Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase 2 non-comparative randomised controlled trial

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Summary

Rifampicin induces genes involved in the metabolism and transport of dolutegravir, resulting in significantly lower dolutegravir exposure. This drug-drug interaction can be overcome by doubling the dose of dolutegravir to 50 mg 12 hourly, which was well tolerated with good rates of virologic suppression in a phase 2b study of patients with HIV-associated tuberculosis. However, the additional dose of dolutegravir will be difficult to implement in high burden settings; for this reason, the South African national guidelines on dolutegravir continue to recommend an efavirenz-based ART regimen for ART-naive patients with tuberculosis.

Three lines of evidence support studying standard dose dolutegravir in patients with HIV-associated tuberculosis. First, the phase 2b study (SPRING-1) of dolutegravir plus dual nucleoside reverse transcriptase inhibitors showed similar rates of virologic suppression with dolutegravir dosed at 10 mg, 25 mg, or 50 mg daily and no pharmacokinetic-pharmacodynamic relationships between dolutegravir exposure and virologic outcomes could be established. Second, we conducted a drug-drug interaction study of dolutegravir dosed at 50 mg or 100 mg once daily in healthy volunteers with rifampicin and showed that concomitant rifampicin significantly reduced dolutegravir exposure at both doses, as expected, but all dolutegravir trough concentrations on rifampicin were above the protein-adjusted IC_{90}. Furthermore, the geometric mean ratio of the area under the curve (AUC) of dolutegravir 50 mg once daily with rifampicin (versus 50 mg daily without rifampicin) was similar to the geometric mean ratio AUC of 10 mg dolutegravir (versus 50 mg dolutegravir), which performed as well as 50 mg daily in the SRING-1 study. Third, exposure to the first-generation integrase inhibitor raltegravir is also significantly reduced with concomitant rifampicin and, as is the case with dolutegravir, the induction can be overcome by doubling the dose of raltegravir. However, a phase 2 study (ANRS 12 180 Reflate TB) in patients with HIV-associated tuberculosis showed that virologic outcomes were similar with standard and double dose raltegravir. It is plausible that findings could be similar with dolutegravir.

We propose to conduct a phase 2 randomised (1:1) double-blind placebo-controlled trial of the dolutegravir-lamivudine-tenofovir fixed dose combination tablet daily with an additional 50 mg dose of dolutegravir/matching placebo taken 12 hours later in ART-naïve or first-line ART treatment interrupters (either on ART for <6 months at the time of interruption or a suppressed viral load [<50 copies/mL or LDL] <6 months before the time of interruption) HIV-infected patients with CD4 counts >100 cells/µL on rifampicin-based anti-tuberculosis therapy. The primary endpoint is virologic suppression at week 24. Key secondary endpoints include the emergence of antiretroviral resistance mutations and dolutegravir trough concentrations.

The main risk to participants will be the emergence of antiretroviral resistance mutations, which will be mitigated by frequent viral load monitoring, close monitoring by a data safety monitoring committee, performing genotypic antiretroviral testing in participants with virologic failure, and providing antiretroviral therapy directed by the resistance test results.

CONTENTS

1.0 BACKGROUND AND RATIONALE

Dolutegravir is being rolled out to replace efavirenz in first-line antiretroviral therapy (ART) in low-middle income countries (LMICs) because it is more effective, better tolerated, and has a considerably higher genetic barrier to resistance.

Tuberculosis is the commonest cause of HIV-related morbidity and mortality in LMICs, and continues to occur at a higher incidence than in the general population despite normalisation of CD4 counts on ART. Rifampicin, which is a key component of anti-tuberculosis therapy, induces the following genes that are important in the metabolism and transport of dolutegravir: *UGT1A1*, *ABCB1* (which encodes for P-glycoprotein), *ABCG2* (which encodes for breast cancer resistance protein (BCRP)), and *CYP3A4*. The resulting drug-drug interaction between dolutegravir and rifampicin significantly reduces dolutegravir exposure, which can be overcome by increasing the dose of dolutegravir to 50 mg 12 hourly [Dooley 2013]. Interim 24-week data from the INSPIRING study, a randomised controlled trial (RCT) of double dose dolutegravir versus efavirenz in patients with tuberculosis, reported double dose dolutegravir was well tolerated and rates of virologic suppression were similar in both arms, but the study wasn't powered for efficacy comparisons [Dooley 2018].

