CAPRISA 093

INSTI's FOR THE MANAGEMENT OF HIV-ASSOCIATED TB (INSIGHT STUDY):

A phase 2b study to evaluate the efficacy, safety and pharmacokinetics of a combination of Bictegravir, Emtricitabine, and Tenofovir Alafenamide Fumarate for treatment of HIV-1 infection in patients with drug-susceptible tuberculosis on a Rifampicin-based treatment regimen:

A Phase 2b Open-label Randomised-Controlled Trial

A research protocol prepared by:

Centre for the AIDS Programme of Research in South Africa
CAPRISA

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APPENDICE 1: PARTICIPANT INFORMED CONSENT 50

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INVESTIGATOR SIGNATURE FORM
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Centre for the AIDS Programme of Research in South Africa CAPRISA

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THE NATIONAL INSTITUTES OF HEALTH AND THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

Grant # 1R01AI152142-01

I, the Investigator of Record/Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol. I have read and understand the information in the Investigator's Brochure(s)/Package inserts, including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

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Signature _____ _____

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ACRONYMS

Acquired Immunodeficiency Syndrome	AIDS
Lamivudine	3TC
Adverse Events	AE
Antiretroviral Treatment	ART
Area under the concentration time curve	AUC
Bictegravir	BIC
Biktarvy	BIC/TAF/FTC
Below Limit of Quantification	BLQ
Centre for the AIDS Programme of Research in South Africa	CAPRISA
Maximum concentration	Cmax
Co - Principal Investigator	Co - PI
Case Report Forms	CRF
Trough concentration	Ctrough
Cytochrome P450	CYP
Division of Acquired Immunodeficiency Syndrome	DAIDS
Dried Blood Spot Test	DBS
Data Safety Monitoring Committee	DSMC
Dolutegravir	DTG
Estimated glomerular filtration rate	eGFR
Calibur Flow Cytometer	FACS
Food and Drug Administration	FDA
Emtricitabine	FTC
Good Clinical Practice	GCP
Hair Analysis Laboratories	HAL
Hepatitis B virus	HBV
Human Immunodeficiency Virus	HIV
Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	HRZE
International Council for Harmonisation	ICH
Integrase Strand Transfer Inhibitor	InSTI
Immune Reconstitution Syndrome	IRIS
KwaZulu – Natal	KZN
Low and Middle-Income Countries	LMIC
Latent TB co-infection	LTBI
Mother to Child Transmission	MTCT
Non - Nucleoside Reverse Transcriptase Inhibitor	NNRTI
Peripheral Blood Mononuclear Cell	PBMC
Pharmacodynamics	PD
Post-Exposure Prophylaxis	PEP
p-glycoprotein	p-gp
Principal Investigators	PI
Pharmacokinetics	PK
High Performance Liquid Chromatography and Mass Spectrometry	PLC/MS-MS
People Living with HIV	PLWHIV
Pre-Exposure Prophylaxis	PrEP
South Africa	SA

South African Department of Health	SA DoH
Serious Adverse Events	SAE
Standard Deviation	SD
Standard of Care	SOC
Schedule of Events	SoE
Standard Operating Procedure	SOP
Tenofovir Alafenamide	TAF
Tuberculosis	TB
Tenofovir Disoproxil Fumarate	TDF
Tenofovir Diphosphate	TFV - DP
TDF/3TC/DTG	TLD
University of Cape Town	UCT
UDP-glucuronosyltransferases	UGT
University of KwaZulu Natal	UKZN
World Health Organisation	WHO

SCHEMA

Rationale: This study is being conducted to assess the antiretroviral activity of a fixed-drug, single tablet, combination of Bictegravir 50mg/ Emtricitabine 200mg/ Tenofovir alafenamide 25mg (Biktarvy®) dosed twice daily in HIV-1 infected, ART-naïve and ART non-naïve patients with TB co-infection receiving a rifampicin-based tuberculosis (TB) treatment regimen. This study will assess the activity of Bictegravir and dolutegravir-containing ART regimens in patients with drug-susceptible TB through 48 weeks.

Design: This is a phase 2b open-label non-comparative randomised-controlled trial among HIV positive, ART naïve and ART non-naive, adult patients (>18 years) with drug-sensitive TB who are receiving a rifampicin-based first-line TB regimen. The primary objective is to assess the efficacy, safety and pharmacokinetics (PK) of twice daily, co-formulated Bictegravir (BIC) 50mg/ Emtricitabine (FTC) 200mg/ Tenofovir alafenamide (TAF) 25mg in HIV-positive ART-naïve and ART non-naïve patients with TB who are receiving a rifampicin-based treatment regimen and to characterize viral suppression rates at week 24 through to week 48 in the BIC/FTC/TAF arm. A concurrent control arm in which participants receive a dolutegravir-based regimen (standard of care, SOC) will also be enrolled

Duration: 48 weeks

Sample Size: ~120 participants

Population: The study will include adults (18 years and over) who are HIV positive, ART-naïve and ART non-naïve. Patients with drug-sensitive TB who are on a first-line rifampicin-based treatment will be included.

Randomization: Patients will be randomized in a 2:1 ratio to the Intervention or Control arm of the study

Intervention Arm/BIC Arm: Bictegravir-emtricitabine-tenofovir alafenamide (BIC/FTC/TAF 50mg- 200mg-25mg –Biktarvy® fixed-drug combination single tablet) dosed twice daily during TB treatment and for two weeks following completion of TB treatment, then once daily thereafter.

Control Arm/DTG Arm: Dolutegravir 50mg /Lamivudine 300mg/ Tenofovir 300mg (***TLD***-fixed- drug combination single tablet) **plus Dolutegravir 50mg evening dose during TB treatment** and for two weeks after completion of TB treatment, then TLD once daily thereafter- as per Standard of Care (SOC)

Objectives:

Primary objective: To characterize viral suppression rates (proportion of patients with suppressed viral load) at week 24 in the BIC arm

Secondary objectives:
To characterize viral suppression rates at weeks 12, 24 and 48 in the standard of care treatment (SOC) arm (currently, TDF 300mg/3TC 300mg/DTG 50mg) 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 characterize 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.

Study Endpoints:

Primary endpoint: Viral suppression rate (HIV-1 RNA <50 copies/mL) at week 24 in the BIC arm (using the FDA snapshot algorithm)

Secondary Endpoints:
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 twice daily 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

