

Zidovudine, lamivudine and dolutegravir (AXD) Relative to Tenofovir, lamivudine and dolutegravir (TXD) In Second Line Antiretroviral Therapy (ARTIST) Trial: a randomised controlled trial

ARTIST Trial Protocol Version 2.1

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Summary

As the HIV epidemic matures and more patients are initiated on antiretroviral treatment, focus is on ensuring that those on antiretroviral therapy are virologically suppressed. The strategy to support virological suppression on second-line includes the provision of ART that has a low pill burden, good tolerability, low toxicity, is easily monitored, has a high barrier to resistance and that is low cost. A fixed-dose combination of tenofovir, lamivudine and dolutegravir (TDF/3TC/DTG: TXD) fulfils these criteria.

Indirect evidence suggests that recycling the TDF/3TC backbone from first through to second line could protect the regimen from the development of resistance mutations to DTG. This study will be a randomised, open-label, active-controlled trial aiming to determine the virological suppression of patients failing the standard of care first-line regimen (TDF/emtricitabine(FTC)/efavirenz(EFV)) who have been switched to a DTG based second line with a recycled TDF/3TC backbone. It will comprise two stages, with stage one providing a supplemental dose of DTG for 14 days to compensate for the enzyme-inducing effect of the discontinued EFV. Stage two will compare the fixed-dose TXD without supplemental DTG to the World Health Organization-recommended second-line regimen (zidovudine/3TC/DTG).

1. Background and rationale

As the HIV epidemic matures, focus is turning to the last 90 in the 90-90-90 strategy: aiming for 90% of those on treatment to be virally suppressed by 2020 (1). Antiretroviral (ARV) drug resistance necessitates a change in regimen and is a major obstacle to achieving this target. Resistance results not only in poor outcomes for individuals, but also compromises public health treatment strategies, interferes with efforts to reduce transmission and financially burdens healthcare systems (2).

By 2020, 25.6 million people could be receiving ARVs in Sub-Saharan Africa, and up to 3 million (15.6%) will be on second-line treatment (under conditions of perfect retention, immediate switching and universal viral load (VL) monitoring, as is done in the South African context) (3). This proportion is expected to increase further by 2030 (3). The reasons for this potential growth in demand for second-line treatment are diverse, but include the fact that the cohort on ARVs is maturing; about half the patients on ARVs worldwide started treatment before 2010 (3) and as patients remain on treatment long-term, their cumulative incidence of disengagement increases (4). This population of patients with poor engagement has a large requirement for second-line treatment, as 30% who then restart first-line treatment have been shown to have resistance mutations (5). Challenges with ART adherence while on treatment also contribute to first-line ART failure and requirement for second-line.

1.1. Dolutegravir as second-line

Currently in the Western Cape, the standard of care for first-line treatment is the fixed dose combination of tenofovir, emtricitabine and efavirenz (TDF/FTC/EFV – TXE regimen, where X can stand for FTC or lamivudine (3TC) interchangeably) unless there are contraindications, and the first choice second-line is

zidovudine, lamivudine and lopinavir/ritonavir (AZT/3TC/LPV/r) (6). This guidance is in-line with World Health Organization (WHO) recommendations (7).

Those requiring second-line treatment often have health facility and regimen-related barriers to engaging with treatment, but second-line options are less ‘adherence-friendly’ than the first-line ARVs that have already failed. Second-line options are currently 2.5 to 3 times more expensive than WHO recommended first-line treatment (3,8), require additional monitoring (haemoglobin for AZT toxicity and cholesterol and triglycerides for LPV/r) (6), require a more burdensome twice daily dosing (9) and are poorly tolerated (6,9). The gastro-intestinal side effects of the protease inhibitors (PIs) make adherence difficult, increasing the risk of the development of virologic failure and contributing to the reluctance of patients and clinicians to switch to second-line.

The WHO recommends regimens that have low toxicity, low cost, high genetic barriers to resistance, high potency, and usefulness across different populations (10). Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), fulfils many of these criteria: it has good tolerability and has been shown to have a lower risk of discontinuation in a regimen with two nucleoside reverse transcriptase inhibitors (NRTIs), has a low pill burden with once daily dosing (11,12), as well as a lower potential for drug-drug interactions than the current standards of care (EFV and LPV/r) (12). At \$75 per person per year, a new generic fixed dose formulation of DTG with TDF and 3TC is cheaper than both current first and second-line options (13). A major transition to newer drugs, including DTG, could represent savings up to US\$3 billion globally by 2025 (14) and allow more people to be on ART within available resource limits (15).

