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For numbered affiliations see end of article.

Correspondence to

Dr Anushka Naidoo;
anushka.naidoo@caprisa.org

Anushka Naidoo ,¹ Kelly E Dooley,² Kogieleum Naidoo,^{1,3} Nesri Padayatchi,^{1,3} Nonhlanhla Yende-Zuma,¹ Rubeshan Perumal,^{1,3} Gillian Dorse,¹ Resha Boodhram,¹ Emmanuella Chinonso Osuala¹

ABSTRACT

Introduction Cotreatment of HIV and tuberculosis (TB) reduces morbidity and mortality in coinfecting patients. Availability of antiretroviral treatment (ART) drug options, including within drug classes, is important, particularly in high HIV/TB burden low and middle-income countries.

Methods and analysis This is a phase 2b, open-label, non-comparative randomised controlled trial to assess the antiretroviral activity of a fixed-drug, single tablet, combination of bicitegravir (BIC) 50 mg/emtricitabine (FTC) 200 mg/tenofovir alafenamide (TAF) 25 mg (Biktarvy). The primary objective is to determine the efficacy, safety and pharmacokinetics of two times per day, coformulated BIC 50 mg/FTC 200 mg/TAF 25 mg in HIV-positive ART-naïve patients with TB who are receiving a rifampicin-based treatment regimen and to characterise viral suppression rates at week 24 through to week 48 in the BIC/FTC/TAF arm. We will enrol 120 patients randomised in a 2:1 ratio to the intervention or control arm of the study. A non-comparative contemporaneous control arm in which participants receive a dolutegravir-based regimen (standard of care) will also be enrolled.

Ethics and dissemination The University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) and the South African Health Products Regulatory Authority (SAHPRA) have granted regulatory approval (trial reference numbers: BREC/00001300/2020 and SAHPRA 20200810).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study will be the first to generate new data that may support the use of a potent antiretroviral Fixed Drug Combination, Biktarvy, in HIV-1-infected adult patients with tuberculosis coinfection.
- ⇒ The study includes intensive pharmacokinetic sampling and resistance testing providing data on the associations between drug exposures in plasma, clinical outcomes and development of resistance mutations to the Integrase Strand Transfer Inhibitors's (INSTI's).
- ⇒ The study has a non-comparative design and thus not powered to compare efficacy of Biktarvy, and the standard of care regimen.
- ⇒ The study does not include pregnant women, adolescents or patients with lower CD4 cell counts and further study will be needed in these subpopulations.
- ⇒ Safety and efficacy of doubling the FDC of Biktarvy are not known although the study includes several strategies to mitigate the risks of treatment failure and safety concerns.

Trial results will be disseminated through conference presentations, peer-reviewed publications and the clinical trial registry.

Trial registration number Clinicaltrials.gov; Trial registration number: NCT04734652; South African National Clinical Trials Register (SANCTR DOH-27-012021-6789)

INTRODUCTION

Currently, there are approximately 40 million people living with HIV (PLWHIV) worldwide, and about half of PLWHIV live in Eastern and Southern Africa.¹ By the end of 2019, an estimated 25 million people were accessing antiretroviral treatment (ART) globally.¹ South Africa has the largest HIV epidemic in the world with more than 7 million PLWHIV and the largest treatment programme with 4.4 million people on ART; >25% live in KwaZulu-Natal.¹ The WHO, currently recommends the Integrase Strand Transfer Inhibitor (InSTI), dolutegravir as the preferred backbone of first-line ART regimens for the treatment of HIV-1 infection in adults, adolescents and children, particularly in low and middle-income countries (LMIC) regions such as Southern and Eastern Africa, where pre-treatment drug resistance to Non Nucleotide Reverse Transcriptase Inhibitors (NNRTI's) reaches 10%.^{2,3} Second generation InSTIs such as dolutegravir and a newer drug, Bictegravir (BIC), have high antiviral potency, better safety and tolerability profiles than protease inhibitors (PIs) and NNRTIs, and are suitable for once daily administration with a high barrier to the development of HIV-1 resistance.⁴⁻⁷ BIC may also demonstrate activity against some variants with reduced susceptibility to dolutegravir. In large Phase 3 trials of BIC-emtricitabine -tenofovir alafenamide (BIC/FTC/TAF 50-200-25, now co-formulated as Biktarvy), there were no cases of emergent resistance.⁴ In phase 3 trials, BIC/FTC/TAF and dolutegravir (given with abacavir/lamivudine or FTC/TAF) displayed similarly high efficacy in establishing virologic suppression in treatment-naïve adults over 96 weeks of treatment.^{7,8}