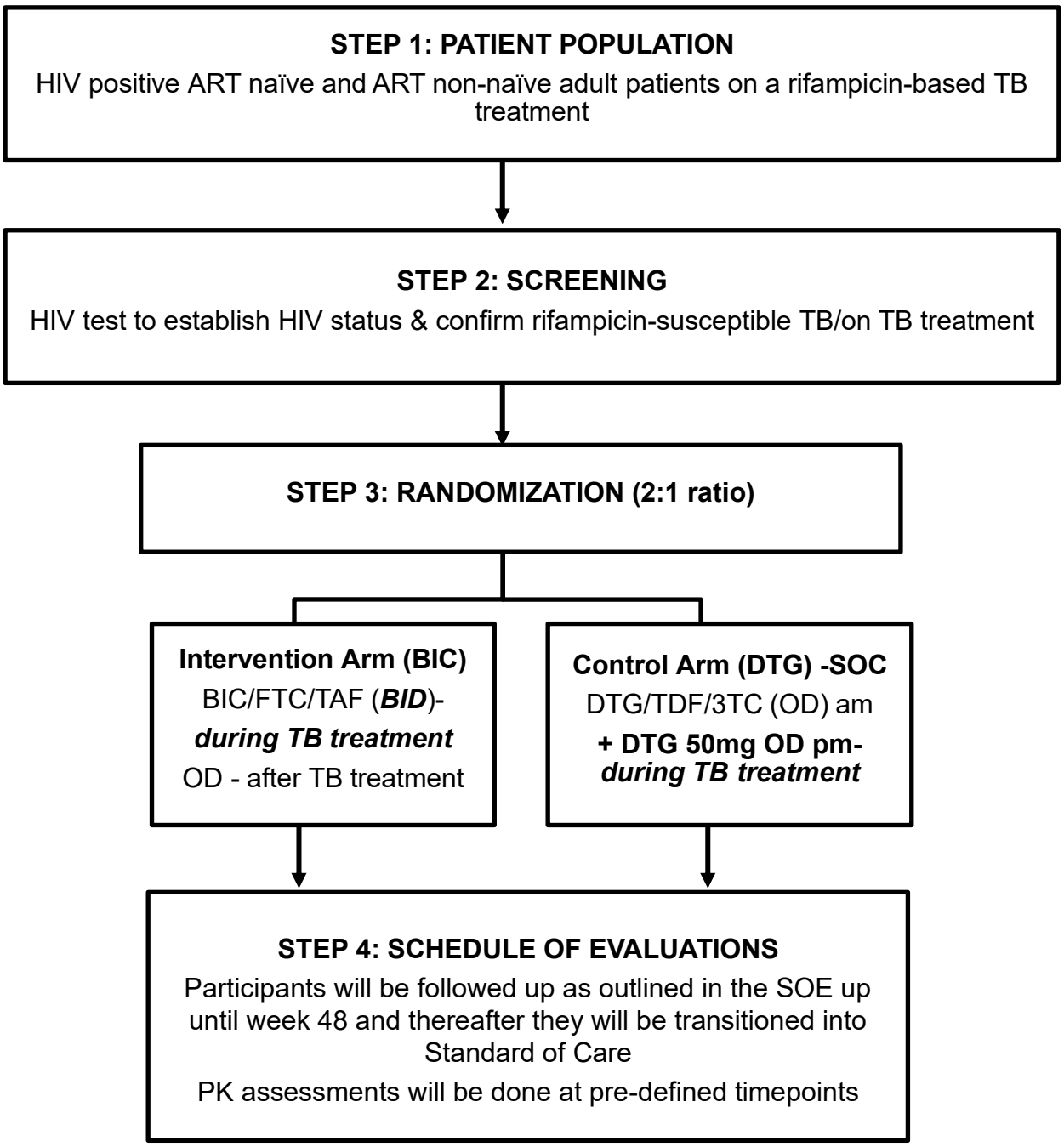

Figure 1: INSIGHT study patient screening and randomization plan

1. INTRODUCTION

1.1. Background and Rationale

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 2017, an estimated 21.7 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 World Health Organisation (WHO), currently recommends the Integrase Strand Transfer Inhibitor (InSTI), Dolutegravir (DTG) as the preferred back-bone 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 NNRTI reaches 10%.[2,3] Second generation InSTI's such as DTG and a newer drug, Bictegravir (BIC), have high antiviral potency, better safety and tolerability profiles than protease inhibitors (PI) and NNRTI's, 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 DTG. In large Phase 3 trials of BIC-emtricitabine-tenofovir alafenamide (BIC/FTC/TAF 50-200-25, now co- formulated as Biktarvy®), there was not a single episode of emergent resistance.[4] In phase 3 trials, BIC/FTC/TAF and DTG (given with abacavir/lamivudine or FTC/TAF) displayed similar, high efficacy in establishing virologic suppression in treatment-naïve adults over 96 weeks of treatment.[7,8]

Among PLWHIV, tuberculosis (TB) disease is the #1 cause of death. Of 10 million people incident cases of TB globally in 2017, 10% had HIV.[9] In South Africa, 50-80% of PLWHIV have latent TB co-infection (LTBI).[9] While ART reduces risk of progression from LTBI to TB disease, many patients only discover they have HIV at the time of pulmonary 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 is to treat HIV and TB concurrently, rather than starting ART after completion of TB treatment, with ART started within 2-8 weeks after TB treatment initiation—this reduces 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 sterilizing 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, availability of some TB or HIV drugs in local programs, and toxicity.

ART scale-up in sub-Saharan Africa is progressing at a rapid pace. There are still areas for optimization, though, related to drug resistance and toxicity. Co-formulated InSTI's such as BIC and DTG with reduced pill burden, fewer toxicities, reduced risk of virologic failure while preserving future treatment options, will ultimately maximize 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 programs) is extremely important, particularly in South Africa and KwaZulu Natal, the epicentre of the TB/HIV co-epidemic. This allows HIV programs 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 metabolized predominantly by CYP3A and UGT1A1. In a study involving **HIV-negative healthy volunteers**, BIC trough (C_t) concentrations when given twice daily (as part of BIC/TAF/FTC) with rifampicin 600 mg once daily versus once daily alone, were reduced from 3070 mcg/mL to 608 mcg/mL (80% reduction), and AUC_{0-24} was reduced by approximately 60%.[13] Trough concentrations of InSTI's including BIC have been shown to be strongly associated with antiviral activity. The protein adjusted 95% effective trough concentration (pa EC_{95}) of BIC is approximately 162ng/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 EC_{95}. Despite the 80% reduction in BIC C_t with rifampicin co-administration, average C_t remained 3.1-fold higher than the pa EC_{95}, and all subjects in the healthy volunteer study, maintained C_t concentrations higher than the pa EC_{95}. However, a modelling exercise using data from phase 3 trials suggested that in a larger population of patients, giving BIC twice daily with rifampicin may result in rare patients (about 3 in 1000) having trough concentrations lower than the pa EC_{95}.[13] 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.[14,15] In a trial among healthy HIV-negative volunteers, TAF when dosed once daily alone compared to once daily with rifampicin 600mg, was shown to have decreased plasma TAF exposure by 47%, while intracellular TFV-DP was decreased by 40%.[16] However, intracellular TFV-DP concentrations were still over 4-fold higher on average than those achieved by standard dose TDF. These data support of the use of TAF when co-administered with rifampicin in patients with HIV and TB.[16] In the same study, rifampicin did not affect FTC PK.

What is the clinical relevance, though, of the above-described drug interactions among patients taking combination HIV treatment (BIC/TAF/FTC twice daily) and receiving full 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 5 mg 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).[17] At those doses, no PK-PD relationships could be seen, and no resistance emerged. Bictegravir is not available as a single 50mg tablet formulation.

The PK of TAF and FTC when dosed twice daily with HRZE, and the safety and efficacy of these drugs as part of combination therapy in patients with HIV-associated TB is untested. FTC, though, is a well-tolerated drug, even at higher dosing levels (300 mg once daily [18]or 200 mg twice a day).[19] Among patients with moderate renal impairment receiving the standard 200mg dose, increases in FTC exposure did not have an impact on safety.[20] Genvoya® (FDC containing elvitegravir, cobicistat, FTC, and TAF) full-strength tablets have been given to children as light as 25kg, 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.[21] In a study in HIV-infected adults with end- stage renal disease, standard-dose Genvoya® produced elevated drug concentrations, but the overall safety profile was not affected.[22] 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 (i.e., among those

listed in the prescribing information as having at least 10% incidence), was carried out separately in the study. The overall incidence of these prespecified events occurred in nearly half of study participants; however, those events considered related to study drug were reported for less than

10%, all were grade 1 or 2 in severity, and none led to premature discontinuation of study drug.[22] 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 taking full treatment for both HIV and TB,[23-26] so these studies must be conducted in careful and rigorous manner in the relevant study population

This phase 2 open-label randomised controlled trial will compare the efficacy, safety and PK of a single combination pill of BIC, FTC and TAF dosed twice daily versus current standard of care treatment for HIV positive, ART-naïve and ART non-naïve, adult patients with TB co-infection on a rifampicin-based first-line TB treatment regimen, in Durban, South Africa. We hypothesize that this combination will be highly effective, given the potency of TAF (and anticipated higher intracellular concentrations of TFV-DP when it's given twice daily, even with rifampicin), contribution of FTC (potentially higher when given twice daily), and high potency of BIC with theoretical reductions below the pa EC_{95} being rare and mitigated by twice daily dosing, making any potential time below this threshold short, as well as strong companion agents.

1.2. Benefit and Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with Biktarvy® can be found in the most current version of the Investigator's Brochure (IB) and the package insert/FDA Label. The following section outlines the risk assessment and mitigation strategy for the use of Biktarvy® as described in this protocol.
The approved country product labels should be referenced for rifampicin and all other components of the TB treatment regimen and dolutegravir as well as the fixed-dose combination of Dolutegravir [Tenofovir/Lamivudine/Dolutegravir (***TLD***)] being used as standard of care in South Africa.

1.2.1. Risk Assessments

All medications have adverse event (AE) profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Some considerations when using BIC are presented in Table 1, however a full description of risks are described in the approved package insert/FDA label and investigator brochure.
All clinical and safety data [AE's, Severe adverse events (SAE's), treatment interruptions], HIV RNA viral load and CD4 cell counts, including immune reconstitution syndrome (IRIS) events will be collected and recorded on study case report forms (CRF's). Events will be monitored using SAE reports and alerts for Grade 3 or 4 laboratory toxicities (according to the Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity grading for HIV-infected patients as described in the protocol and study procedure manuals or SOPs. All AE and SAE reporting will be done in accordance with ICH-GCP and local guidelines as outlined in the study management plan. Serious/severe events will be managed appropriately including, but not limited to, investigational product (IP) being withdrawn, and will be followed to resolution by the study investigators. Severity of AEs will be assessed using the DAIDS (Division of Acquired Immune Deficiency Syndrome) Table for Grading the Severity of Adult Adverse Events, Version 2.1, July 2017.

There is some uncertainty regarding the safety and efficacy of twice daily Biktarvy® for the treatment of HIV-1 infection during rifampicin co-treatment in patients with TB. We will carefully monitor safety and efficacy outcomes in the study, and planned interim analyses to review safety, viral load, and PK data. Data Safety Monitoring Committee (DSMC) meetings will be held after the first 10 patients in the BIC arm have completed the 24-week visit and again after half the study population from both arms has reached 24 weeks on-treatment. 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. There is evidence to suggest that twice daily Biktarvy® will be safe and effective during rifampicin co-treatment. Although preliminary data from healthy volunteer studies suggested that significant reductions in bictegravir concentrations during rifampicin- coadministration will occur, these concentrations remained above the paEC$_{95}$ which is strongly associated with antiviral activity, in all patients. Furthermore despite >40% reductions in TAF and TFV-DP when TAF is given with rifampicin, intracellular concentrations of the active drug, TFV-DP, were still 4-fold higher on average than those achieved by standard dose TDF. 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 taking full treatment for both HIV and TB,[23-26] so these studies must be conducted in careful and rigorous manner in the relevant study population to provide accurate, clinically relevant information.
The safety of FTC twice daily dosing needs to be monitored, however high exposures in several studies suggest that FTC twice daily may be safely administered. Should safety and efficacy data be unfavourable in the Biktarvy® arm the study will be stopped and patients will be switched to an appropriate SOC regimen.