The additional dose of dolutegravir will be difficult to implement in high burden settings where nurses prescribe ART, making complex regimens undesirable, and pharmacies would need to stock dolutegravir as a single tablet as well as the fixed dose combination formulation (dolutegravir-lamivudine-tenofovir), increasing the risks of stock outs. Furthermore, the additional dolutegravir tablet increases pill burden and costs. Our experience is that double dose lopinavir-ritonavir, which is recommended with rifampicin-based antituberculosis therapy, is often not implemented in ART programs. For this reason, the draft South African national guidelines for the dolutegravir roll out in 2019 are recommending that efavirenz continue to be used in patients with tuberculosis who are starting ART.

If standard dose dolutegravir is shown to be effective in patients with tuberculosis this would sweep away one of the major barriers to its implementation in low-middle income countries (LMICs). There are three lines of evidence to support studying standard dose dolutegravir in patients with HIV-associated tuberculosis.

First, there are compelling pharmacokinetic and pharmacodynamic data supporting the therapeutic efficacy of lower dolutegravir exposure. Dolutegravir trough concentrations were found to be the key pharmacokinetic parameter for virologic efficacy in a phase 2a study of different doses of dolutegravir monotherapy [Min]. However, no pharmacokinetic-pharmacodynamic relationships between dolutegravir exposure (including trough concentrations) and virologic outcomes could be established in the phase 2b study (SPRING-1) of different doses of dolutegravir given as part of a combination ART regimen together with dual nucleoside reverse transcriptase inhibitors (NRTIs) [Van Lunzen]. In SPRING-1 all doses of dolutegravir (10 mg, 25 mg, and 50 mg daily) resulted in similar, high rates of virologic suppression [Van Lunzen]. The trough concentrations of dolutegravir 50 mg daily are 19 times above the protein-adjusted IC_{90} [Van Lunzen], indicating that the drug has a lot of "forgiveness". An important pharmacodynamic characteristic of dolutegravir may mitigate against the emergence of resistance in patients with potentially sub-therapeutic dolutegravir trough concentrations: dolutegravir binds avidly to its receptor, integrase, with a dissociative half-life of 71 hours [Hightower]. Therefore, the pharmacokinetic-pharmacodynamic data and the SPRING-1 study results indicates that lower exposures of dolutegravir have a high likelihood of success.

Second, we have conducted a drug-drug interaction study (RADIO) of dolutegravir dosed at 50 mg or 100 mg once daily in healthy volunteers with rifampicin [Wang]. Although, as expected, concomitant rifampicin significantly reduced dolutegravir exposure at both doses, all dolutegravir trough concentrations on rifampicin were above the protein-adjusted IC_{90} and the median trough concentrations were 2.3 times and 4.3 times above the protein-adjusted IC_{90} for the 50 mg and 100 mg dolutegravir doses respectively. The geometric mean trough concentration of the 10 mg dose in SPRING-1 was 0.3 µg/mL; and 0.156 and 0. 251 µg/mL for the 50 mg and 100 mg dolutegravir doses on rifampicin respectively in RADIO. The geometric mean ratio of the area under the curve (AUC) of dolutegravir 50 mg once daily with rifampicin versus dolutegravir 50 mg once daily without rifampicin was 44% (90%CI 37, 52), which is similar to the geometric mean ratio of 40% reported for 10 mg versus the 50 mg dolutegravir dose in the SRING-1 study [Van Lunzen]. As noted above, 10 mg dolutegravir performed as well as 50 mg in SPRING-1 [Van Lunzen].