Among PLWHIV, tuberculosis (TB) is the leading cause of death. Of 10 million incident cases of TB globally in 2019, 10% occurred in PLWHIV.⁹ In South Africa, 50–80% of PLWHIV have latent TB co-infection (LTBI).⁹ While ART reduces the risk of progression from LTBI to TB disease, many patients only discover they have HIV at the time of TB diagnosis. There is a morbidity and mortality benefit of treating HIV and TB concurrently, rather than starting ART after completion of TB treatment, especially for patients with low CD4 counts.¹⁰ Current standard of care (SOC) is to treat HIV and TB concurrently, rather than sequentially, with ART started within 2–8 weeks after TB treatment initiation—a strategy which reduces the risk of death as well as new opportunistic infections substantially.^{10,11} Co-treatment of HIV and TB, though, has its challenges. Rifampicin is a critical component of standard first-line TB drug regimens because of its unique sterilising activity.¹¹ No drug can adequately substitute for rifampicin in the TB drug regimen. However, rifampicin

is a potent inducer of cytochrome P450 (CYP) enzymes, the UDP-glucuronosyltransferases (UGT) and drug transporters such as p-glycoprotein (p-gp) and, therefore, causes several significant drug–drug interactions.¹² HIV-TB co-treatment options, thus, are limited by drug–drug interactions, limited availability of some TB or HIV drugs in local programmes, and an increased burden of drug toxicity.

ART scale-up in sub-Saharan Africa is progressing at a rapid pace. There are still areas for optimisation, though, related to the mitigation of drug resistance and toxicity. Co-formulated InSTI's such as BIC and dolutegravir with reduced pill burden, fewer toxicities, and reduced risk of virologic failure, will ultimately maximise cost-effectiveness and clinical benefit in disease endemic resource-limited settings. Having different options for InSTI-based regimens that can be used together with standard rifampicin-based first-line treatment regimens (provided as fixed-dose combinations by TB programmes) is extremely important. Most currently available ART classes have more than one drug available for use in treatment programmes and this can mitigate the risk for stockouts that are common in resource-limited settings, toxicities, resistance and interactions. BIC has been shown in vitro to have a slightly better resistance profile than dolutegravir and we are not yet clear if the weight gain and other emerging concerns with dolutegravir will also be seen with BIC. This also allows HIV programmes to use the same drugs to treat patients with and without TB.

Rationale for Biktarvy and drug interaction between co-formulated BIC/TAF/FTC (Biktarvy) and rifampicin-based TB drug regimens in patients with TB

BIC is metabolised predominantly by CYP3A and UGT1A1. In a study involving HIV-negative healthy volunteers, BIC trough concentrations (Ct) when given twice daily (as part of BIC/TAF/FTC) with and without rifampicin 600 mg once daily were reduced from 3070 mcg/mL to 608 mcg/mL (80% reduction), and AUC₀₋₂₄ was reduced by approximately 60%.¹³ Trough concentrations of InSTIs including BIC have been shown to be strongly associated with antiviral activity. The protein adjusted 95% effective trough concentration (pa EC₉₅) of BIC is approximately 0.162 mcg/mL. In phase 3, efficacy studies of BIC once daily in HIV-1 infected individuals, BIC trough concentrations were found to be 16 times higher than the pa EC₉₅.¹⁴ Despite the 80% reduction in BIC Ct when dosed twice daily with rifampicin co-administration, the average trough concentration remained 3.1-fold higher than the pa EC₉₅, and all subjects in the healthy volunteer study maintained trough concentrations higher than the pa EC₉₅. However, a modelling exercise using data from phase three trials suggested that in a larger population of patients, giving BIC twice daily with rifampicin may rarely (about 3 in 1000) result in patients having trough concentrations lower than the pa EC₉₅.¹³ BIC has the longest dissociation half-life of