Table 1: Considerations when using Bictegravir

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
For full information refer to the Investigational Product (Biktarvy [BIC]) Package insert/FDA label and Investigator		
GI intolerance (nausea, diarrhea)	Two randomized, double-blind, active-controlled trails (Trial 1489 and 1490 N=314 and N=320 respectively) identified the most common adverse reactions (all Grades) reported nausea, diarrhoea and headache in at least 5% of subjects in Biktarvy® group. 87% of adverse events were Grade 1	Routine monitoring of these symptoms/and clinical and laboratory evaluations will be done
Pregnancy/Neural Tube Defects	There are insufficient human data on the use of Biktarvy® during pregnancy to inform a drug- associated risk of birth defects and miscarriage. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of Biktarvy® at exposures that were either not maternally toxic (rabbits) or greater than (rats and mice) those in humans at the recommended human dose (RHD) *Bictegravir:* Data from an observational study in Botswana showed that dolutegravir, another	All participants will be excluded from the study if pregnant at screening phase Females of child-bearing potential must have a negative pregnancy test at screening and be willing to adhere to two effective methods of contraception (barrier and a non- barrier form of contraception during the study, starting at least 14 days prior to enrolment) if sexually active. Pregnancy testing will be done at all study visits

	integrase inhibitor, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. Data available to date from other sources including the APR, clinical trials, and post marketing data are insufficient to address this risk with BIC.	
Immune Reconstitution Syndrome	This has been reported in patients with combination antiretroviral therapy During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.	Routine monitoring of these symptoms/and clinical and laboratory evaluations will be done. Steroids will be used, in accordance with standard of care to manage patients with clinical manifestations of IRIS.
Potential drug interactions	Because Biktarvy® is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection, substrates of OCT2 and MATE1, a strong inducer of CYP3A, dofetilide, anticonvulsants and antimycobacterials is not recommended. Antacids (aluminium (Al) or magnesium (Mg) based) should be used with caution.	Concomitant medications will be monitored and Biktarvy® will not be administered with other antiretroviral drugs or with drugs known to have significant interactions with the drug with the exception of rifampicin which is being studied in this protocol. Patients will be counseled to use Biktarvy at least 2 hours before antacids containing Al or Mg
Renal Function	Changes in Serum Creatinine: BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function Changes in Bilirubin: In Trials 1489 and 1490, total bilirubin increases were observed in 12% of subjects administered Biktarvy® through Week 48. Increases were primarily Grade 1 (1.0 to 1.5 x ULN) (9%) and Grade 2 (1.5 to 2.5 x ULN) (3%).	Routine monitoring of these symptoms/and clinical and laboratory evaluations will be done at each study visit
Liver function	Graded bilirubin increases in the ABC/DTG/3TC, and DTG + FTC/TAF groups, were 4% and 6%, respectively. Increases were primarily Grade 1 (3% ABC/DTG/3TC and 5% DTG + FTC/TAF) or Grade 2 (1% ABC/DTG/3TC and 1% DTG + FTC/TAF).	
Nervous system and Neuropsychiatric	Headache, Abnormal dreams and insomnia reported. Suicidal ideation, suicide attempt, and	Monitored as part of targeted physical exam and clinical monitoring

adverse events	depression suicidal occurred in <1% of subjects administered BIKTARVY; all events were serious and primarily occurred in subjects with a pre-existing history of depression, prior suicide attempt or psychiatric illness	

1.2.2. Benefit Assessment

Co-treatment of HIV and TB reduces morbidity and mortality in co-infected patients. Availability of treatment options of ART drug regimens and within drug classes is important, particularly in high HIV burden settings in LMIC countries. Currently Dolutegravir is the only first-line InSTI available for use in adult patients for ARV programs 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 where this drug is already available. 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 largest incidence of HIV and TB co-infection rates in the world. If co-formulated BIC/TAF/FTC given twice daily is safe and effective in patients with HIV-associated TB, this will be an important option for these patients. As it is easier for programs 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 introduction of BIC/TAF/FTC, a highly- popular FDC in the US 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 lack of data in HIV-TB co-infected patients.

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

1.2.3. Overall Risk and Benefit Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with Biktarvy® (using twice daily dosing) may be justified by the anticipated benefits that may be afforded to HIV-1/TB co-infected ART-naïve and ART non-naïve adults if this regimen is shown to be safe and effective. There are no data to support the safety and efficacy of Biktarvy® twice daily for the treatment of HIV-1 infection in patients with TB on rifampicin co-treatment and it is unlikely that this highly potent, safe, drug with a high resistance profile, that may provide effective future ART treatment options, will be made available in Africa if it cannot be used in patients with tuberculosis.

2. STUDY AIM AND OBJECTIVES

2.1. AIM

To assess the efficacy, safety and pharmacokinetics of twice daily, co-formulated BIC 50mg/FTC 200mg/TAF 25mg in HIV positive, ART naïve and ART non-naïve patients with drug susceptible tuberculosis who are receiving a rifampicin-based regimen in

South Africa. A concurrent, non- comparative control arm of participants receiving current standard of care HIV treatment will be enrolled.

2.2. Primary objective

To characterize viral suppression rates (proportion of patients with HIV VL<50) at week 24 in the BIC/FTC/TAF arm.

2.3. Secondary objectives

To characterize viral suppression rates (proportion of patients with HIV VL<50) at weeks 12, 24 and 48 in the standard of care treatment (SOC) arm (currently, TDF 300mg/3TC 300mg/DTG 50mg) 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 characterize 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.

2.4. Exploratory objectives

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.

3. INVESTIGATIONAL PLAN

3.1. Study Design and Setting

This is a phase 2b open-label randomized-controlled clinical trial evaluating Biktarvy® for treatment of HIV positive, ART-naïve and ART non-naïve patients with TB co-infection on a rifampicin first-line TB treatment regimen. The study will enrol approximately 120 participants.
Patients will be randomized to receive one of the two ART treatment regimens as listed below in a **2:1 ratio**.

"Study drugs" refer to the drugs listed in the Intervention/BIC arm in Table 2 and drugs used in the Control/DTG arm of the study are considered standard of care (SOC).

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 (***twice daily***)-	BIC/FTC/TAF (***once daily***)-
Control Arm/DTG Arm (SOC) ~40 participants	DTG/TDF/3TC (***once daily***) **+** DTG 50mg once daily (evening/pm dose)	DTG/TDF/3TC (***once daily***)

BIC – Bictegravir 50mg; DTG – Dolutegravir 50mg; FTC – Emtricitabine 300mg; TDF – Tenofovir 300mg; TAF – Tenofovir Alafenamide 25mg; 3TC – Lamivudine 300mg
BIC/FTC/TAF fixed-drug combination -***Biktarvy®*** and TDF/3TC/DTG fixed drug combination- ***TLD***

The study will enrol and follow up participants for 48 weeks and ART therapy will be provided over 48 weeks for the Intervention Arm, and the Control Arm in accordance with randomization.

3.2. Study Site and Population

The study will be conducted primarily at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) Springfield Clinical Research Site in Durban, Kwa-Zulu Natal. This research clinic is located at a district hospital that provides HIV and TB testing and treatment services. This site initiates approximately 30-50 newly diagnosed HIV infected patients on ART each month. In addition, the TB clinic at the district hospital initiates ~30-40 patients on TB treatment per month. CAPRISA works closely with surrounding primary health care clinics and the local TB program and receives referrals from those programs within the eThekwini district (Durban).The eThekwini district registered 19106 HIV-1 positive TB patients in 2017/2018, and 15767 TB-HIV co-infected patients on ART (with a 83% co-infection rate).[27] Individuals that are interested in study participation and are willing to provide informed consent will be screened for study eligibility.

