent one of the other outcomes listed in the definition of serious, was considered as serious.

Clinical laboratory test

Haematology, biochemistry and various other assessments (Refer to protocol section 5.3).

DEXA Scan

Area, BMC, BMD (total and Ward's), T-score, Z-score, AM (%), WHO Category of Diagnosis and fracture risk assessment; Whole body fat, Trunk fat, Limb fat, Percentage whole body fat, Whole body lean mass, Trunk lean mass, Limb lean mass.

Body Composition

Weight and BMI.

Pregnancy test

Urine pregnancy test, for women of child bearing potential.

Vital signs

Systolic and diastolic blood pressure, temperature and heart rate.

Physical examination

Compulsory screening examination and symptom-led thereafter (including TB symptom screen).

Prior and concomitant medication

Concomitant medication that was monitored during the study.

Analysis Populations

The following analysis sets will be used in the statistical analyses:

Full analysis set:	All trial participants that signed informed consent.
All-randomised set:	The all-randomised set will consist of all randomised patients, regardless of whether any study treatment dosing was completed. Participants will be analysed according to the treatment they were randomly assigned to.
Intent to treat (ITT) set:	The ITT set will consist of those participants from the all randomised set, who received at least one dose of study medications.
*Per-protocol set:	The PP set will consist of those participants from the all randomised set, who fully comply with the inclusion and exclusion criteria, have received at least 80% of all doses of study treatment up to Week 48, and have an evaluable plasma HIV-1 RNA level assessment at Week 48. Patients will be analysed according to the treatment they received.
Safety set:	The safety set will consist of all patients who received at least one dose of randomly assigned study treatments. All safety analyses will be performed using the safety set. Patients will be analysed according to the treatment they received.

*The following may be considered major protocol deviations to exclude a participant from the PP population:

- ARV pre-treated patients in violation of the inclusion and exclusion criteria,
- Participants taking the wrong treatment (not randomised correctly)
- Participants using other investigational ARVs in addition to their randomised treatment
- Patients who discontinue from the study or are lost to follow up, with no significant adverse events

- Patients taking prohibited concomitant medications

All efficacy analyses will be performed using the all-randomised, ITT and PP sets. All safety analyses will be performed using the safety set.

The Intent to treat (ITT) population will be the primary population for the statistical analysis. The safety and all-randomised populations will only be analysed if there is a difference of more than 10 patients (1%) from the ITT populations. The Per Protocol population will only be conducted if there is a difference of at least 20 patients (2%) from the ITT population.

General Analysis Methods

Statistical Significance Level

The three primary treatment comparison hypotheses are tested according to the predefined sequence, namely:

- Treatment group 1 versus treatment group 3 (with Treatment 1 as the test treatment and treatment 3 as the standard treatment)
- Treatment group 2 versus treatment group 3 (with Treatment 2 as the test treatment and treatment 3 as the standard treatment)
- Treatment group 1 versus treatment group 2 (with Treatment 1 as the test treatment and treatment 2 as the standard treatment)

Each hypothesis is assigned an initial significance level (alpha) of 0.017 (that is 0.05 divided by the number of comparisons, namely 3) and with each rejection of a hypothesis, the significance level used for testing the next hypothesis accumulates. The significance level to be used in the second comparison is 0.017 * 2 = 0.034, and if rejected the third comparison will be done at an alpha-level of 0.05. If the second test is significant at the p=0.034 level, the third test will use a p-value of 0.05. Whenever a hypothesis is not rejected, the next hypothesis in the sequence will be tested at the initially allocated p=0.017 level. Non-inferiority will be evaluated using two one one-sided tests.

Non-inferiority limit

For the first comparison (groups 1 *vs.* 3), a 98.3% confidence interval will be calculated, and should the lower limit of this interval be ≥ -0.1, the deduction would be that the test treatment in not inferior to the standard treatment. The confidence intervals to be calculated for the second (groups 2 *vs.* 3) and third comparison (groups 1 *vs.* 2), should the previous hypothesis be rejected, is 96.6% and 95%, respectively.