all the currently available INSTI's. BIC has a long (163 hours) dissociation half-life from the integrase enzyme, which will likely mitigate against potential breakthrough viraemia in the small minority of participants who might theoretically have trough concentrations below the protein-adjusted EC95 on rifampicin.¹⁵ For TAF, while the tenofovir disoproxil fumarate (TDF) formulation of tenofovir can be used without dose adjustment with TB drugs, there has been concern that TAF, a p-gp substrate, might not achieve target concentrations when given with rifampicin. TAF undergoes phosphorylation to form the active moiety tenofovir diphosphate (TFV-DP) within lymphoid cells, where it also exerts its activity.^{16 17} In a trial among healthy HIV-negative volunteers, TAF when dosed once daily alone compared with once daily with rifampicin 600mg, was shown to have decreased plasma exposure by 47%, while intracellular TFV-DP was decreased by 40%.¹⁸ However, intracellular TFV-DP concentrations were still over four-fold higher than those achieved by standard dose TDF. These data support the use of TAF when co-administered with rifampicin in patients with HIV and TB.¹⁸ In the same study, rifampicin did not affect FTC pharmacokinetics (PK).

What is the clinical relevance of the above-described drug interactions among patients taking combination HIV treatment (BIC/TAF/FTC twice daily) and concomitantly receiving first-line TB treatment (isoniazid, rifampicin, pyrazinamide, ethambutol, HRZE)?

In the initial phase 1B trial of BIC monotherapy in which the drug was given at doses of 5, 25, 50 or 100 mg daily for 10 days to HIV treatment-naïve patients (mean baseline HIV viral load of 4.4 log), even the 5mg dose was potent, reducing viral load substantially (1.5 log in 10 days), without emergence of resistance after stopping the drug.⁶ Subsequent phase 2 and 3 trials of combination therapy evaluated the drug at 75 mg (phase 2) or 50 mg (phase 3).¹⁴ At those doses, no PK-PD relationships could be seen, and no resistance emerged. BIC is not available as a single 50 mg tablet formulation.

The PK, safety and efficacy of TAF and FTC when dosed twice daily with HRZE in patients with HIV-associated TB are untested. FTC is a well-tolerated drug, even at higher dosing levels (300mg once daily or 200mg twice a day).^{19 20} Among patients with moderate renal impairment receiving the standard 200mg dose, increases in FTC exposure did not have an impact on safety.²¹ Genvoya (FDC containing elvitegravir, cobicistat, FTC and TAF) full-strength tablets have been given to children as light as 25 kg, resulting in high mg/kg doses and FTC and TAF exposures that were 75% and 71% higher than average in adults, yet participants tolerated the regimen well; there were no serious adverse events or adverse event-related discontinuations.²² In a study involving adult PLWHIV with end-stage renal disease, standard-dose Genvoya produced elevated drug concentrations, but the overall safety profile was not affected.²³ Moreover, because FTC is renally eliminated and its exposures had previously been observed to be increased in adults with

mild-to-moderate renal impairment, analysis of adverse events potentially associated with FTC (ie, among those listed in the prescribing information as having at least 10% incidence) was of specific interest in the study. The overall incidence of these prespecified events occurred in nearly half of study participants; however, those events considered drug-related were reported in less than 10%, all were grade 1 or 2 in severity, and none led to premature discontinuation of study drug.²³ In the healthy volunteer study of BIC/TAF/FTC twice daily with rifampicin, FTC concentrations were, not surprisingly, doubled; no additional safety concerns were reported, although long-term data will be needed.¹³ As seen previously, PK and safety results in healthy HIV-negative volunteers do not reliably predict PK, safety and efficacy among patients with HIV-TB receiving concomitant treatment for both diseases.²⁴⁻²⁷ Therefore, future studies must be conducted in a careful and rigorous manner in the relevant study population.

Currently, dolutegravir is the only first-line InSTI available for use in adult patients for ARV programmes in South Africa. This study will be the first to generate new data that may support the use of a potent antiretroviral FDC, Biktarvy, in HIV-1 infected adult patients with TB co-infection taking rifampicin-containing first-line treatment with HRZE. This will create a new and highly desirable treatment option for patients with HIV-associated TB in settings. Importantly, demonstrating that Biktarvy can be used in patients with TB will fill a critical gap and help support the case for its introduction into Africa, where ~70% of the global burden of HIV is concentrated and in particular in South Africa, which has one of the highest incidence rates of HIV and TB co-infection in the world. If co-formulated BIC/TAF/FTC is safe and effective in patients with HIV-associated TB, this will be an important new option for these patients. As this can mitigate the risk for stockouts that are common in resource-limited settings, toxicities, resistance and interactions. There are at least two drugs within most available drug classes for example, efavirenz and nevirapine. As it is easier for programmes in LMIC to deliver similar formulations of drugs for different patient populations (rather than different drugs for patients with and without TB), this will also be a helpful missing piece for the introduction of BIC/TAF/FTC, a highly popular FDC in the USA and Europe, to Africa. Given that BIC/TAF/FTC is potent, safe, available in a single-tablet FDC and has activity even against some InSTI-resistant strains, it is very important that it be available in African settings. Additionally, it will be helpful for TAF roll-out, a drug that has a better safety profile for bone and renal adverse events than TDF, which has been hindered, in part, by a lack of data in HIV-TB co-infected patients.