3.3. Study Endpoints

Primary Endpoint:

- **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 Endpoints:

- 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 twice daily 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 endpoints:

- PK of FTC, TAF, and intracellular TFV-DP when given twice daily 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 (e.g. UGT1A1, CYP3A, p-gp) on BIC/FTC/TAF/DTG PK
- Association between hair PK and virologic suppression

4. INCLUSION AND EXCLUSION CRITERIA

4.1. Inclusion criteria

- Adults ≥ 18 years of age with Karnofsky score ≥ 70
- Confirmed rifampicin-susceptible tuberculosis and/or
- On first-line rifampicin-based tuberculosis treatment (not > 8 weeks at the time of enrolment)
- Documented HIV-1 infection, ART-naïve OR ART non-naïve (patients to have no exposure to ART medication at least ≥ 3 months at the time of enrollment)
- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m^2
- Alanine aminotransferase (ALT) ≤3 times the upper limit of normal (ULN)
- Total bilirubin ≤2.5 times ULN
- Creatinine ≤2 times ULN
- Hemoglobin ≥ 7.0 g/dL (6.5 g/dL for females)
- Platelet count ≥ 50,000/mm^3
- 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

4.2. Exclusion criteria (at the time of screening)

- 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) < 3 months at the time of enrolment
- Hepatitis B surface antigen positive OR Hepatitis B virus (HBV) infection OR active systemic infections (other than HIV-1 infection) requiring systemic antibiotic or antifungal therapy current or within 30 days prior to baseline that could, in the opinion of the investigator, interfere with study procedures or assessment of study outcomes
- Participants with a CD4+ cell count of < 50 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 (> 500mg, 12hourly)
- Patients with an uncontrolled psychiatric co-morbidity. Patients who, in the investigator's judgment, pose a significant suicidality risk. Recent history of suicidal behavior 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 **(NB there is a semi-intensive PK substudy which is <u>optional)</u>**

NOTE: All potential participants will undergo screening evaluations to determine eligibility. The Principal investigator (or designate) will assess eligibility and ensure that the participant meets all of the inclusion criteria. Participants may be deemed ineligible at the discretion of the principal investigator or designate based on safety or other criteria

5. RANDOMIZATION PROCEDURES

A sufficient number of patients will be screened and those deemed eligible will be randomized in a 2:1 ratio to **Intervention/*BIC arm*** or to a non-comparative **Control/*DTG arm.*** Participants will be randomized according to a predetermined random order by the study statistician. The computer- generated randomisation list will be generated by a statistician, where random permutation blocks of different sizes will be used. Either opaque sealed envelopes or electronic randomisation system will be used for study arm allocation. The envelopes will be stored in a locked cupboard and opened in sequential order by study team members authorized to perform randomization procedures by the Principal Investigator. In the case of electronic randomization, the password protected randomisation list will be sent to the data manager so that it can be uploaded into the database. The study will be open label.

6. STUDY TREATMENT

6.1. Regimens, Administration and Duration

Participants will be randomized in a 2:1 ratio as outlined above to either the Intervention (BIC) Arm or Control (DTG) Arm as described below.

The ***Intervention Arm ART regimen*** is a fixed-drug combination of a single tablet co-formulated regimen containing Bictegravir 50mg Emtricitabine 200mg and tenofovir alafenamide 25mg (BIC/FTC/TAF; Biktarvy®) that will be taken twice a day during rifampicin-containing TB treatment and 2 weeks after stopping TB treatment, thereafter the BIC/FTC/TAF single tablet co-formulation will be taken once daily.
Treatment should be initiated as soon as possible after randomization.

6.2. Description of Study drug:

Biktarvy® is a fixed dose combination, single tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.
BIC is an integrase strand transfer inhibitor (INSTI). FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI). TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′- monophosphate. Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

Standard of Care (SOC) ART regimens for the non-comparative Control arm will be provided in accordance with the current National South African ART Treatment guidelines and will be accessed through the South African Department of Health (DoH) government facilities and pharmaceutical services to the study clinic for provision to participants during the study. The standard ART regimen consists of a triple drug, single pill, fixed-dose combination, comprising Tenofovir 300mg, Lamivudine 300mg and Dolutegravir 50mg (TDF/3TC/DTG)/ (***TLD***), and is the current SOC first-line ART regimen recommended in the South African National ART Treatment guidelines. The recommended dosing for patients on TB treatment who are receiving rifampicin is DTG 50mg twice daily and TDF/3TC once daily (i.e. TLD once daily and a single DTG 50mg tablet in the evening). Patients will receive study treatment until two weeks after completing TB treatment, after which dosing will be transitioned to once daily.

Standard-first line anti-TB drug treatment consisting of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol (HRZE) will be provided in accordance with the current National South African TB Treatment guidelines in both arms of the study. Participants in our study will receive the current standard of care TB drug treatment that will be accessed by the study, through the South African Department of Health (DoH) governmental clinics and/or hospitals, for provision to participants.

6.3. Study product adverse effects information

Table 2 outlines possible adverse effects and drug interactions. However, this list is not all inclusive and each adverse effect must be examined in conjunction with the full clinical picture. At each clinic visit patients will be asked about adverse events that have occurred since their previous visit and a physical examination will be performed.
Refer to the current investigator brochure/package insert for a full list of adverse events and drug interactions.

Table 3: Possible adverse effects and drug interactions.
For full list of all adverse events, drug interactions and special precautions refer to the drug package insert/FDA label or investigator brochure

Study Drug	Adverse effects	Drug interactions	Comments
Biktarvy® (BIC/FTC/TAF)	Severe acute exacerbations of hepatitis B, immune reconstitution syndrome, new onset or worsening renal impairment, lactic acidosis/severe hepatomegaly with steatosis Diarrhea, nausea, headache, fatigue, abnormal dreams, dizziness, insomnia	Dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life – threatening events Herbal products (St John Wort, Other) may decrease the effect of BIC and TAF	Biktarvy® is a combination regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.
Dolutegravir	Insomnia, headache, Dizziness Potential for weight gain Neural tube defects Allergic reaction which may cause a rash. You may develop a rash with any of the following signs or symptoms: Fever General ill feeling Extreme tiredness Muscle or joint aches Blisters or sores in your mouth Blisters or peeling skin Redness or swelling of your eyes Swelling of your mouth, face, lips, or tongue Trouble breathing Liver problems – drug Induced Liver Injury Nausea or vomiting Loss of appetite Pain, aching, or tenderness on your right side below your ribs Changes in liver test results, more common in people with hepatitis B or C.	Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. Dolutegravir is reduced with non-nucleoside reverse transcriptase inhibitor: Etravirine and Non-nucleoside reverse transcriptase inhibitor: Efavirenz, Non-nucleoside reverse transcriptase inhibitor: Nevirapine, Protease inhibitors: Fosamprenavir/ritonavir Rifampicin Oral calcium or iron supplements, including multivitamins containing calcium or iron	Yellowing of your skin or whites of your eyes (jaundice) Dark or tea- colored urine or pale- colored bowel movements

	Increase in fat around the waist and stomach area -Increase in fat on the back of the neck Thinning of the face, legs, and arms Breast enlargement		
Tenofovir	Diarrhoea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash Severe Acute Exacerbations of Hepatitis B New Onset or Worsening Renal Impairment Lactic Acidosis/Severe Hepatomegaly with Steatosis Bone Effects of Tenofovir DF Immune Reconstitution Syndrome	When tenofovir DF was administered with didanosine the Cmax and AUC of didanosine increased significantly. Higher didanosine concentrations could potentiate didanosine- associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily. Tenofovir decreases the AUC and Cmin of atazanavir Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations	
Lamivudine	Headache Feeling tired Dizziness Numbness, tingling, and pain in the hands or feet Depression Trouble sleeping Rash Upset stomach, vomiting, nausea, loose or watery stools Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting. Abnormal pancreatic and liver function blood tests	Methadone: An increased methadone dose may be required in a small number of patients. -Coadministration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol- containing medicines with lamivudine-containing medicines	
Rifampicin	Gastro-intestinal: nausea, anorexia, mild abdominal pain, diarrhoea. Cutaneous reactions: mild flushing and pruritus. Hepatitis especially if alcoholic or history of liver disease.	Efavirenz, nevirapine, protease inhibitors. Rifampicin is an enzyme inducer and increases metabolism of oral anticoagulants (warfarin), oral diabetic drugs, digoxin, phenobarbitone and other anti- epileptics and several other drugs and drug classes.	Colours urine, sweat and tears orange-pink.

	Serious: flu-like syndrome and shock		

6.4. Pharmacy: Product Supply, Distribution, Accountability and Storage

All ART treatment, with the exception of the fixed dose combination BIC/FTC/TAF (Biktarvy®) will be procured from the SA Department of Health or municipal facilities and/or pharmaceutical wholesalers, where necessary. Biktarvy® will be procured from Gilead Sciences in patient ready pack-sizes for the duration of the study.
The study pharmacy will maintain accountability records of all investigational drugs and study products dispensed. In addition, records of manufacturer, batch number and expiry information will be maintained by the study pharmacist. Unused study product will be re-issued to the participant at the discretion of the study pharmacist and in accordance with the stipulated dosing schedule.
Dispensing of study product will be done either directly to the study patient or to authorized study staff if the patient is unable to present in person to the study pharmacy. Study product will be stored between 15- 25°C (< 30°C) or in accordance with manufacturer instructions and temperature records will be maintained at the study pharmacy. Unused or never dispensed study drug (IP) may be returned to Gilead Sciences if required, by the sponsor, or may be destroyed on site. Destruction of unused and never dispensed study product will be managed in accordance with in-country regulations and the study pharmacy standard operating procedure (SOP) for study product destruction, after study PI and Gilead sciences Inc, approval.

6.5. Adherence to study products

Adherence monitoring will be done using pharmacy pill count and medication refill information as well as participant self-report. Adherence to study product will be assessed at the study pharmacy at each study visit. This will be achieved by pill count reconciliation and will be documented on a case report form (CRF). Patient self-reported reasons for non-adherence will be assessed and adherence counseling will be provided, if needed, based on pill count and self-report.