Third, exposure to the first-generation integrase inhibitor raltegravir is also significantly reduced with concomitant rifampicin. A study in healthy volunteers showed that double dose raltegravir overcame the

pharmacokinetic drug-drug interaction with rifampicin [Wenning], but a subsequent phase 2 study (ANRS 12 180 Reflate TB) in patients with HIV-associated tuberculosis showed that virologic outcomes were similar with standard and double dose raltegravir [Grinsztejn]. It is plausible that findings could be similar with dolutegravir.

Finally, a recent retrospective cohort study from Botswana reported virologic outcomes in patients with tuberculosis on rifampicin-based anti-tuberculosis therapy who were on a dolutegravir-based ART regimen; the dolutegravir dose was not doubled while on antituberculosis therapy in 44% [Modongo]. Virologic suppression was achieved in 204/214 (95.3%) and 241/254 (94.9%) in those on standard and double dose dolutegravir respectively. In a multivariable analysis virologic suppression was more likely with CD4 counts >100 cells/µL.

Our hypothesis is that virologic outcomes with standard dose dolutegravir-based ART will be acceptable in patients on rifampicin-based anti-tuberculosis therapy. If the proportion of participants who achieve virological suppression on standard dose dolutegravir is acceptable, this would pave the way for a phase 3 trial of dolutegravir 50 mg daily versus an appropriate standard of care regimen, like efavirenz-based ART, in patients with HIV-associated tuberculosis. A variety of safety measures will be put in place to ensure that no harm will come to participants.

2.0 STUDY DESIGN

Phase 2 randomised (1:1, computer generated) double-blind placebo-controlled trial of the dolutegravir-lamivudine-tenofovir fixed dose combination tablet daily with an additional 50 mg dose of dolutegravir or matching placebo taken 12 hours later in HIV-infected patients on rifampicin-based antituberculosis therapy.

2.1 STUDY SITES:

The study will primarily be conducted at Site B/Ubuntu community health clinic in Khayelitsha, Cape Town and will receive referrals for recruitment from 2 satellite sites – Michael Mapongwana and Nolungile/Site C community health clinics.

2.2 RECRUITMENT AND ENROLMENT:

108 ART-naïve or first-line ART treatment interrupters with HIV-associated tuberculosis attending the study clinics will be approached by study staff to obtain written consent for study screening. If they are eligible for the study (see inclusion and exclusion criteria below) they will be invited to participate in the study and provided with the patient information leaflet and informed consent documents.

Inclusion criteria:

- ≥18 years old
- HIV-1 infection as documented by screening plasma HIV-1 RNA >1000 c/mL;
- ART-naïve (short-term antiretroviral use for prevention of mother-to-child transmission will be allowed)

  or

  ART treatment interrupters (see rationale below):
  - on ART <6 months prior to interruption or
  - virologically suppressed (<50 copies/mL or LDL) <6 months prior to interruption
- On rifampicin-based therapy for tuberculosis for <3 months
- CD4 counts >100 cells/µL
- Women of child-bearing potential willing to use adequate contraception (defined as either an IUCD or hormonal contraception as per national guidelines)

Our rationale for enrolling first-line ART treatment interrupters into the study is to make the study findings more generalizable – the majority (~70%) of HIV-positive patients with TB who aren't on ART have interrupted ART rather than being ART-naïve. There is a potential risk of impaired virologic response in participants who are treatment interrupters as they may harbour NRTI resistance mutations – however, this risk will be mitigated by only selecting participants who have a low risk of NRTI viral resistance mutations (either on ART for <6 months at the time of interruption or a suppressed viral load <6 months before the time of interruption). As per the study schedule we are doing frequent viral load measurements and resistance testing for participants with virological failure – those who develop resistance will be placed on an appropriate regimen.

Exclusion criteria:

- Pregnant/breastfeeding
- Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease (MDRD) study)
- ALT >3 times upper limit of normal (ULN)
- Allergy or intolerance to one of the drugs in regimen
- Concomitant medication known to significantly reduce or increase dolutegravir exposure (except rifampicin)
- Active psychiatric disease or substance abuse
- On treatment for active AIDS-defining condition other than tuberculosis (participants on maintenance therapy may be enrolled)
- Malignancy
- Any other clinical condition that in the opinion of an investigator puts the patient at increased risk of participating in the study.