Our proposed study is important as it will improve the chances of access to a potent ART co-formulation in Africa, where it is most needed.

METHODS AND ANALYSIS

Patient and public involvement

Patients or members of the public were not directly involved in protocol development however CAPRISA has a Community Advisory Board (CAB), which is involved in community engagement, study planning and recruitment of participants as guided by Good Participatory Practice guidelines. The CAB members includes local community leaders, traditional leaders, leadership of local HIV/AIDS organisations, local health service provider representatives, previous study participants and PLWHIV within the local community. During trial preparation and prior to study start, the study protocol is presented to the CAPRISA CAB, AfroCAB and Global TBCAB members for their engagement.

Study setting

The CAPRISA 093 INSIGHT study will be conducted at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) Springfield Clinical Research Site in Durban, KwaZulu-Natal. This research clinic is located within the King Dinuzulu District Hospital that provides HIV and TB testing and treatment services. CAPRISA works closely with surrounding primary health-care clinics and the local TB programme and receives referrals from those programmes within the eThekweni district (Durban).

Study population and selection

The study population will include 120 adults (18 years and over) who are living with HIV and ART-naïve. Patients

with drug-sensitive TB who are on or will be initiated on a first-line rifampicin-based regimen, who meet study eligibility criteria and agree to study participation will be recruited (table 1).

Study design

CAPRISA 093 INSIGHT is a phase 2b open-label randomised-controlled clinical trial evaluating Biktarvy for treatment of ART-naïve PLWHIV with TB co-infection on a rifampicin-containing regimen. Eligible patients will be randomised to receive one of the two ART treatment regimens in a 2:1 ratio (table 2). The study will enrol and follow-up participants for 48 weeks.

Study objectives and endpoints (table 3):

Study procedures

Recruitment

Participants will be recruited from local department of health clinics involved in the diagnosis and management of tuberculosis and HIV. The study recruitment team will identify potential participants using laboratory reports, electronic clinic information systems or referrals from clinic staff who have been informed of the study.

Informed consent

Written informed consent will be obtained from each study participant prior to screening and enrolment. Written informed consent will also be obtained for long-term specimen storage and possible future analyses. The informed consent procedure will be conducted in either English or isiZulu as per participant preference.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Adults ≥18 years of age with Karnofsky score ≥70 ▶ Confirmed rifampicin-susceptible tuberculosis (GeneXpert, Sputum smear and/or culture) ▶ On first-line rifampicin-based tuberculosis treatment (not >8 weeks at the time of enrolment) ▶ Documented HIV-1 infection, ART-naïve ▶ Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² ▶ Alanine aminotransferase (ALT) ≤3 times the upper limit of normal (ULN) ▶ Total bilirubin ≤2.5 times ULN ▶ Creatinine ≤2 times ULN ▶ Haemoglobin ≥7.0 g/dL (6.5 g/dL for women) ▶ Platelet count ≥50 000/mm³ ▶ Absolute neutrophil count (ANC) ≥650/mm³ ▶ Able and willing to provide written informed consent ▶ Female patients agree to use both a barrier and a non-barrier form of contraception during the study, starting at least 14 days prior to enrolment 	<ul style="list-style-type: none"> ▶ Pregnancy or breastfeeding (or planned pregnancy within 12 months of study entry) ▶ Prior use of antiretroviral drugs for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) ▶ Hepatitis B surface antigen positive, Hepatitis B virus (HBV) infection, active infections (other than HIV-1 infection) requiring systemic antibiotic or antifungal therapy current or within 30 days prior to baseline ▶ Participants with a CD4+ cell count of <100 cells/μL ▶ Any verified grade 4 laboratory abnormality, with the exception of, grade 4 triglycerides. A single repeat test is allowed during the screening period to verify a result ▶ Patients on metformin (>500 mg, 12 hourly) ▶ Patients with an uncontrolled psychiatric co-morbidity. Patients who, in the investigator's judgement, pose a significant suicidality risk. Recent history of suicidal behaviour and/or suicidal ideation may be considered as evidence of serious suicide risk ▶ Other condition or circumstance deemed by clinician/investigators to be detrimental to patient safety or study conduct ▶ Unwilling to be part of the main pharmacokinetic (PK) study and have PK blood draws done