6.5.1 Adherence measured by an Electronic Dose Monitoring (EDM) device

In addition to pill counts and patient self-report we will utilize an EDM device to measure adherence of the patients ART medication. EDM devices are an important tool to measure and support adherence. If a pill is missed, recognized through failure to open the pillbox, a SMS will be sent to the patient reminding him/her of the missed dose. In patients who have missed 3 or more doses of their ART medication based on the EDM which will submit real-time short message system (sms) to the study staff, the participants may be called in to the study clinic for enhanced adherence counselling and a single pre-dose PK sample may be taken to determine drug exposure.

7. CLINICAL AND LABORATORY EVALUATIONS

7.1. Schedule of Events (SoE)

Table 4: Study Table of Evaluations

Schedule of Evaluations:									
Description	**Screening**	**Randomization and Enrolment***	**Follow-up**						**End of study**
Trial Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Day/week	**Screening**	**D0 Enrolment**	**D28/ Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 32**	**Week 40**	**Week 48**
Informed consent	X								
Age verification	X								
HIV confirmatory test	X								
Urine pregnancy test in females	X	X	X	X	X	X	X	X	X
Vital signs (incl. height and weight)	X	X	X	X	X	X	X	X	X
Targeted Physical exam/Clinical safety monitoring	X	X	X	X	X	X	X	X	X
Verification of eligibility		X							
Randomization		X							
Safety bloods (Hb, Urea, Creatinine, e-GFR, ALT, AST, Bilirubin, Amylase, platelets FBC *and other* ***as clinically indicated***) #	X	**X**#	X	X	X	X	X	X	X
HEP B surface antigen	X			X		X			X
Drug-susceptible TB diagnosis and/or confirmation of previous results (GeneXpert - including Rif resistance)	X								
Sputum Smear testing*	X			X		X			
Sputum Culture* (genotypic/ phenotypic testing for RIF/INH resistance at month 6 only if positive)				X		X			
CD4+ cell count	X					X			X
HIV-RNA viral load **	X		X	X	X	X		X	X
ART administration		X	X	X	X	X	X	X	X

TB treatment (duration may vary)	X	X	X	X	X				
AEs/SAEs assessment			X	X	X	X	X	X	X
TB associated IRIS Assessment			X	X	X				
Concomitant medication Review	X	X	X	X	X	X	X	X	X
PK blood draws***			X	X	X	X	X		X
Dry blood spots for PK analysis***			X	X	X	X	X		X
Pharmacogenetic sample storage (buffy coat)		X							
PBMC Cell Storage		X				X			X
Hair sample##			X	X	X	X	X		
Stored plasma sample for HIV- 1 genotyping$		X				X$			X$
Electronic Dose Monitoring ®		X	X	X	X	X	X	X	X

* TB tests in accordance with SOC and as indicated

Safety bloods will be repeated at enrolment unless this visit (Enrolment) is within 72 hours of screening, and/or if deemed necessary by clinician/investigator
Screening evaluations to determine eligibility must be completed ≤14 days prior to randomization.

** **if viral load detectable any time after week 24 or at week 24 or 48 participants may be counselled and a VL retest may be done 2-4 weeks later**

*** sampling timepoints and required visits for PK sampling and DBS are specified in protocol section **7.2.3** per arm. Sampling timepoints are also specified for semi-intensive PK sub-study in section **7.2.3. ALL other timepoints marked are considered optional/not required**

6.5.1 Single pre-dose sampling will be done where required in patients with poor adherence (more than 3 missed doses) based on an EDM

hair samples are optional

$ samples will be stored for genotyping in patients with detectable HIV-RNA viral load at week 24 and 48, but may be stored at visits after week 24 if VL detectable after retest at 2-4 weeks
We will conduct resistance testing in real-time for all drugs in the regimen including integrase inhibitor in patients with suboptimal viral responses*. If at week 12 and after, if viral load increases by a log or greater compared to the most recent visit, and after counseling/retest, if there is no improvement of viral load on retest, then resistance testing for integrase and other ARV drug resistance will be done as indicated.*
In patients who are ARV non-naïve may have real time resistance done at baseline if required and at the discretion of the study PI and/or study clinician

® Provision of EDM devices to study participants are optional

The study SoE will be followed except when procedures are clinically indicated or not in accordance with clinical judgement.

7.2. Timing of Evaluations

Refer to Table 4 above for a summary of the evaluations.

7.2.1. Screening Evaluations (Visit 1)

Informed Consent
After identifying potential participants for the study, written screening informed consent will be obtained from these participants.

Age verification
Age verification will be done using the participant SA identification document or other relevant official document to verify the date of birth and age (>18 years)

HIV and TB Testing

HIV confirmatory testing will be carried out using a licensed rapid HIV test. HIV positive results will be confirmed by a second licensed rapid HIV test. Discordant results may be confirmed by ELISA. A sputum sample will be obtained for sputum smear testing, GeneXpert analysis and 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 program). All TB tests will be done in accordance with SOC and TB treatment guidelines. IF participants have been initiated onto TB treatment prior to screening then the duration of TB treatment and baseline TB test screening results will be documented to ensure not > 8 weeks of rifampicin-based TB treatment has been taken and baseline confirmation of TB infection (clinical or microbiological) and rifampicin-sensitive TB on GeneXpert will be documented, where applicable.

Clinical and Laboratory Evaluations

Patients will have all vital signs (including height and weight) measured, a targeted clinical exam or clinical safety monitoring will be done. Safety blood will be drawn for Haemoglobin (Hb), Urea, Creatinine, calculation of Estimated glomerular filtration rate (e-GFR), Aspartate transaminases (AST), Alanine aminotransferase (ALT), total bilirubin, amylase, platelets and full blood count.
Hepatitis B surface antigen testing will be done. Any other testing will be done as clinically indicated. A pregnancy test (using urine sample) is required at every visit if patient is a woman/female of child-bearing potential.

Baseline CD4 count and Viral Load Testing
CD4 cell-counts and HIV-RNA viral load testing will be done.

TB Treatment
If a participant has already initiated on rifampicin-based TB treatment the duration of treatment will be determined and documented to ensure not > than 8 weeks of rifampicin treatment has been completed. TB treatment will be provided and continued in the study as per SOC.

Concomitant Medication Review
Concomitant medication (ConMed) will be reviewed and documented on a ConMed CRF or other source document by the study clinician or designated clinical staff.

Screening evaluations to determine eligibility must be completed ≤14 days prior to randomization.

Screening Failures:

In addition to data being collected on participants who enrol into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the study database. A participant is considered as a screen failure if the participants conditions change upon providing an informed consent, or the outcome of the any baseline tests and assessments fail to meet one or more of the entry criteria or as per investigator discretion.
Participants who has failed screening procedures may be rescreened for entry into the study, at the discretion of the clinician or investigators.

7.2.2. Baseline, Randomization and Enrollment (Visit 2)

Randomization.

Informed Consent
Once the participants meet all the conditions of the inclusion criteria, the informed consent form will be reviewed at enrolment.

Verification of Eligibility and Randomisation
Eligibility criteria will be assessed by a study clinician and documented prior to randomization. On- study entry evaluations will occur after randomization. If the patient meets the enrolment criteria and verification of eligibility, the site must then randomize each new patient according to Randomization Procedures outlined in the protocol. Baseline evaluations (according to SoE, Table 3) will be completed at the screening and enrolment visits (unless otherwise stated by the Study PI or study clinician) and patients should start on assigned study therapy as soon as possible after randomization.

Clinical and Laboratory Evaluations
Patients will have all vital signs (including weight) measured, a targeted clinical exam or clinical safety monitoring 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 bloods done at screening visit.

A pregnancy test (using urine sample) is required at every visit if patient is a woman/female of child-bearing potential.

Culture for genotypic/phenotypic testing for RIF/Isoniazid INH resistance testing will be done as per standard of care for TB treatment.

ART Administration and *TB Treatment*

ART treatment will be administered in accordance with the study arm to which the participant is randomized. The Intervention Arm ART will consist of BIC/FTC/TAF as a fixed dose single tablet, coformulation (Biktarvy®). Control arm participants will receive a DTG-based regimen in accordance with standard of care.
All TB treatment will be in accordance with standard of care and South African National TB treatment guidelines. All participants must be on a rifampicin-based TB treatment regimen (i.e have rifampicin-sensitive tuberculosis). If a participant has already initiated on rifampicin-based TB treatment the duration of treatment will be determined and any further changes to regarding TB treatment since screening will be documented to ensure not > than 8 weeks of rifampicin treatment has been completed.

Concomitant Medication Review
Concomitant medication (ConMed) will be reviewed and any changes from screening will be documented on a ConMed CRF and new concomitant medication will be recorded.

HIV-1 Genotyping
Plasma samples will be stored for later HIV-1 genotyping in patients meeting criteria for virologic failure at visits at Week 24 or later (virologic failure defined as viral load > 400 copies/mL on repeat VL testing 2-4 weeks after that visit, following adherence counselling). Real-time resistance testing may be done at any time in the study, due to sub-optimal viral responses based on clinical judgment after discussion with investigators. We will conduct resistance testing in real-time for all drugs in the regimen including integrase inhibitor in patients with suboptimal viral responses. If at week 12 and after, if viral load increases by a log or greater compared to the most recent visit, and after counseling/retest, if there is no improvement of viral load on retest, then resistance testing for integrase and other ARV drug resistance will be done.

Pharmacogenetic testing
Buffy coat samples will be stored for future pharmacogenetic testing in patients who agree on informed consent for storage of these samples.