2.3 SCREENING VISIT:

Should occur within 8 weeks before the commencement of ART (Baseline). All eligible patients (see inclusion and exclusion criteria below) will sign informed consent. Medical history, method of diagnosis of tuberculosis, physical exam, safety blood monitoring will be done, as well as a urine pregnancy test for women of childbearing potential.

2.4 BASELINE VISIT:

Participants who are eligible for the study will return for a baseline visit (within 8 weeks of screening). A mental health questionnaire and sleep assessment will be conducted. All eligibility criteria will be checked, and, at the investigator's discretion, the participant will be enrolled into the study. A blood sample for storage will be taken if the participant consents to stored samples. The participant will be randomised, and drug will be dispensed by a registered pharmacist according to the randomisation. Randomisation will be done with a computer-generated randomisation plan and stratified by baseline ART-naïve or first-line ART treatment interrupter status. Site pharmacists will manage a system of sealed envelopes with all participants assigned a unique randomisation number based on the randomisation plan. Participants will be assigned 1:1 to either dolutegravir-lamivudine-tenofovir fixed dose combination tablet daily with an additional 50 mg dose of dolutegravir or matching placebo taken 12 hours later. The trial will be double-blind. Only the study statistician will have access to the randomisation code. We do not anticipate that breaking the randomisation code will be necessary as the intervention and control arms differ only by dolutegravir lower dose.

2.5 FOLLOW UP VISITS:

The participant will return every 4 weeks for a physical exam, adverse event check, sleep assessment, mental health questionnaire (every 12 weeks) and serum biochemical tests (ALT, creatinine, potassium and albumin). HIV-1 viral loads will be done at weeks 4, 8, 12, 24 and 48. An additional sample for storage will be taken with each viral load sample, this will be for antiretroviral resistance testing should it become necessary. Contraception use will be checked at every visit for women of child-bearing potential. Dolutegravir trough concentrations and tenofovir-diphosphate dried blood spot testing will be done at weeks 4, 8, 12, 24 and 48 only (note that these assays will be done batched at the end of the study).

2.6 END OF STUDY VISIT

After 48 weeks, the participant will return to the site for a final study visit. They will be referred out to their local clinic and dispensed with one month of medication. A follow up call to the participant will be made to ensure that they have accessed continuing care.

2.7 DATA MANAGEMENT:

Upon screening, participants will receive a screening number, the screening document will identify the patient based on his/her hospital folder number only. At the enrolment visit participants will receive a randomisation number, completely deidentifying the participant. From this point the randomisation number will be the only

identifier. Blood samples taken will be identified only by the assigned randomisation number given to each participant. This will be attached with a sticker to each blood sample.

The study visit case record form (CRF) will be completed as soon as possible after the study visit. Data will be captured for this study on an electronic data capture system using a password protected platform. The principal investigator has overall responsibility for ensuring the data collected are complete, accurate, and recorded in a timely manner. Confidentiality of records must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

Once the CRF is completed the document needs to be signed and dated. Corrections can only be done by study staff and must be signed and dated.

2.8 WITHDRAWAL AND LOSS TO FOLLOW UP:

Participants reserve the right to withdraw from the study at any stage, without an obligation to provide reasons for their withdrawal. Should a participant voluntarily withdraw their consent after receiving study treatment, the study team will attempt to ascertain the reason for withdrawal and encourage the patient to complete a withdrawal/final study visit as soon as possible, while respecting the participants decision.

Participants who fail to keep a study visit or appointment will be contacted telephonically and the visit rescheduled (if feasible). If, in the opinion of the investigator, a participant's continued participation in the study poses unacceptable risks to themselves, a withdrawal/final study visit should be performed whenever possible.

Participants who develop adverse events deemed related to dolutegravir that requires discontinuation will be withdrawn from the study. Participant safety will be ensured by continued follow-up after withdrawal from the study. Their data will be part of the primary and secondary outcomes in the intention-to-treat analysis. Switches of one or both of the dual NRTIs for toxicity will be allowed.