Table 2 Study regimens

Arm	During TB treatment (and for 2 weeks after rifampicin is stopped)	After TB treatment (through week 48)
Intervention arm/BIC arm ~80 participants	BIC/FTC/TAF (two times per day)	BIC/FTC/TAF (one time per day)
Control arm/DTG arm (SOC) ~40 participants	DTG/TDF/3TC (one time per day) + DTG 50 mg once daily (evening/pm dose)	DTG/TDF/3TC (one time per day)

BIC/FTC/TAF fixed-drug combination -*Biktarvy* and TDF/3TC/DTG fixed drug combination- *TLD*.
 BIC, bicitegravir 50 mg; DTG, dolutegravir 50 mg; FTC, emtricitabine 300 mg; TAF, tenofovir alafenamide 25 mg; TB, tuberculosis; 3TC, lamivudine 300 mg; TDF, tenofovir 300 mg.

Table 3 Study objectives and endpoints

Study objectives	Study endpoints
Primary objective <ul style="list-style-type: none"> ▶ To characterise viral suppression rates (proportion of patients with HIV-1 RNA <50 copies/mL) at week 24 in the BIC/FTC/TAF arm 	Primary endpoint <ul style="list-style-type: none"> ▶ Proportion of patients with suppressed viral load (HIV-1 RNA<50 copies/mL) at week 24 in the BIC arm (as per FDA snapshot algorithm)
Secondary objectives <ul style="list-style-type: none"> ▶ To characterise viral suppression rates (proportion of patients with HIV-1 RNA <50 copies/mL) at weeks 12, 24 and 48 in the standard of care treatment (SOC) arm (currently, TDF 300 mg/3TC 300 mg/DTG 50 mg) and at weeks 12 and 48 in the BIC/FTC/TAF arm ▶ To compare the pharmacokinetics (PK) of BIC when given twice daily and co-administered with Rifampicin during tuberculosis treatment vs when given alone after discontinuation of Rifampicin ▶ To assess the incidence of TB associated IRIS in each arm, through week 24 ▶ To characterise the tolerability of treatment in each arm by assessing frequency of clinician- initiated treatment interruptions or switches through week 48 ▶ To assess frequency of ART drug resistance mutations in participants with detectable viral load at study visit weeks 24 and 48 	Secondary endpoints <ul style="list-style-type: none"> ▶ Viral suppression rates (HIV-1 RNA<50 copies/mL) at weeks 12, 24 and 48 in the DTG arm and at 12 and 48 weeks in the BIC arm ▶ PK of BIC when given two times per day and co-administered with Rifampicin vs during TB treatment vs when given alone after TB treatment completion ▶ Incidence of TB associated IRIS through week 24, by arm ▶ Grade 3 or higher AEs, SAEs; clinician-initiated treatment interruptions or switches through week 48 ▶ Frequency of ART drug resistance mutations in participants with detectable viral load at weeks 24 and 48
Exploratory objectives <ul style="list-style-type: none"> ▶ To determine the effects of pharmacogenetics (genetic variability in drug metabolising enzymes or drug transporters including but not limited to UGT1A, p-glycoprotein) on BIC/FTC/TAF PK ▶ To compare the pharmacokinetics (PK) of TAF, intracellular TFV-DP, FTC and DTG when given twice daily and co-administered with Rifampicin during tuberculosis treatment vs when given alone after discontinuation of Rifampicin ▶ To determine the PK of TB drugs ▶ To describe the PK in hair of BIC, FTC, TAF during and after co-treatment with Rifampicin. To describe maternal and fetal outcomes among women who become pregnant on-study 	Exploratory endpoints <ul style="list-style-type: none"> ▶ PK of FTC, TAF and intracellular TFV-DP when given two times per day and co-administered with Rifampicin vs during TB treatment vs when given alone after TB treatment completion ▶ PK of TB drugs ▶ Effects of pharmacogenetics of drug metabolising enzymes or drug transporters (eg, UGT1A1, CYP3A, p-gp) on BIC/FTC/TAF/DTG PK ▶ Association between hair PK and virologic suppression

AEs, adverse events; ART, antiretroviral treatment; BIC, bicitegravir; FTC, emtricitabine; SAEs, serious AEs; TAF, tenofovir alafenamide; TB, tuberculosis.