7.2.3. Post Entry Evaluations: Follow-ups (Visits 3 to 9)

Clinical and Laboratory Evaluations

Patients will have all vital signs (including weight) measured, a targeted clinical exam or clinical safety monitoring 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** at all follow up visits. Hep B surface antigen testing will be done at **visit 4, 6 and 9**. A pregnancy test (urine) is required at every visit if patient is a woman of child-bearing potential.

TB Testing
Sputum smear testing may be done **at visit 4, and 6** or as indicated as per standard of care in the National TB treatment guideline. Sputum for Culture will be done in accordance with SOC and TB treatment guidelines at **visit 4, 6.** Genotypic/phenotypic testing for RIF/INH resistance may be done at visit 6 if culture positive.

CD4 count and Viral Load Testing

CD4 cell-counts (**at visit 6 and 9**) and HIV-RNA viral load testing (**at visit 3, 4, 5, 6, 8 and 9**) will be done.
If viral load is detectable any time *after* week 24, or *at* week 24 or 48, participants may be counselled and a retest done 2-4 weeks later.

ART Administration and *TB Treatment*

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). TB treatment will be provided in accordance with standard of care until completed.

Adverse events (AEs) and Serious adverse events (SAEs) assessment

All participants will be assessed for any Aes and SAEs at every visit and these will be documented and reported accordingly.

*TB associated (*Immune Reconstitution Syndrome) *IRIS assessment*

A TB associated IRIS assessment will be done at **visit 3, 4 and 5.** Monitoring and assessment for and management of IRIS will be done at specified visits and as clinically indicated as well as in accordance with time of TB treatment initiation.

Concomitant Medication Review

Concomitant medication (ConMed) will be reviewed and any further changes from screening and enrolment will be documented on a ConMed CRF at all follow up study visits as per SOE.

Pharmacokinetic (PK) Study

PK assessments will be performed in the study. The pharmacokinetic sub-study aims to assess the PK of BIC, FTC, TAF, and intracellular TFV-DP and DTG when given twice daily and co- administered with Rifampicin vs. during TB treatment vs when given alone after TB treatment completion. All participants who consent to participation in this sub-study will be included. 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. PK sampling may be delayed/deferred if the participant missed the last dose/s of drug or if rifampicin has been temporarily withheld for any reason during TB treatment.

PK sampling:

PK samples (~ 4 ml plasma and DBS) will be collected on all participants **in the BIC arm** using sparse sampling techniques as follows:

Visits 3 and 5

Pre-dose (within 10-14 hours post *previous* dose *during twice daily dosing*),
At 1 to 4 hours post-dose in the study clinic

After the completion of TB treatment (discontinuation of rifampicin) **at Visit 7 or after** (if extended TB treatment duration)
at pre-dose (**20-28hr post previous dose** for once daily
dosing) At **1 to 4 hours post-dose** in the study clinic

Additional pre-dose PK samples (~4ml plasma and DBS) **in both the BIC and DTG arm of the study** will be collected **at Visits 4, 6, and 9** (to correlate with VL results, where applicable).

Pre-dose (i.e. within 20-28h of previous dose during once daily dosing after TB treatment completion; within 10-14h post previous dose during twice daily dosing)

Semi-Intensive PK sampling study in a subset of patients in the BIC arm ONLY

Semi-intensive PK sampling (~ 4 ml plasma and DBS) **on a subset of approximately 30-40 patients in the BIC arm** will be conducted as follows:

at Pre-dose 0, 1, 2, 4, 6 and 8-12 hours, post-dose at Visit 3 and 5 [during twice daily dosing on rifampicin]

at pre-dose 0, 1, 2, 4, 6-8 and 24-25 hours, at Visit 7 or after [once daily dosing after rifampicin stopped].

This proposed PK study in a subset of patients will be used to help stabilize the PK model so that we can fully characterize the PK profile of study drugs with and without co-administered TB treatment. Sparse data on the full group from the sparse sampling done on all patients will help characterize magnitude of and sources of variability. The preference will be for these participants to be enrolled early in the trial so that these PK data can contribute to interim analyses, if needed.

Hair sampling.

Optional hair samples will be collected at **Visit 3, 4, 5, 6 and 7.**

Peripheral Blood Mononuclear Cell (PBMC) Cell Storage

PBMC samples may be taken for storage and future testing.

HIV-1 Genotyping

Plasma samples will be stored for later HIV-1 genotyping in patients at visit 6 and 9 (or any timepoint after visit 6) in patients meeting criteria for virologic failure at visits at Week 24 or later (virologic failure defined as viral load > 400 copies/mL on repeat VL testing 2-4 weeks after that visit, following adherence counselling).
Real-time resistance may be done at any time in the study, due to sub-optimal viral responses based on clinical judgment after discussion with investigators. We will conduct resistance testing in real-time for all drugs in the regimen including integrase inhibitor in patients with suboptimal viral responses. If at week 12 and after, if viral load increases by a log or greater compared to the most recent visit, and after counseling/retest, if there is no improvement of viral load on retest, then resistance testing for integrase and other ARV drug resistance will be done as indicated.

7.2.4. Study Visit Window and Unscheduled Visits

The window period for all scheduled monthly study visits (visit 3, 4, 5) is ±7 days and ± 14 days for visit , 6 7, 8 and 9. Any visit for which a patient attends outside of the specified visit window but not in addition to those required as per the 'schedule of evaluations' should be considered as an early/late visit. The assessments which are undertaken as part of an early/late visit should reflect those for the visit which will be or has been missed. Any additional assessments should be undertaken as clinically indicated.

7.3. Evaluations during study

7.3.1. HIV testing will be done using approved rapid tests (initial and confirmatory). TB evaluations will be done to confirm drug-susceptible TB and document rifampicin-based TB treatment regimens, where required.

7.3.2. Targeted Physical Exam/Clinical safety monitoring

A targeted physical examination and clinical safety monitoring will be performed at every study visit after baseline (in accordance with the SoE) and on subsequent clinically required visits. This will include neuropsychiatric evaluations.

7.3.3. Pregnancy Testing

For women of reproductive potential: The pregnancy test using a urine-test performed at all visits study according to SoE must be negative.

7.3.4. Concomitant medication reviews will be conducted by the clinical staff.

8. CLINICAL MANAGEMENT ISSUES

8.1. Clinical Management Issues at baseline and follow up during study conduct

Patients who meet study eligibility criteria at screening and are enrolled into the study will be followed for 48 weeks. All other safety and clinical will be done in accordance with the **Schedule of Evaluations** (SoE) and in line with current South African Department of Health Adult ART Guidelines and the TB treatment guidelines in co-infected patients.

The INSIGHT study will use the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table) Version 2.1, July 2017 to assess and grade adverse events or baseline abnormalities.

8.2. Specific Clinical Management Scenarios

8.2.1. Withdrawal of study drug

A clinician/investigator may withdraw one or all drugs in the study treatment in the event of a serious or life-threatening adverse event that is possibly or probably related to study drug, if this is deemed to be in the patients' best interest. This will be discussed with the study PI or designee before the decision is made, unless in an emergency situation. All safety issues need to be followed up until resolution to < Grade 2 (DAIDS Table for Grading Adult and Paediatric Toxicity Events)

8.2.2. Virological suppression and definition of treatment failure

HIV-1 RNA (viral load) testing will be done and monitored during follow-up to ensure adequate viral suppression from baseline. If patients rebound after achieving <50 copies per/ml then adherence counselling will be done. 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. A treatment failure will be defined as a participant with a viral load >400 copies/mL at week 24 or 48 or as defined by the FDA snapshot algorithm. Patients with confirmed virological failure will be switched to an appropriate second-line regimen in accordance with standard of care and the National ART Treatment guideline and followed up in the study until transition to standard of care within a DoH or other healthcare facility.

Real-time resistance testing may be done at any time in the study, due to sub-optimal viral responses based on clinical judgment after discussion with investigators. We will conduct resistance testing in real-time for all drugs in the regimen including integrase inhibitor in patients with suboptimal viral responses. If at week 12 and after, if viral load increases by a log or greater compared to the most recent visit, and after counseling/retest, if there is no improvement of viral load on retest, then resistance testing for integrase and other ARV drug resistance will be done.

8.2.3. Reporting AE's

The most common adverse effects known to be associated with the study drugs are included in the current version of the Investigator brochure and package insert/FDA label for Biktarvy. Some of these are summarized in the protocol (see Table 2 above). The investigators are responsible for reporting all Grade 3 and Grade 4 adverse events that are observed or reported during the study, regardless of whether they are thought to be related to the study drugs as recorded in patients chart notes. All Adverse Events including SAEs will be reported in accordance with ICH and SA GCP guidelines.

8.2.4. TB treatment

If participants who are randomized and enrolled into the study are later determined to be resistant to any of the drugs in the TB regimen then treatment for TB will be adjusted in accordance with standard of care- for resistance (e.g. isoniazid -monoresistance) or if rifampicin mono-resistance or multi-drug resistance is confirmed then the participant will be treated in accordance with national TB treatment guideline. If the patient is in the standard of care (SOC) arm on dolutegravir-based ART, then the participant will be continued on dolutegravir and the dose adjusted in accordance with SOC for patients who on rifampicin-based/non-rifampicin-based TB treatment. If the patient is in the intervention arm on Biktarvy the participant will either be continued on Bictegravir once daily (if not on rifampicin) or switched to appropriate SOC ART (based on investigator discretion) and continued to be followed up in the study in accordance with intention to treat analysis.