Efficacy analyses

All efficacy endpoint analyses will be done on the all-randomised, ITT and PP populations.

Primary efficacy endpoint

Derivation(s):

- Participants with undetectable plasma HIV-1 RNA levels will be defined as those with plasma RNA levels of < 50 copies/mL.
- Any HIV RNA sample with an initial result of 50-199 copies/mL will be retested. Only if the second result is above 50 copies/mL will the patient be classified as having HIV RNA >50 copies/mL. This is in order to avoid patients being classified as treatment failures if their HIVRNA level is marginally above 50 copies/mL owing to testing error.
- If a participant has multiple HIV RNA samples within a single time period window, the latest HIV RNA result within the window will be used.
- Participants with missing week 48 data will be classified as undetectable if HIV RNA samples from week 36 and wee 60 are both <50 copies/mL. All other participants with missing data at week 48 will be considered as not having reached undetectable plasma HIV-1 RNA levels.
- Participants who have stopped randomised medication but are still being followed up in the trial with HIV RNA data at the week 48 visit will be included in this analysis (Intent to Treat approach).

***DO NOT have data on patients switching treatments

Analysis:

The proportion of participants with undetectable plasma HIV-1 RNA levels at Week 48, will be calculated for each treatment group and summarised. Results will also be listed on an individual basis.

Confidence intervals will be estimated for the difference in proportions, as described above. Non-inferiority of the respective test and standard treatment will be concluded if the lower limit of the estimated confidence interval is $\geq$ -0.1. The general hypothesis test structure to be applied will take the following form:

$$H_0: \theta - \mu \geq -0.1$$

$$H_1: \theta - \mu < -0.1$$

where, μ, represents the expected value of the active control treatment group and θ represents the expected value of the test treatment group, as given below. The results of this analysis will be summarised in a table. Results will be graphically presented in the form of a forest plot.

Comparison	Test treatment	Active control treatment
Groups 1 *vs.* 3	Group 1	Group 3
Groups 2 *vs.* 3	Group 2	Group 3
Groups 1 *vs.* 2	Group 1	Group 2

The primary analysis will be repeated for the adolescent cohort.

Secondary efficacy endpoints

Secondary endpoint no. 1

Derivation(s) - 'FDA snapshot algorithm':

- Participants with undetectable plasma HIV-1 RNA levels will be defined as those with plasma RNA levels of < 50 copies/mL. HIV-1 RNA results from all participants should be included in this analysis, whether the participant is on or off IMP. Successes/responders will be defined as those participants on each regimen with undetectable plasma HIV-1 RNA levels at Weeks 48 and 96. Applicable time windows are given below:

Visit week	Window (in weeks)	Window (in days)
04	0-06	0-42
12	06-18	43-126
24	18-30	127-210
36	30-42	211-294
48	42-54	295-378
60	54-66	379-462
72	66-78	463-546
84	78-90	547-630
96	90-102	631-714

Success/response should be determined by the last available measurement while the participant is on treatment and continued with the trial within the time window (as outlined above).

Examples:
- HIV-RNA = 580 copies/mL at Day 336, HIV-RNA below 50 copies/mL on Day 350. This should be categorized as HIV-RNA below 50 copies/mL, even if an aliquot from the same sample was retested.
- In the rare example that someone would have HIV-RNA below 50 copies/mL at Day 336 and then equal to or above 50 copies/mL at Day 350, the result would be counted as above 50 copies/mL (we believe this will be rare, because undetectable patients would not likely have a second lab result in a window).

- Participant missing week 48 HIV RNA sample, HIV-RNA below 50 copies/mL on day 275, HIV-RNA below 50 copies/mL on day 415. This should be categorised as HIV-RNA below 50 copies/mL.