If a participant is illiterate, an impartial witness will be present throughout the informed consent procedure to ensure that all questions are answered to the satisfaction of the potential participant.

Screening

All participants who provide informed consent will have eligibility assessments (in accordance with Inclusion and Exclusion criteria on [table 1](#)) performed and provide relevant identification documents for verification of age, and details will be checked against a Biometric Co-Enrolment Prevention System to prevent co-enrolment. HIV pre-test counselling will be offered, and HIV confirmatory testing will be carried out using two licensed rapid HIV tests. Discordant results will be confirmed using an ELISA-based antibody test. A sputum sample will be obtained for sputum smear testing and GeneXpert Ultra analysis to confirm TB infection and rifampicin (RIF) resistance, where required (if these tests have not already been done or results are not available from the local TB programme). All TB tests will be done in accordance with SOC and TB treatment guidelines. If participants have been initiated on TB treatment prior to screening, then the duration of TB treatment and baseline TB test screening results will be documented to ensure not more than 8 weeks of rifampicin-based TB treatment has been taken. Screening evaluations will be done in accordance with the Schedule of Evaluations (SoE). Patients will have vital signs (including height and weight) measured, a targeted clinical exam performed, as well as clinical safety monitoring activities and a urine pregnancy test. Safety blood will be drawn for haemoglobin (Hb), urea, creatinine, calculation of the estimated glomerular filtration rate (eGFR), aspartate transaminases (AST), alanine aminotransferase (ALT), total bilirubin, amylase, platelets and full blood count. Hepatitis B surface antigen testing, CD4 cell count and HIV-RNA viral load testing will also be performed. Concomitant medication will be reviewed and recorded. TB treatment will be provided and continued in the study as per SOC. Screening evaluations to determine eligibility will be completed <14 days prior to randomisation.

Randomisation

A sufficient number of patients will be screened and those deemed eligible will be randomised in a 2:1 ratio to Intervention/BIC arm or to a non-comparative control/dolutegravir arm. Participants will be randomised according to a computer-generated randomisation list, where random permutation blocks of different sizes will be used. An electronic randomisation system will be used for study arm allocation. A password protected randomisation list will be sent to the data manager so that it can be uploaded into the database.

Enrolment

Eligibility criteria will be assessed by a study clinician and documented prior to randomisation. Informed consent

will be reviewed at enrolment. On study entry evaluations in accordance with the SOE will occur after randomisation procedures. Patients will have all vital signs (including weight) measured, a targeted clinical exam, clinical safety monitoring and urine pregnancy test will be done. Safety blood will be drawn for Hb, urea, creatinine, (e-GFR calculated), AST, ALT, total bilirubin, amylase, platelets and FBC *and any other safety testing* as clinically indicated unless within 72 hours of safety blood done at screening visit. Culture for genotypic/phenotypic testing for RIF/Isoniazid INH resistance testing will be done as per SOC for TB treatment. ART treatment ([table 2](#)) will be administered in accordance with the study arm to which the participant is randomised. All TB treatment will be continued in accordance with SOC and South African National TB treatment guidelines.

Follow-up

Patients will have vital signs measured, a targeted clinical exam performed and a clinical safety monitoring assessment at all visits. Safety blood will be drawn for Hb, urea, creatinine, (e-GFR calculated), AST, ALT, total bilirubin, amylase, platelets and FBC and pregnancy test (urine) and any other safety testing will be done as clinically indicated at all follow-up visits. Hep B surface antigen testing, CD4 cell counts and viral load testing will be done as per SOE. TB treatment, testing and follow-up using genotypic and phenotypic (smear and culture) are done in accordance with SOC. ART treatment based on arm allocation will be provided at each visit until week 48 unless discontinuations or disruption to treatment due to safety or other issues occur. If the HIV viral load is detectable any time after week 24, or at week 24 or 48, participants may receive enhanced adherence counselling (focused adherence counselling with guidance on addressing common areas contributing to poor adherence), and a retest done 2–4 weeks later. Real-time resistance testing may be done for sub-optimal viral responses (at week 12 and after, if viral load increases by a log or greater compared with the most recent visit, and after counselling/retest, if there is no improvement of viral load on retest) Concomitant medications will be recorded at each visit and TB associated (Immune Reconstitution Syndrome) IRIS assessments will be done.