Participants who become pregnant on the study will be withdrawn and the dolutegravir switched to efavirenz. Pregnancy outcomes for the participant and the infant will be recorded. This is especially important in this study as a recent report has implicated dolutegravir as a cause of neural tube defects [Zash].

All participants who withdraw from the study will be referred to their local HIV clinic for ongoing care.

Participants who miss two consecutive visits will be deemed lost to follow up and withdrawn from the study. All possible efforts will be made to ensure participants attend the final safety assessment. These include contacting participants telephonically and rescheduling a visit if feasible.

Data from participants who do not complete the study will be used for secondary endpoint analyses.

2.9 STUDY TREATMENTS:

Dolutegravir 50 mg tablet (Myltega®, Mylan) or matching placebo will be administered 12 hours after the morning dose of fixed dose combination dolutegravir-tenofovir-lamivudine from the start of the study until 2 weeks after stopping anti-tuberculosis therapy. The study pharmacist will prepare, package, and label dolutegravir/placebo for each participant according to the randomisation code and dispense a month's supply to be taken together with fixed dose combination dolutegravir-tenofovir-lamivudine.

The ingredients of the placebo will be the standard excipients found in dolutegravir 50 mg tablet without the active ingredient. None of these have any biological effect.

Anti-tuberculosis therapy and fixed dose combination dolutegravir-tenofovir-lamivudine will be supplied by the clinics as part of standard of care.

Dolutegravir has recently been implicated as a cause of neural tube defects [Zash]. As per the exclusion criteria above, women of child-bearing potential must be on adequate, reliable contraception, defined as an IUCD or hormonal contraception as per national guidelines. Women of child-bearing potential in the study who do not have an IUCD will be given hormonal contraception on site for the duration of the study. As rifampicin is a known potent inducer, thereby reducing the effectiveness of oral contraceptives by enhancing their metabolism, we

recommend the use of injectable progesterone-only contraceptives such as medroxyprogesterone acetate (Depo-Provera® 150 mg 12 weekly).

2.10 ADVERSE EVENTS / SAFETY PROCEDURES:

An adverse event is any untoward medical occurrence developing in participants from the first dose of study drugs until the end of the study or developing after this period and thought to be not related, possibly, probably, or likely related to the study drug.

Drug-related adverse events reported by participants or observed by the investigator, and any remedial actions, will be recorded in the source documents and the participant's CRF. The nature of the event, the time of onset, duration, severity (rated according to the Division of AIDS [DAIDS] table for grading the severity of adult and pediatric adverse events vs 2, Nov 2014, DAIDS, NIH) and causality assessment will be recorded in the individual CRFs and included in the study report.

Any serious adverse events (SAE; defined as resulting in death, being life threatening, requiring hospitalization, resulting in significant or persistent disability/incapacity, or jeopardizing the participant, or requiring intervention to prevent significant or persistent damage or disability) will be reported to the principal investigator immediately. SAEs and all unexpected adverse events suspected to be related to the study drugs, will be reported to UCT's Human Research Ethics Committee (HREC) and SAHPRA according to their current guidelines and in line with Good Clinical Practice (GCP) guidelines.

2.10.1 COLLECTION AND DOCUMENTATION OF ADVERSE EVENTS:

The occurrence of adverse events will be solicited from participants at each study visit using a standardized adverse events collection tool with which participants will be encouraged to report any untoward change in their condition and questioned about specific adverse events related to insomnia (using a sleep assessment questionnaire developed by the ADVANCE study team – ADVANCE is a randomised controlled trial of dolutegravir versus efavirenz for ART-naïve patients being conducted in Johannesburg, PI Francois Venter), new or worsening neuropsychiatric symptoms (using a mental health questionnaire developed by the ADVANCE study team), and symptoms of hepatotoxicity. Participants will also be asked to contact the study team immediately should they develop any untoward changes in their medical condition.

All laboratory reports will be reviewed by clinical investigators, with the review signed and dated.