For participants where no data were recorded within the time window, the reason for missing data should be counted. Reasons include:

1. Participants on study, but missing data in window.
    a. If a participant has no data during days 295 to 378, but have HIV RNA <50 copies/mL during both the week 36 window and week 60 window, the participant would be categorised as HIV-RNA below 50 copies/mL
    b. If a participant has no data during days 295 to 378, and have HIV RNA <50 copies/mL during only one of the week 36/week 60 window's, the participant would be categorised as HIV-RNA > 50 copies/mL. For example, if there is no data during Days 295 to 378, on day 280 HIV-RNA is <50 copies/ mL and on day 382 HIV-RNA is 56, the participant would be categorised as HIV-RNA > 50 copies/mL.
2. Any participant who discontinued because of an AE or death before the week 48 window should be classified as Discontinued: AE or Death (as appropriate), if the HIV-RNA is below 50 copies/mL at the time of discontinuation. However, if a patient has an HIV-RNA value in the week 48 time window and discontinues after the viral load was tested in the time window, the viral load data should be used to classify the patient's response. This is the Virology First hierarchy.
    a. Example: HIV-RNA below 50 copies/mL at Day 336 and discontinues because of AE or even dies on Day 360 — this person is categorized as having HIV-RNA below 50 copies/mL. Likewise, if HIV-RNA is 552 copies/mL on Day 336 and the patient discontinues on Day 360, the patient is categorized as having HIV-RNA equal to or above 50 copies/mL.

3. Any participant who discontinued for Other Reasons before the week 48 window should be classified as Discontinued: Other Reasons, if the HIV-RNA is below 50 copies/mL at the time of discontinuation.
    a. The examples above also apply to this category.
4. If a participant discontinues from the study before the week 48 window and HIV RNA is equal to or above 50 copies/mL, then the patient should be included in the HIV-RNA equal to or above 50 copies/mL and not in the Discontinued for AE or Death/ Discontinued for Other Reasons rows.
    a. To further clarify, for patients who Discontinued, it is important to realize that in the Virology First hierarchy only patients who have achieved virologic suppression can be counted as Discontinued for Other Reasons or Discontinued for AE/death.
    b. If a patient discontinues because the subject withdrew consent and his or her HIV-1-RNA result at the time of discontinuation was equal to or above 50 copies/mL, then he or she should be categorized as HIV-RNA equal to or above 50 and NOT as Discontinued for Other Reasons.

c. However, if a patient discontinued because of Lost to Follow-Up and the last HIV-RNA result was 49 copies/mL, then the patient can be categorized as Discontinued for Other Reasons.
d. If patients changed background treatment, they should be considered an efficacy failure and captured in the HIV-RNA equal to or above 50 copies/mL row.

***DO NOT have data on patients changing background treatment

Additional derivation(s):

- Change from baseline HIV-RNA levels will be calculated with baseline taken as the last non-zero observation taken prior to IMP administration

Analysis:

Proportion of responders, using the standardised FDA Snapshot algorithm, will be summarised by means of a frequency table. A two-sample test of proportions will determine significant differences between treatment groups. Plasma HIV-1 RNA levels will be listed per visit (visits 4-96) on an individual basis per treatment group. Changes from baseline will be calculated and presented in an additional listing. Observed (both linear and log transformed) and change from baseline plasma HIV-1 RNA levels will also be presented graphically in the form of bar graphs.

Secondary endpoint no. 2

Derivation(s):

- Participants with undetectable plasma HIV-1 RNA levels will be defined as those with plasma RNA levels of < 200 copies/mL. Successes/responders will be defined as those participants on each regimen with undetectable plasma HIV-1 RNA levels at Week 48.

Analysis:

Proportion of responders at Week 48 will be summarised in a frequency table and a per treatment listed on an individual basis. A two-sample test of proportions will determine significant differences between treatment groups.