PK sampling

PK assessments will be performed in the study. The time of last dose of all ART and TB drugs and time of dose taken in clinic (observed dose) will be recorded for all PK visits. At each timepoint approximately 4 mL of whole blood will be collected in EDTA tubes. PK samples will be taken to the onsite laboratory immediately to be processed and stored at -80°C for later analysis. Sampling timepoints for each of the arms and for the subset of participants in the BIC arm who are enrolled into the semi-intensive PK Study are outlined in [table 4](#).

Table 4 PK sampling timepoints

Study visit/week	Visit 3/week 4	Visit 4/ week 8	Visit 5/week 12	Visit 6/ week 24	Visit 7/week 32 or after*	Visit 9/ week 48
Bictegravir arm general PK						
Timepoint 1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
Timepoint 2	1–4 hours post dose		1–4 hours post dose		1–4 hours post dose	
Bictegravir arm semi-intensive PK†						
Timepoint 1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
Timepoint 2	1 hour post dose		1 hour post dose		1 hour post dose	
Timepoint 3	2 hour post dose		2 hour post dose		2 hour post dose	
Timepoint 4	4 hour post dose		4 hour post dose		4 hour post dose	
Timepoint 5	6 hour post dose		6 hour post dose		6–8 hour post dose	
Timepoint 6	8–12 hour post dose		8–12 hour post dose		24–25 hour post dose	
Dolutegravir arm general PK						
Timepoint 1	Pre-dose			Pre-dose		Pre-dose

*This sampling is done at least 2 weeks after RIF-based TB treatment is stopped and may be done after Visit 7 if TB treatment duration is extended or participant still on RIF.

†Only bictegravir arm participants who agree on informed consent to be included in the semi-intensive PK study will be included.

Approximately ~30–40 participants may be included, if participants are unable or unwilling to complete the semi-intensive PK sampling at required visits then additional participants may be included if deemed necessary by the investigators.

PK, pharmacokinetics; RIF, rifampicin; TB, tuberculosis.

Safety monitoring: adverse events and serious adverse events assessment

All participants will be assessed for any adverse events (AEs) and serious AEs (SAEs) at every visit, and these will be documented and graded according to the Division of Acquired Immune Deficiency Syndrome (DAIDS) V.2.1, July 2017 and reported accordingly.

Statistical analysis

Sample size determination

The study is not designed to compare primary and secondary outcomes between the two study arms. Rather, the sample size is based on precision for estimating the response rate in the BIC arm, following similar design in the REFLATE²⁸ and INSPIRING²⁵ trials. Assuming an 85% response rate for BIC/FTC/TAF at week 24,^{7 8 14} a sample size of 66–80 subjects in the BIC arm would have >85% power to detect a response rate of greater than 70%. The sample size has been chosen to provide an adequate number of subjects for assessing the antiretroviral activity of BIC/FTC/TAF. A non-comparative control group of 30–40 patients will be enrolled in the dolutegravir arm to provide safety and efficacy parameters for standard-of-care treatment in the local setting, to contextualise the BIC arm results and to serve as a baseline comparator group for safety and efficacy parameters.

Analysis of the primary endpoint will be conducted on all participants who are randomly assigned and receive at least one dose of the study drug, regardless of attendance of post-enrolment study visits (modified intent to treat population) who have drug-sensitive TB and were on rifampicin-based TB treatment. The primary endpoint of viral suppression at 24 weeks will be assessed after all

enrolled participants have either completed 24 weeks of study follow-up or have prematurely discontinued the study drug or were deemed lost to follow-up. Any patient with a detectable HIV viral load (>50 copies/mL) at Weeks 24 or 48 will undergo counselling and adherence support and have a recheck in 2–4 weeks. If suppressed at recheck, that will count as a success. The primary efficacy endpoint is the proportion of patients with a viral load (HIV-1 RNA) of <50 copies per ml at week 24 in the BIC/FTC/TAF arm using the FDA snapshot algorithm.

Secondary endpoints or outcomes will be reported for both arms. Secondary endpoints are proportion of patients with a viral load (HIV-1 RNA) of <50 copies per mL at week 12 and 48 in the BIC/FTC/TAF arm and at week 12, 24 and 48 in the SOC arm. The proportion of participants with viral suppression at week 12 and week 48 will be reported (both mITT and per protocol analyses). Safety data will be summarised for all patients. To assess tolerability and safety, we will report proportions of participants who will experience grade 3 or 4 AEs, SAEs as well as the proportion with treatment interruptions or switches. Depending on the number of incident TB-IRIS cases, the incidence rate or the proportion will be reported.