If the eGFR declines to <50 mL/min then tenofovir will be discontinued and replaced with abacavir as per national guidelines. Tenofovir may be reintroduced if there is an alternative explanation for the decline in renal function once the eGFR has increased to >60 mL/min.

2.10.2 MANAGEMENT OF SUSPECTED DRUG-INDUCED LIVER INJURY:

Dolutegravir, cotrimoxazole, and several antituberculosis drugs (isoniazid, rifampicin, and pyrazinamide) can cause drug-induced liver injury.

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology during administration of dolutegravir and the follow-up period. Dolutegravir, cotrimoxazole, and antituberculosis therapy (if the participant is still taking this) will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3 x ULN (or 3 x baseline ALT if this was above ULN) and bilirubin ≥2 x ULN
- ALT ≥3 x ULN (or 3 x baseline ALT if this was above ULN) with symptoms of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash;
- ALT ≥5 x ULN irrespective of bilirubin and symptoms

Participants who develop ALT ≥5 x ULN should be followed weekly until resolution or stabilization (ALT <5 x ULN on 2 consecutive evaluations).

Participants should not restart dolutegravir due to the risk of a recurrent reaction unless an alternative diagnosis is made for the liver chemistry abnormalities (e.g. viral hepatitis).

2.10.3 VIRAL LOAD MONITORING AND DETECTION OF ANTIRETROVIRAL RESISTANCE

Frequent viral load monitoring will be done during the study as per the schedule of events table.

Antiretroviral resistance testing will be done in participants who do not have virologic suppression at week 24 or in participants who suppress their viral loads and then subsequently rebound. Resistance testing will also be done on stored plasma from the baseline visit in participants who have antiretroviral resistance mutations to distinguish emergent from pre-treatment resistance. Participants who have antiretroviral resistance mutations will have an appropriate ART regimen, using antiretrovirals available in national guidelines (which includes efavirenz, zidovudine, and lopinavir-ritonavir). Currently no other analyses of stored blood samples are planned. Blood samples will be kept for a period of 3 years after the end of the study and then destroyed.

2.10.4 Independent Data and Safety Monitoring Committee (IDSMC):

An IDSMC will be established consisting of three experienced HIV clinical researchers and the study statistician (quorum will be two HIV clinical researchers). The IDSMC will review study data 6 monthly. The IDSMC will discuss in closed session whether the study should be stopped, modified or continued, and will communicate a recommendation to the principal investigator. As this is a non-comparative study, there are no formal stopping rules – a decision to stop the study for serious harm will be at the discretion of the IDSMC. The findings from the research will be published even if the trial is terminated early based on an IDSMC recommendation.

2.11 Pharmacokinetic analyses

Dolutegravir trough concentrations and tenofovir-diphosphate in dried blood spots will be determined at regular intervals as outlined in the schedules of events (note that these assays will be batched and done after study completion). The Clinical Pharmacology Laboratory at UCT has developed validated assays for both of these analytes on liquid chromatography-mass spectrometry. We will use thresholds of tenofovir-diphosphate concentrations in dried blood spots that have been determined to predict different adherence levels [Castillo-Mancilla].

*Table: Schedule of events **(WOCBP = women of child-bearing potential)***

Visit	Screening	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 48	Wk 52
Informed consent	X									
Inclusions & exclusions	X	X								
Medical history	X									
Physical exam	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	
Mental health questionnaire		X			X			X	X	
Sleep assessment questionnaire		X	X	X	X	X	X	X	X	
Dispense study drug and accountability		X	X	X	X	X	X	X	X	
Pregnancy test	X (urine β-HCG)	X (urine β-HCG)	X (urine β-HCG)	X (urine β-HCG)	X (urine β-HCG)	X (urine β-HCG)	X (urine β-HCG)	X (urine β-HCG)	X	
Contraception use (for WOCBP)	X	X	X	X	X	X	X	X	X	
Creatinine, potassium, ALT, & bilirubin	X		X	X	X			X	X	
HIV viral load	X		X	X	X			X	X	
CD4 count	X							X	X	
DTG trough			X	X	X			X	X	
Tenofovir-diphosphate dried blood spots			X	X	X			X	X	
Plasma for storage		X	X	X	X			X	X	
Antiretroviral resistance testing		If viral load is >1000 copies/mL at week 24 or if viral load was suppressed and then rebounded to >1000, resistance testing will be performed on a stored plasma sample, and compared to the baseline stored sample to determine pre-treatment vs emergent resistance mutations.								
Referral to public sector care										X