Secondary endpoint no. 3

Derivation(s):

- Virologic failure will be defined as confirmed HIV-1 RNA levels ≥ 1000 copies/mL at week 12-24 or ≥ 200 copies/mL at or after week 24

Analysis:

Proportion of patients with virologic failure will be summarised and listed.

Secondary endpoint no. 4

Derivation(s):

- Virologic failure will be defined as confirmed HIV-1 RNA levels ≥ 1000 copies/mL at week 12-24 or ≥ 200 copies/mL at or after week 24
- Time to virologic failure will be calculated in days as follows:
  - τ = FLOOR (Date of first recorded virologic failure − date of first IMP administration)
- Gender
  - Female = 0
  - Male = 1
- Use of prohibited concomitant medications as defined in the protocol
  - Yes = 1
  - No = 0

Secondary endpoint no. 5

Derivation(s):

- None

Analysis:

Individual patient CD4 counts will be summarised and listed by treatment and visit, together with changes from screening/enrolment CD4 values. Observations (linear) will also be presented graphically, over time, in the form of line plots.

This analysis will be repeated for the adolescent cohort.

Secondary endpoint no. 6

Derivation(s):

- None

Analysis:

Individual patient plasma HIV-1 RNA levels will be summarised and listed by treatment and visit, together with changes from screening/enrolment plasma HIV-1 RNA levels. Observations (linear and log transformed) will also be presented graphically, over time, in the form of line plots.

This analysis will be repeated for the adolescent cohort.

Secondary endpoint no. 7

Derivation(s):

- None

Analysis:

The following data/estimations will be summarised in those patients that develop TB:

- Pharmacokinetic (PK) data (Non-compartmental analysis)
  - C_{max}, C_{min}, T_{max}, AUC_{0-t}, AUC_{0-inf}, CL_{ss}/F, V_z/F, $T_{½}$, λ_z
- Virological efficacy
  - Frequency table of successes *vs.* failures
- Tolerability
  - AE summary table, by preferred term

This analysis will be presented in a supplementary analysis plan.

Secondary endpoint no. 8

Derivation(s):

- As for secondary endpoint no. 7

Analysis:

As for secondary endpoint no. 7 but analysing those subjects that fell pregnant during the trial.

Secondary endpoint no. 9

Derivation(s):

- None

Analysis:

Individual patient weight will be summarised and listed by treatment and visit, together with changes from screening/enrolment weight values. Mean change in weight from baseline will be presented graphically, over the study period, in the form of a bar graph.

Secondary endpoint no 10.

Derivation(s):

- None

Analysis:

Individual patient DEXA results will be summarised and listed by treatment and visit, together with changes from baseline DEXA values. DEXA measures will include total whole-body fat, limb fat, trunk fat, total body percentage fat, and lean mass. Individual participants will be categorised into underweight, healthy, overweight and obese based on gender and age specific DEXA categories for percentage of whole-body fat. Additionally, BMI will be summarised and listed by treatment and visit, together with changes from baseline BMI values.

Safety analyses

Safety analyses will be performed using the Safety analysis set only. Changes in vital sign measurements, physical examination data, previous and concomitant treatments, medical history, mental health, sleep, neuropathy screen and quality of life questionnaires, actigraph readings, urine dipsticks, clinical laboratory parameters, lipids, creatinine clearance (Cockcroft-Gault formula > 18 years old; modified Cockcroft-Gault ≤ 18 years old), measures of renal function, and DEXA will be summarised by treatment group and visit, where relevant.

Adverse events

The following information will be included in the listings: AE number, Investigator description, system organ class (SOC), preferred term, start date/time, stop date/time (or ongoing if applicable), treatment, whether the AE was classified as a SAE, whether the AE was intermittent or a single event, action taken, causality, severity and outcome.

A summary table will be presented, summarised by treatment, SOC and preferred term including the number of patients dosed in treatment group and number and percentage of subjects with AEs.