8.3. Guiding Principles of Toxicity Management

For adverse events, that is in the investigator's judgment may be due to study drugs, the following general approach to management should be applied however clinical judgement and investigator decision may be overriding: General management principles

8.3.1. Grade 1 Adverse Events

In general, for grade 1 events the patient will be followed carefully and the study drugs will be continued.

8.3.2. Grade 2 Adverse Events

For grade 2 events the patient will be followed more closely, with additional laboratory and/or clinic visits as necessary; drugs should be continued unless in the view of the clinician/investigator this would be unsafe.

8.3.3. Grade 3 and 4 Adverse Events

Any grade 3 or 4 event should be carefully assessed. The research clinician should rule out other possible causes of the symptoms before discontinuing study medication. When possible, concomitant medications should be with-held first at the discretion of the research clinician/and or after discussion with investigators, if causality is suspected. If after careful assessment and in the clinician's judgment the event is due to study drug(s), the causative study drug(s) may be withheld, after discussion with investigators unless in an emergency situation. The patient should be permanently discontinued from study medications if it is in their best interests to do so. Further HIV treatment will be directed by the clinician in consultation with the investigator. The patient will continue to be followed according to the protocol. Other adverse events of any grade not thought to be due to the study drugs, should be managed at the discretion of the research clinician; study treatment should be

continued, if possible.

8.4. Specific toxicity management

Liver toxicity:

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of IP and the Follow-up period.
If ALT >2 × ULN, liver chemistries should be monitored weekly for 2 weeks, then every 2 weeks thereafter until normalized.

While receiving IP co-administered with TB treatment, both will be stopped if any of the following liver chemistry criteria are met:
ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required) NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
ALT ≥3 × ULN with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR
ALT ≥5 × ULN; regardless of symptoms
After completion of TB treatment, while receiving IP, ART will be stopped if any of the following liver chemistry criteria are met:
ALT ≥3 × ULN **and** bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required) NOTE: Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 × ULN, then the event meets liver stopping criteria;
ALT ≥3 × ULN (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 ≥3 × 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 ≥ 5 × ULN and <8 × ULN (after TB treatment is complete) that persists ≥2 weeks (with bilirubin <2 × ULN and no signs or symptoms of acute hepatitis or hypersensitivity); ALT ≥5 × ULN but <8 × ULN (after TB treatment is complete) and cannot be monitored weekly for >2 weeks; and subjects who develop ALT ≥5 × ULN should be followed weekly until resolution or stabilization (ALT <5 × ULN on 2 consecutive evaluations);
ALT > 8 × ULN; regardless of symptoms.
If liver stopping criteria are met, the study team, in collaboration with investigators where will determine next steps, which may include a liver-sparing TB regimen, relevant laboratory tests to look for alternative causes, or other measures.

Renal Toxicity, Immune Reconstitution Inflammatory Syndrome (IRIS) events and Neuropsychiatric adverse events will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table) Version 2.1, July 2017 and will be managed in accordance with local guidelines and recommendations for Biktarvy based on investigator brochure. Additional specific clinical management criteria will be outlined in the study specific manual or clinical SOPS.

8.5. Reporting Serious Adverse Events (SAEs)

The following Serious Adverse Event will be reportable to the database and regulatory authorities: AE's that:

- Results in death
- Is immediately life threatening at the time of occurrence
- Results in persistent or significant disability or incapacity
- Requires in-patient hospitalization or prolongs hospitalization
- Results in a congenital anomaly or birth defect
- Is deemed an "important medical event" by the Investigator (may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient e.g. convulsions.
- This will include any adverse event that *is unexpected, but related* to the study product, eg cardiac failure

8.6. Safety Monitoring

Procedures for assessing safety

At each clinic visit patients will be asked about changes (adverse events) that have occurred since their previous visit. Physical assessments will be performed at baseline and on subsequent scheduled visits or as clinically indicated.
Safety laboratory investigations will be performed at screening and in accordance with the schedule of evaluations, as well as determined by the study clinician based on the safety evaluations.

Screening tests and scheduled subsequent visits will include: Liver function, renal function, full blood count: At screening, baseline and study visit until week 48 of follow up.
Pregnancy test: At screening, baseline and every month thereafter as per the SoE. Monitoring for TB associated IRIS events, as per SOE and SOC Neuropsychiatric adverse events, symptoms of depression and suicidal ideation

Any adverse events detected will be graded according to a modified version of the toxicity criteria produced by the Division of AIDS and coded using Medra Coding or similar. Serious adverse events will be reported to SAPHRA and the UKZN Biomedical Research Ethics Committee. (BREC) according to their specific requirements.

Discontinuation of study treatment:

The investigator may discontinue a patient from study drug or treatment/s in the event of a severe or serious adverse event, or at any time he/she thinks it is in the patient's best interest. If there is a medical reason for withdrawing study treatment, the patient will remain under the supervision of the investigator until satisfactory health has returned irrespectively of the reason for discontinuation. The frequency of patient review will be determined by the clinical need to ensure optimal care.

Withdrawal from the study

Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time for any reason. Patients who withdraw their consent will not have to undergo any follow up procedures. The study investigator may withdraw participants from the study if it is in the participants best interest to do so or if participant unable or unwilling

to adhere to study visits or procedures.

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 data safety monitoring committee (DSMC). The DSMC will be comprised by 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. If at week 12 and after, if viral load increases by a log or greater compared to the most recent visit, and after counseling/retest, if there is no improvement of viral load on retest, then resistance testing for integrase and other ARV drug resistance will be done i.e. if viral loads are declining and then stop declining (even with adherence counseling and retest ~2 weeks later), after 12 weeks on treatment, then real time resistance testing will be done and appropriate steps taken should resistance be detected. Resistance testing data will be shared with the DSMC.
A full DSMC review will be scheduled at least annually after opening to accrual or on a frequency determined by the DSMC. For each full review, summaries provided to the DSMC will be described in an open report that is also available to study investigators and provides data from both arms combined and a closed report in which data will be broken down by treatment arm (available only to the statistician and the DSMC and/or DAIDS medical officer, where applicable). Participants' baseline demographic and medical history will be summarized. Review of study conduct will address site accrual, premature study discontinuations and their reasons (administrative or loss to follow-up), tracking of potential losses to follow-up, data completeness. The SMC will also review participants' safety data, frequency and causes of death, as well as incidence of virologic failure.
In addition, internal reviews of patient charts, SAE reports and regulatory submissions will be conducted by the CAPRISA quality assurance (QA) 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.

9. STATISTICAL CONSIDERATIONS

9.1. 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 REFLATE[28] and INSPIRING[24] trials. Assuming an 85% response rate for BIC/FTC/TAF at week 24,[7,8,17] 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 DTG arm to provide safety and efficacy parameters for standard-of-care treatment in the local setting, to contextualize the BIC arm results and to serve as a baseline comparator group for safety and efficacy parameters.

9.2. Analysis including statistical methods:

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 summarized 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.

Pharmacokinetic 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 (C_t, C_{max}, AUC) will be computed for all subjects who undergo semi-intensive sampling. Analytes to be measured include BIC, TAF, intracellular TFV-DP and DTG. PK parameters will be estimated by application of a nonlinear model using standard noncompartmental methods (WinNonlin® software). Descriptive statistics (n, mean, standard deviation (SD), coefficient of variation [%CV], minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI) will be calculated. Geometric mean ratios for C_t, C_{max}, 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.

Optional: Hair samples may be collected as part of the study, and if budget allows, exposures of BIC, TAF and FTC and DTG will be measured. This may help to distinguish issues of adherence vs. low PK due to drug interaction and to determine associations between drug levels in hair and viral suppression.

9.3. Explanation on how the results of this study will be used

Clinical trial data of the safety, efficacy and tolerability of BIC and TAF in HIV endemic African settings, particularly in the context of HIV and TB co-infection, which accounts for approximately 50-80% of prevalent cases, is unavailable.
This study will 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. If the outcome of the study is favourable, there may be potential to have a new and highly desirable treatment option for patients with HIV-associated TB in settings where this drug is already available. 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 largest incidence of HIV and TB co-infection rates in the world.

9.3.1. Publication of results: Study results will be published in a peer-reviewed journal/s and disseminated at appropriate national or international conferences.

10. HUMAN PARTICIPANTS

10.1. Patient Recruitment

Patients will be recruited from the King Dinuzulu, District Hospital where the CAPRISA Springfield Clinical Research site is located in Durban, KZN, well as from surrounding SA DoH and municipal clinics or facilities. Recruiters will be stationed within the HIV/TB facilities and potential patients can be approached through several mechanisms:

HCT services – HIV testing and counselling is routinely offered at the SA DoH and municipal facilities which provides an ideal opportunity to conduct pre-screening.
Each Health Care Facility has an in-house National Health Laboratory Service. All HIV-infected, new patients with a positive smear and GeneXpert Rifampicin sensitive can be identified at the laboratory and followed-up by a CAPRISA recruiter based at the facility.
Clinic referrals - Clinicians or Professional Nurses at selected DoH and/ municipal facilities will be informed on the study protocol and can refer patients for enrolment.