PK analysis plan

PK assessments will be performed in the BIC arm in participants provided informed consent. PK samples in the control arm may be stored for later analysis. PK parameters (Ct, Cmax, AUC) will be computed for all subjects who undergo semi-intensive sampling. Analytes to be measured include BIC, TAF, intracellular TFV-DP and dolutegravir. PK parameters will be estimated by

application of a nonlinear model using standard noncompartmental methods (WinNonlin software). Descriptive statistics (n, mean, SD, coefficient of variation [%CV], minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI) will be calculated. Geometric mean ratios for Ct, Cmax, AUC will be generated, comparing these parameters during TB treatment vs without concurrent TB treatment. For concentration values below limit of quantification (BLQ), the number of subjects with values of BLQ will be presented and treated as missing data. Using data from both the semi-intensive PK sub-study and the sparse sampling in the overall study population, a population PK model (non-linear mixed effects models) will also be developed, both to describe the PK in the larger population as well as to assess determinants of variability in trough concentrations.

Data safety monitoring and review

Participant safety will be closely monitored both internally by the protocol safety review team (PSRT) and externally by a data safety and monitoring committee (DSMC).

The PSRT will provide clinical safety oversight on study. The PSRT will consist of study investigators and an independent external clinician (infectious diseases specialist/physician). The membership, scope of responsibility, role, and modus operandi of the PSRT will be detailed in the terms of reference as part of the study management plan.

This study will be reviewed by a DSMC. The DSMC will be comprised of a statistician, and at least two experts in TB or HIV clinical trials (infectious disease specialist and/or clinical pharmacologist preferable), all independent of the study team. The study DSMC will conduct an interim review of safety, PK, and viral load data after the first 10 participants have completed the 24-week visit in the BIC arm. An interim analysis at week 24 when at least half of the trial participants have been enrolled will be conducted to review safety and efficacy in the two arms. These data will be reviewed by the DSMC, and recommendations will be made to the study team. We will conduct PK analysis during the study once the first 10 participants in the BIC arm have reached/completed their week 12 visit. This will allow for PK data to be available to be included for the DSMC interim review of safety, viral load, and clinical outcomes after the first 10 participants complete the *week 24 visit*, as outlined above. The study team will also review PK data as soon as these are received and will share these with the DSMC in advance of the planned interim analysis if there are any concerns. We will conduct resistance testing in real time for all drugs in the regimen including integrase inhibitor in patients with suboptimal viral responses. Resistance testing data will be shared with the DSMC.

In addition, internal reviews of patient charts, SAE reports and regulatory submissions will be conducted by the CAPRISA quality assurance team in accordance with stipulated timelines. External monitoring may be conducted by an independent monitor designated by the study investigators to conduct study compliance or quality

assessments and or DAIDS medical officer or committee where applicable.

Data management

The entry, storage and cleaning of study data will be conducted under the oversight of the CAPRISA Data Management core. Data will be collected on case report forms (CRFs) or electronic CRFs (e-CRF's) which will be developed by the study team to specifically address protocol requirements. Data will be managed by the CAPRISA Data Management department, using DFdiscover (DF/Net Research, Inc), software specifically designed for clinical trial data management. The site will record data on paper CRFs that will be directly captured onto the DFdiscover system and validated by the data management staff. All source documents will be kept in the participants' study files and medical charts at the clinical research site. All original CRFs and study-related documents will be securely stored at the site, during the study and after study completion. SAS V.9.4 (SAS Institute, Cary, NC) is used for analysis purposes.

Ethics and dissemination

The University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) and the South African Health Products Regulatory Authority (SAHPRA) have granted regulatory approval (trial reference numbers: BREC BREC/00001300/2020 and SAHPRA 20200810). Trial results will be disseminated through conference presentations, peer-reviewed publications and the clinical trial registry.

Author affiliations

¹Centre for the Aids Programme of Research in South Africa, Durban, KwaZulu-Natal, South Africa

²Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

³MRC-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit, Doris Duke Medical Research Institute, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

Contributors AN, KD and KN conceptualised and designed the study and wrote the protocol. RP assisted in protocol development, protocol review and the review of this manuscript. NP and NYZ contributed to the study design and assisted in protocol writing. GD, RB and ECO reviewed and commented on the manuscript draft. All authors reviewed the final version of this manuscript and consented to publication.

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ORCID iD

 Anushka Naidoo <http://orcid.org/0000-0001-9550-9501>

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