Additional tables will be presented, summarised by treatment, SOC, preferred term and causality, and severity. Any AEs with missing causality or missing intensity will be treated as 'related' and 'severe' (worse-case scenario) for the tabulations. For the purpose of tabulations, any AE that falls under 'possibly related' will also be treated as 'related'.

All summary tables for AEs will show the number of patients who experienced each AE as well as the number of events each patient experienced. This will be presented in a n (%) n' format. Percentages are based on the number of safety set patients in each treatment group.

In the case that an AE is not coded using the appropriate MEDRA preferred term, these AEs will fall under the category of 'uncoded' and will be presented in the tables under each treatment group.

For the purpose of the safety analysis, only treatment emergent AEs will be presented in the summary tables. Therefore, only AEs that occurred following the patient's start date of the trial will be tabulated.

Prohibited, prior and concomitant medication

Prohibited, prior and concomitant medication will be listed. The listings will include the following information: medication name (trade name), WHO-DD term, ATC, flag (prior/concomitant), start date and time, stop date and time (or ongoing if applicable), dose, dose date and time for each treatment, unit, route, frequency and indication.

Clinical laboratory tests

Laboratory values (haematology and biochemistry) will be listed per visit, treatment and subject. Values outside the laboratory reference ranges will be flagged as CS (clinically significant) or NCR (not clinically significant) in listings. Change from baseline will be presented for each laboratory measurement at each assessment time. Baseline will be taken as the last non-missing observation prior to IMP administration. In addition, laboratory parameters will be summarised by descriptive statistics.

All other laboratory tests will be listed per patient, treatment and visit.

For all clinical laboratory tests, grading will be done according to the Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events. (See Appendix 1) In the case where upper limits of normal (ULN) are used to define a grade, BARC Global Central Laboratory chemistry and haematology reference ranges will be used to identify appropriate ULNs based on the patient's age and sex. (See Appendix 2).

As Gamma-glutamyl transferase (GGT) does not have a DAIDS definition, grading for this toxicity will be done following the same method for grading both Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST). The BARC chemistry reference range contains ULN for GGT based on age and sex.

For example:

- Grade 1 (Mild GGT): 1.25 to <2.5 x ULN
- Grade 2 (Moderate GGT): 2.5 to <5.0 x ULN
- Grade 3 (Severe GGT): 5.0 to <10.0 x ULN
- Grade 4 (Potentially life-threatening): ≥ 10.0 x ULN

Summary tables will also be produced to show the change from baseline in all clinical laboratory results. A Mann-Whitney U test and T test will determine significant differences between treatment groups.