3.0 STATISTICAL CONSIDERATIONS AND ANALYSES

3.1 SAMPLE SIZE:

We assume that 85% of participants will achieve virologic suppression at week 24. With 49 patients per group the lower 95% confidence interval (CI) of virological suppression at week 24 would exceed 70% (actual value is 73%) with power of 80% and α of 5% (one-sided test). We selected this lower 95% CI of virologic suppression based on the outcomes in two randomised controlled trials with efavirenz-based ART in patients with HIV-associated tuberculosis, which achieved suppression of 74% and 70% at 48 weeks [Bonnet, Havlir]. Assuming a 10% rate of loss to follow we plan to enroll 54 participants per arm. The study is not powered for formal comparison of efficacy between the two arms.

3.2 PRIMARY ENDPOINT:

Proportion with HIV viral load <50 copies/mL at 24 weeks analysed by modified intention to treat (ITT), which includes all participants who received at least one dose of dolutegravir, and according to the FDA snapshot algorithm. The FDA snapshot algorithm regards the following categories of participants as failures: HIV viral load ≥50 copies/ml, missing HIV viral load within the visit window, or those who have discontinued ART. Switching of the NRTI component of the ART regimen for intolerance or adverse event will not be regarded as failure, but switching or stopping of dolutegravir will be regarded as failure. Switching due to pregnancy will not be regarded as failure.

3.3 SECONDARY ENDPOINTS:

- Proportion with HIV viral load <50 copies/mL at 12 weeks analysed ITT
- Proportion with HIV viral load <50 copies/mL at 48 weeks analysed ITT
- Proportion with HIV viral load <50 copies/mL at 12, 24 and 48 weeks analysed per protocol
- Primary and secondary virological endpoints stratified by baseline ART-naïve or treatment interruption status
- Change in CD4 count from screening at week 24
- Proportion with dolutegravir trough concentrations above the protein-adjusted IC_{90} at weeks 4, 8, 12, 24, and 48.
- Tenofovir-diphosphate in dried blood spots, which is an objective medium-term ART adherence measure, at weeks 4, 8, 12 ,24 and 48.
- Grade 3 or 4 drug-related adverse events
- Change from baseline of sleep assessment and mental health questionnaires
- Serious adverse events
- Adverse events requiring discontinuation of any drug in the ART regimen
- Emergence of antiretroviral resistance mutations in participants with virologic failure (resistance testing will be done on stored plasma at baseline in those with on study antiretroviral resistance mutations to distinguish emergent from pre-treatment resistance – see schedule of events)

3.4 ANALYSIS PLAN

The proportions of participants with virologic suppression will be determined with 95% CIs. Intention to treat and per protocol analyses will be performed as outlined in the primary and secondary endpoints above. Between-group differences for secondary endpoints will be analysed with chi-squared tests (or Fisher's exact tests if the number in any cell is ≤5) for categorical data and with Wilcoxon rank sum tests for continuous data. As noted above in the sample size section, no formal between group comparisons will be made of the primary endpoint as we do not have sufficient power.

4.0 STUDY MONITORING

Monitoring systems with procedures to maximise the quality of every aspect of the study will be implemented.