10.2. Ethics

Study Impact and Justification:
Our study will fill key knowledge gaps, on the use of InSTI's for the treatment of HIV-1 infection in the context of patients with tuberculosis co-infection on a rifampicin -based treatment regimen. The study will have high impact given that firstly, South Africa and KwaZulu Natal in particular are in the epicentre of the TB-HIV co-epidemic with >70% co-infection rates among TB patients.
Secondly, there are no data to support the safety and efficacy of Biktarvy® twice daily for the treatment of HIV-1 infection in patients with TB on rifampicin co-treatment and it is unlikely that this highly potent, safe, drug with a high resistance profile, that may provide effective future ART treatment options, will be made available in Africa if it cannot be used

in patients with drug- susceptible tuberculosis. 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 lack of data in HIV-TB co-infected patients

10.3. Regulatory and ethical review

The study will be conducted under the oversight of the University of KwaZulu-Natal, Nelson R Mandela School of Medicine Biomedical Research Ethics Committee (BREC) and the South African Health Products Regulatory Authority (SAPHRA). The study protocol will be submitted to the ethics committee and regulatory entities by the Principal Investigator and reviewed and approved by the ethics committee prior to study initiation. The investigator will provide progress reports and all other information required by the ethics committee/regulatory institutions to conduct its reviews. On approval of the study we will register the study with SANCTR (South African National Clinical Trials Register). We will also seek approval for the study from the SA DoH and/or other relevant stakeholders

10.4. Informed consent process

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. However, consent for specimen storage is not a pre-condition for study participation. Participants will be provided with a copy of their informed consent forms if they wish to receive them.

Study informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The informed consent forms will also be translated into *isiZulu* and the accuracy of the translation will be verified through independent back-translation.

The study consent process will include an assessment of each potential participant's understanding of the study and the risks and benefits of study participation, which are essential for an informed decision. Participants who are not able to demonstrate adequate understanding of key concepts will not be enrolled in the study.

10.5. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only.
Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ethics committee or the sponsor's designee. CAPRISA External monitors will also review clinical information. QA officers and Head of QA will not be on delegation of Authority Log as these staff serve as internal and/or external monitors.

10.6. Good Clinical Practice

The study will be carried out according to ICH-GCP and South African Good Clinical Practice Guidelines (SA GCP). The Principal Investigator and/or designee will ensure that the study staff are conducting the trial in accordance with current SA GCP and ICH-GCP guidelines, ensure appropriate human subjects training for all study staff and safety of all trial participants. The study protocol and patient informed consents and all future revisions of these latter documents, will be reviewed and approved by the UKZN Biomedical Research Ethics Committee (UKZN BREC) and South African Health Product Regulatory Authority (SAPHRA)) prior to implementation. Quality control officers will perform daily

quality checks on patient data and a Data manager will oversee the maintenance and completeness of the patient data.

All Serious Adverse Events (SAE's) will be reported to UKZN BREC and SAPHRA within 7 business days of site awareness. The Data Safety Monitoring Committee (DSMC) will meet at designated timepoints to analyse and discuss safety data and make recommendations for the continuation of the trial and participant care.

11. DATA MANAGEMENT

The entry, storage and cleaning of study data will be conducted under the oversight of the CAPRISA Data Management core.

11.1. Data Collection and Methods

Data will be collected on one-ply case report forms (CRFs) or E-CRFs which will be developed by the study team. All site study staff will be trained in the correct completion of CRFs. If data entered on the CRFs are taken from an external source (e.g., laboratory reports, patient records), the source documents will be maintained in the participant's medical chart or study file at the site and will be available for review. When CRFs undergo changes, appropriate authorization is obtained from the study team and all the changes are clearly documented. Each revision of the CRF will contain a clearly identified version number. Case Report Forms (CRFs) will be provided for each patient. At screening participants will be issued a Screening Identification number (SID) by the site, where applicable. At enrolment participants will be identified by a patient identification number (PID) provided by the CAPRISA Data Management Center. This PID is used on all CRFs to identify the participant for the duration of the study.
Data will be collected at all study visits. Patients will be required to attend at the clinic for a screening visit and if found to be eligible, informed consent will be administered and the patient will be enrolled into the study. Post enrollment visits will be done in accordance with the SoE and where clinically indicated.

11.2. Information management (Database) and analysis software

The INSIGHT study will be using the DFdiscover clinical trial database system, 2018 V 5,1,4, which is compliant with FDA 21 CFR Part 11 regulations and the software is ISO 9001:2015 certified. DFexplore is a desktop/ laptop software application that forms part of the DFdiscover clinical trial management system, which supports data collection by paper, scanned document and fax. All methods can be used in the same study. which is used to enter, review and modify subject data, and to submit it over the internet to a DFdiscover server, also known as Electronic Data Capture or EDC. DFcollect is a mobile software application that forms part of the DFdiscover clinical trial management system, by using a compatible mobile device. Statistical Analysis Software (SAS) is used for analysis purposes.

11.3. Data Security, Protection/Confidentiality, Flow, Imported Data and Data coding

<u>Database security:</u>
CRFs will be scanned to the DFdiscover server via encrypted communication, and makes use of electronic signatures, consisting of usernames and passwords. Permission levels are assigned based on study data collection and review requirements. Study data is stored

on the CAPRISA server housed at the CAPRISA head office at DDMRI (Doris Duke Medical Research Institute) and will be backed up at regular intervals, with backups stored in a secure location with restricted access.

Data Protection/Confidentiality

Participants will be assigned a unique identifier. Any participant record or data set will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred externally. The participant will be informed that his/her study-related data will be used in accordance with local data protection law. The level of data disclosure will also be explained to the participant. The participant will be informed that his/her study records may be examined by monitors or other authorized personnel appointed by the PI/sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Data flow:

For paper-based studies:

CRFs will be scanned into DFexplore which uses optical character recognition (OCR) to read the check boxes and numerical fields on the CRFs and store them in the study database. Any fields not recognized by the OCR system will be entered manually by the Data Encoders. A Data encoder will validate all data by cross-checking the scanned version to what is recorded through OCR, into the database. A second data encoder will validate the same set of data for verification. Data encoders will create queries, should any data be invalid or illegal. All queries arising during validation of the data will be recorded in quality control (QC) reports and sent to the sites on a regular basis. Any queries resulting in a change to the database will be documented and attached to the original CRF.

Imported data:

Any data that will be imported into a study database will include an encryption component in order to ascertain the reliability of the data. Files will be stored on the CAPRISA Sharepoint server.

Data coding:

This study will make use of MedDRA coding for all Adverse Events. This function will be performed by the study clinician or designee. MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry.

Instructions concerning the recording of study data on CRFs will be provided by the CAPRISA Data Management core. Completed CRFs must be checked by the designated on-site Quality Control officer and upon approval, must be submitted into the data management system.

CAPRISA Data encoders and Data Managers located at the CAPRISA offices verify and validate the patient data. Quality control reports are produced, and approved data then added to the study database according to CAPRISA data management (SOPs) Study Operating Procedures.

It is the responsibility of the CAPRISA data management core to assure the quality of computerized data for the study. Study staff will be trained in source documentation requirements and in proper forms completion techniques.

11.4. Data Storage

Original and electronic copies of study CRFs and related documents will be stored securely both during and after study completion. During the study, the original completed forms for each participant will be kept on-site at the CAPRISA Springfield Research

site/other CAPRISA site/offices. The forms will be stored in an access secured, double-locked, fire and waterproof room. Upon completion of the study, and finalization of the database for analysis, the original forms will be bound and kept off-site (separate site) for long-term storage, where applicable.
Docufile or other relevant storage or archiving facilities, designated by CAPRISA will be used to archive large amounts of documents. Database files will be password-protected, and access to the files will be limited to authorized study staff members only. Quality control and validation checks will be performed and data cleaning steps will be undertaken prior to finalizing the study database for analysis. Analyses will be conducted by study statisticians.

11.5. Quality control (QC)/ Quality assurance (QA)

A quality check of the study forms will be conducted before the forms are entered scanned or faxed. The QC procedures will specify the following types of checks:

- There are no illegible handwritten items, spelling errors, etc.
- Responses are clearly within designated spaces.
- All fields are completed with participant data or reason for no data is noted in or near the field.
- The participant's PID is recorded on all pages of the forms.
- The CAPRISA laboratory manager will also be responsible for checking that all the laboratories involved in the study are complying with QA procedures. The CAPRISA pharmacist will check that all drug related documentation meets Good Clinical Practice (GCP) requirements for drug accountability.
- QC and QA of data will be undertaken according to the relevant SOPs and Study specific procedures manual, where applicable.

12. BIOHAZARD CONTAINMENT

As the transmission of HIV and other pathogens can occur through contact with contaminated needles, blood, blood products, and other secretions, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and collection of other specimens and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDICE 1: EXAMPLE OF PARTICIPANT INFORMED CONSENT

INSIGHT PATIENT INFORMED CONSENT

STUDY INFORMED CONSENT FORM

****The Study Informed Consent has been appended as a separate attachment*