List of haematology and biochemistry tests

Form	Test	Unit	Lab File
Biochemistry	Albumin, serum	g/L	Safety & Serology
Biochemistry	Alkaline Phosphatase	IU/L	Safety & Serology
Biochemistry	Alanine Transaminase /ALT/SGPT	IU/L	Safety & Serology
Biochemistry	Aspartate Transaminase/AST/SGOT	IU/L	Safety & Serology
Biochemistry	Bicarbonate (Total CO2)	mmol/L	Safety & Serology
Biochemistry	Bilirubin Conjugated	umol/L	Safety & Serology
Biochemistry	Bilirubin Total	umol/L	Safety & Serology
Biochemistry	Calcium, serum	mmol/L	Safety & Serology
Biochemistry	Chloride, serum	mmol/L	Safety & Serology
Biochemistry	Cholesterol, serum	mmol/L	Safety & Serology
Biochemistry	Creatinine, serum	umol/L	Safety & Serology
Biochemistry	Creatine Kinase CK/CPK, total	IU/L	Safety & Serology
Biochemistry	CRP - PTA	mg/L	Safety & Serology
Biochemistry	Folic Acid	nmol/L	Safety & Serology
Biochemistry	GGT	IU/L	Safety & Serology
Biochemistry	Glucose (Fasting)	mmol/L	Safety & Serology
Biochemistry	Glucose (Urine Quantitative)	mmol/L	Safety & Serology
Biochemistry	HBA1C (Glycated)	%	Safety & Serology
Biochemistry	HDL, serum	mmol/L	Safety & Serology
Biochemistry	LDH	IU/L	Safety & Serology
Biochemistry	LDL, serum	mmol/L	Safety & Serology
Biochemistry	Phosphate, serum	mmol/L	Safety & Serology
Biochemistry	Potassium, serum	mmol/L	Safety & Serology
Biochemistry	Sodium, serum	mmol/L	Safety & Serology
Biochemistry	Total Protein	g/L	Safety & Serology
Biochemistry	Triglyceride, serum	mmol/L	Safety & Serology
Biochemistry	Urea, serum	mmol/L	Safety & Serology
Biochemistry	Uric Acid, serum	mmol/L	Safety & Serology
Biochemistry	Creatinine clearance	mL/min	Safety & Serology
Flow cytometry	CD4 (%)	%	Safety & Serology
Flow cytometry	CD4 (absolute)	/uL	Safety & Serology
Hematology	Haemoglobin	g/dL	Safety & Serology
Hematology	Mean Cell Volume	fL	Safety & Serology
Hematology	Platelet count	$x10^9/L$	Safety & Serology
Hematology	Neutrophils	$x10^9/L$	Safety & Serology
Hematology	Lymphocytes	$x10^9/L$	Safety & Serology
Hematology	Monocytes	$x10^9/L$	Safety & Serology

Hematology	Eosinophils	$x10^9/L$	Safety & Serology
Hematology	Basophils	$x10^9/L$	Safety & Serology

DEXA Scan

- Frequency tables by treatment group, visit and body area: lumbar spine; and
- left femur; and
- whole body.

DEXA T-score shows the patient's result compared to the ideal peak bone mineral density of a healthy adult. The Z-score compares the patient's DEXA results to the average reference range, which is based on the same age, weight, height and gender of the general population as the patient.

As both the WHO Category of Diagnosis and fracture risk assessment are categorical variables, they will be presented by means of a shift table (showing change in categorical levels). Tables will also be produced to show the change in Bone Mineral Density (BMD) and Bone Mineral Content (BMC) from baseline, by treatment group.

For changes in BMD and BMC over time, for each body area, both a Mann-Whitney U test and T-test will be undertaken to assess for any significant differences between the treatment groups.

DEXA Body Composition

Individual participant's limb, trunk, whole body, trunk: total fat ratio, and percentage of body fat will be summarised and listed by treatment and visit, together with changes from screening/enrolment values. A Mann-Whitney U test and T test will determine significant differences between treatment groups. Additional summaries will also be included for subgroups of all randomised men and women- not including pregnant women.

Individual participants will be categorised into underweight, healthy, overweight and obese based on gender and age specific DEXA categories for percentage of whole-body fat. Participants younger than 20 years old will be excluded from the analysis due to the DEXA categories used. These results will be summarised in a frequency table. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will also be included for subgroups of all randomised men and women- not including pregnant women.

DEXA Categories:

Women 20-40 years old

Classification	Percentage Whole Body Fat
Underfat	< 21%
Healthy	21 - 33%
Overweight	33 – 39%
Obese	> 39%

Women 41-60 years old

Classification	Percentage Whole Body Fat
Underfat	< 23%
Healthy	23 - 35%
Overweight	35 – 40%
Obese	> 40%

Women 61-79 years old

Classification	Percentage Whole Body Fat
Underfat	< 24%
Healthy	24 - 36%
Overweight	36 – 42%
Obese	> 42%

Men 20-40 years old

Classification	Percentage Whole Body Fat
Underfat	< 8%
Healthy	8 - 19%
Overweight	19 – 25%
Obese	> 25%

Men 41-60 years old

Classification	Percentage Whole Body Fat
Underfat	< 11%
Healthy	11 - 22%
Overweight	22 – 27%
Obese	> 27%

Men 61-79 years old

Classification	Percentage Whole Body Fat
Underfat	< 13%
Healthy	13 - 25%
Overweight	25 – 30%
Obese	> 30%

Treatment emergent obesity will also be summarised in a frequency table. Participants who only have one DEXA scan, or those who are classified as obese at baseline will be excluded from this analysis. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will also be included for subgroups of men & women- not including pregnant women.