On site monitoring will be performed by independent study monitors on a regular basis. The monitors will:

- verify completeness of the investigator site file

- confirm adherence to protocol
- review eligibility verification and consent procedures
- look for missed clinical event reporting
- verify completeness, consistency, and accuracy of data being entered on CRFs
- verify completeness, consistency, and accuracy of pharmacokinetic study data and samples
- evaluate drug accountability
- provide additional training as needed
- document findings in a formal feedback letter (monitoring report) to the site

5.0 ETHICAL CONSIDERATIONS AND INFORMED CONSENT

5.1 ETHICAL CONDUCT

This study will be conducted in accordance with the ethical principles laid out in the National Statement on Ethical Conduct in Research Involving Humans, the Declaration of Helsinki (most current version issued, available at www.wma.net), and will be consistent with GCP and applicable regulatory requirements.

The rights, safety, and wellbeing of the study participants are the most important considerations and should prevail over interests of science and society. All personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

Institutional review board/independent ethics committee (IRB/IEC) and local regulatory approval will be documented and kept in the investigator site file, specifying the version number of the protocol and informed consent as well as the date of approval. Any amendments will require IRB/IEC and regulatory approval.

The principal investigator will comply with all IRB/EC and regulatory authorities, reporting requirements for all safety reporting, annual updates, safety updates, end of study reports and any other important information relevant to the conduct of the study.

5.2 COMPLIANCE WITH THE PROTOCOL

The study will be conducted as described in this protocol. The principal investigator will not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IRB/IEC and regulatory authorities of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants. Any significant deviation will be reported to sponsor, IRB/IEC, and local regulatory authority.

5.3 PROTOCOL AMENDMENTS

When revisions to the protocol are made by the sponsor, if the revision is an administrative letter, the principal investigator will submit this for the information of their IRB/IEC. Study documents will be updated in line with the changes required in the protocol amendment.

5.4 INFORMED CONSENT AND PROCEDURES

A study specific informed consent will include all elements required by GCP as well as all local ethics and regulatory requirements.

The principal investigator will ensure that participants are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they participate and that their participation is voluntary. A copy of the informed consent will be given to the participant in a language of their choice. Informed consent process will be conducted as per the trials site standard operating procedures. A copy of the signed informed consent will be given to the participant.

If the patient is illiterate, an impartial witness will be present during the entire consent discussion. A thumb print may be used as a signature.

The informed consent document will be updated with any pertinent information that becomes available during the study.

5.5 USE OF PLACEBO

The use of a 50 mg dolutegravir vs placebo in this study will indicate whether the additional 50 mg dose is adequate to achieve and maintain viral suppression. All participants will be on the fixed dose combination antiretroviral tablet of dolutegravir-lamivudine-tenofovir. The phase 2 INSPIRING study [Dooley], although proving that the additional dolutegravir dose was well tolerated, was not powered to evaluate the efficacy of the additional dose versus the control arm (efavirenz-based ART) and has therefore not been adopted as standard of care.

6.0 CONFIDENTIALITY OF DATA

The site principal investigator agrees that the University of Cape Town and sponsor, IRB/EC or regulatory authorities may consult and/or copy study documents to verify information in the CRF. By signing the consent form the participant agrees to these processes.

Participant confidentiality will be maintained at all times and no documents containing the participant's name or other identifying information will be collected by the sponsor. It may be necessary for the sponsor's representatives, the IRB/EC and regulatory authority representatives to have direct access to the participant's medical records. If study documents need to be photocopied during the process of verifying CRF data, the participant will be identified by a unique code only; full names and other identifying information will be masked.

The principal investigator also agrees to maintain confidentiality with all study information and only divulge necessary information to the staff, ethics committee and regulatory authorities. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

7.0 REFERENCES

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APPENDIX A: GANTT CHART

	Year 1												Year 2												Year 3											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Preparation of CRFs																																				
Staff recruitment																																				
Public engagement and institutional meetings																																				
Training of clinical staff and counsellor																																				
Engagement with laboratory staff																																				
Patient recruitment and follow-up																																				
Analysis of results																																				
Preparation and submission of manuscripts																																				

RADIANT-TB GANNT chart

APPENDIX B: ADVANCE SLEEP ASSESSMENT QUESTIONNAIRE

APPENDIX C: ADVANCE MENTAL HEALTH QUESTIONNAIRE

APPENDIX D: SAMPLE INFORMED CONSENT