Individual patient's limb, trunk and whole-body lean tissue will be summarised and listed by treatment and visit, together with changes from baseline lean tissue values. Additional summaries will also be included for subgroups of all randomised men, women- not including pregnant women.

Vital Body Composition

Weight will be summarised and listed by treatment and visit including changes from baseline. Additional summaries will be included for subgroups of women and men. A Mann- Whitney U test and T test will be used to determine significant differences between treatment groups.

BMI will be calculated by dividing individual patient's weight in kg by the height in metres squared. Individual patients will be classified into categories based on their BMI. Results will be summarised in a frequency table for each visit over the study period. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will be included for subgroups of women and men.

BMI categories:

Underweight	< 18.5
Healthy	18.5 – 24.9
Overweight	25 – 29.9
Obese	30 – 39.9

Furthermore, participants will be categorised into additional categories based on their BMI and the WHO obesity classification system. Results will be summarised in a frequency table for each visit over the study period. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will be included for subgroups of women and men.

WHO obesity classification system:

Underweight	< 18.5
Healthy	18.5 – 24.9
Pre-obesity	25 – 29.9
Obesity class I	30 – 34.9
Obesity class II	35 – 39.9
Obesity class III	> 40

Participants who gain 10% of their baseline weight to week 48 and their last study visit, will be summarised in a frequency table. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will be included for subgroups of women and men.

Participants who were not overweight or obese at baseline but become overweight or obese at week 48 will be summarised in a frequency table. An additional frequency table will show participants

becoming overweight or obese by their last study visit. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will be included for subgroups of women and men.

Treatment emergent obesity, excluding all participants who were obese at baseline, will be summarised in a frequency table. A two-sample test of proportions will determine significant differences between treatment groups. Additional summaries will be included for subgroups of women and men.

Vital signs

Vital signs assessments, taken at screening, including temperature, heart rate, systolic- and diastolic blood pressure will be listed on an individual basis. Only blood pressure and heart rate will be assessed at all other visits. Changes from baseline will be presented in a listing for blood pressure and heart rate. Systolic blood pressure and diastolic blood pressure measurements will be analysed separately.

Drug Resistance Mutations

For patients who two HIV-1 RNA results of at least 1000 copies/mL at any time after week 24, a resistance test will be performed. "Significant resistance" will be defined as a score above 30 in the Stanford algorithm to any of the three antiretrovirals the patients has been randomised to receive.

A summary table will be produced to show the number and percentage of patients with HIV-1 RNA > 1000 copies/mL, the number and percentage of patients who had their resistance tested and all NRTI and NNRTI mutations seen following these tests. A listing will also be produced to show all participants who had their resistance tested and what their consequent result was.

NRTI, NNRTI & INSTI mutations that will be tested are listed below:

All NRTI Mutations	
A62V	D67DN
L74V	K65R
T69TADN	K70KE
M184V	K70KEGR
M184MV	K219KE
M184MIV	T215D
D67G	T215F

All NNRTI Mutations	L100I
E138A	K103N
E138EA	N348I
E138Q	V179D
E138EQ	V179VD
P225H	V179VDE
P225PH	Y181C
V106M	Y181YC
V106VM	Y181V
V108I	Y188L
V108VI	N348I
G190GA	H221HY

All INSTI Mutations	
66A	143H
66I	143KGSA
66K	145S
92G	146P
92Q	147G
92V	148HKR
118R	148N
121Y	151L
138KAT	155H
140SAC	155ST
143CR	263K

Pregnancy test

A pregnancy test will be performed on all females of child-bearing age at all visits. Monthly TAF, TDF and DTG levels will be assessed on women who fall pregnant. The values will be listed in separate tables.

Symptom-led physical examination

The physical examination will be symptom led after screening visit. The parameters will be listed on an individual basis.

TB

As a sub-study, DTG trough levels will be measured in patients receiving treatments 1 and 2, and who were diagnosed with TB during the study. These patients and the DTG concentrations will be listed.

Should patients be diagnosed with TB at other healthcare facilities, TAF levels will be measured.

Liver dysfunction

Patients presenting with elevated ALT values, discontinued study treatment. These patients will be listed, together with the ALT values.

Other safety parameters

The results or outcome of all other safety parameters and scans will be listed and summarised in a table, where applicable.

Questionnaires

Sleep questionnaires and quality of life (QoL) questionnaires will be done at screening and at all post screening visits. The questionnaires will be summarised by category and question for treatment group and visit.

Other analyses

Disposition

The following will be summarised:

- Total screen failures
- Total randomised participants, by group
- Total number of early withdrawals due to any of the following reasons, by group:

- AE, protocol deviation, death withdrawal by investigator, withdrawal of consent, lost to follow-up, pregnancy or any other reason, as given by the 'End of Study' field in the 'Visit 9/EOS' CRF page.
- Unaccounted participants/reasons, i.e. missing data

Adherence to IMP

The adherence will be listed for all follow-up visits. Overall adherence for each participant will be calculated as the average adherence across all visits and all drugs, based on the individual treatment compliances derived in the database from the applicable 'Treatment Group x' eCRF forms. Any overall adherence of less than 80% will be flagged.

Exposure to IMP

The date of first IMP administration will be derived as the first date of dosing from the IMP administration eCRF page. The date of last IMP administration will be taken as the 'Date of last dose of study drug' from the 'End of Study' field, from the 'Visit 9/EOS' eCRF form. If this date is not available, then the visit date of 'Visit 9/EOS' will be used as the last date of dosing.

Interruptions, compliance/adherence, and dose changes will not be considered for calculating the duration of exposure, which will be derived as follows:

- Duration of exposure, t (days):

$$t = Date\ of\ last\ IMP\ administration - Date\ of\ first\ IMP\ administration + 1$$

Protocol violations and deviations

All protocol violations and deviations will be listed per patients citing the treatment group. See the section on Analysis population for protocol deviations which may exclude a participant from the per protocol analysis set.

Interim analyses

A data safety monitoring board (DSMB) will monitor the study to ensure that harm is minimised, and benefits maximised for the study patients. Membership of the DSMB will be completely independent of the study staff. The NIH has agreed to use its existing International DSMB to oversee the study.

In accordance with protocol V3, to allow early stopping, a single interim analysis will be performed on the primary efficacy endpoint: when approximately 40% of all patients have completed the Week 48 assessments. Unblinded primary efficacy analysis and safety analyses will be provided to the DSMB that is independent of the study team. The DSMB will issue recommendations concerning trial continuation.

The significance level of the interim analysis will be set using the Peto rule (P<0.001). This is to preserve the significance level of the primary analysis at 5% (0.05). The treatment arms will be

compared at the interim analysis in the same pre-set sequence as used in the final analysis (Fall-back procedure). This method is described in more detail in the description of the final analysis.

Although, the study treatments will be unblinded to investigators and patients throughout the study to Week 96, only the statistical staff at MetaVirology Ltd and the protocol statistician will be able to review the interim results.

Listings and tables regarding the primary endpoint and safety parameters will be created as required and requested by the DSMB.

Appendix 1: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Laboratory Values*

Chemistries

****add pdf to word file****

Appendix 2: BARC Chemistry and Haematology reference ranges

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