Multiple studies have shown DTG to be a more efficacious option for first-line compared with EFV (SPRING-1 and SINGLE), raltegravir (SPRING-2) and darunavir(DRV)/ritonavir(r) (FLAMINGO) (11). As a second-line regimen it has proved superior to raltegravir with an optimised backbone in patients with resistance to at least two ARV classes, irrespective of the backbone drugs (SAILING) and has been shown to be effective with twice daily dosing at achieving viral suppression even in the presence of resistance to other integrase inhibitors (VIKING, VIKING-3 and VIKING-4).

In the DAWNING study, DTG with two NRTIs (at least one fully active) was superior in safety and efficacy to the current standard of care (LPV/r with two NRTIs) as second-line treatment, achieving 82% viral suppression (VL<50 copies/ml) compared to 69% of the LPV/r patients (16). This provides compelling evidence to consider DTG as the preferential second-line option. The WHO now supports the use of DTG as second-line for its superiority in viral suppression, quicker CD4 recovery, tolerability and safety profile, and suggests that both adults and children failing a non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI based first line regimen should be given DTG as the preferred second-line option (12). The South African public sector is planning to introduce a second-line regimen of AZT, 3TC, Dolutegravir (AXD) for patients failing TXD in the near future (planned mid-2019).

1.2. Choice of NRTI backbone

1.2.1 DTG Resistance

DTG selects for the R263K mutation and sequential mutations along the same pathway that reduce the

efficacy of DTG. However the R263K mutation may reduce viral replicative capacity and reduce the magnitude of viral rebound (11,17). DTG has a very high barrier to resistance, but resistance has been described using DTG monotherapy as maintenance in the DOMONO study (three patients) (18) and the MONCAY study (two patients) (19). In both studies, this resistance was delayed and tended to occur 6-12 months after switch (18,19).

DTG resistance has also been described in patients on DTG as second-line. The DAWNING and SAILING studies each found two patients who developed INSTI (including R263K) mutations (17,20). There have also been reports of the development of integrase resistance in treatment-naïve patients initiating TDF/XTC/DTG (TXD regimen) (21,22), with the R263K mutation as a pathway to the development of resistance (22). This potential for the development of resistance means that the backbone must be carefully considered in order to ensure the durability of a DTG-based second-line regimen.

1.2.2 Optimised backbone

The DAWNING study showed superiority of DTG with an optimised backbone over a PI second-line and the results can be applied when there is at least one fully active NRTI (16). Thus the WHO recommends the use of an optimised backbone to improve the durability of DTG regimens (2,10,12). However, optimisation requires genotypic resistance testing, and in the DAWNING study genotyping was used to ensure the selection of at least one fully active NRTI (16). This testing is not widely available in low and middle income countries (LMICs) (23), and where it is, its use is restricted by cost to second-line failures only. Without genotypic testing to determine the optimum regimen, the WHO recommends AZT (AXD regimen) as the first choice backbone for second-line if failing a regimen containing TDF or abacavir (ABC) (12).

1.2.3 Recycling TDF and XTC (3TC or FTC) in a second-line backbone

However, there are two arguments for recycling TDF and 3TC or FTC as the backbone for a DTG-based second-line (TXD regimen) instead of using an optimised backbone. Firstly AZT is less well tolerated, requires twice daily dosing, needs more intensive monitoring and is less efficacious than TDF if there is no resistance to either drug (6,9).

Secondly, it is well established that NRTI resistance impairs viral fitness in both in vitro and clinical studies, particularly the M184I/V mutations (3TC and FTC). In the EARNEST trial, the NRTI/LPV/r combination outperformed the LPV/r/raltegravir and LPV/r monotherapy arms (86%, 81% and 78% suppression respectively) in patients who were no longer responding to a first-line combination containing two NRTIs, even though 95% of the enrolled patients had at least one NRTI mutation and 59% had no active NRTIs (24). Similar results were found in the SELECT and the SECOND LINE trials (25,26), showing that compromised NRTIs could be recycled with a boosted PI.

Oliveira et al showed that under DTG drug pressure in vitro, only the wild type virus was able to acquire R263K resistance mutations and that K65R (TDF) and M184I/V mutations protected against the development of DTG resistance (an additional advantage over raltegravir and elvitegravir, which were not afforded this protection) (2). In this study the effect of the combination of K65R and M184I/V mutations was not assessed, but as these mutations do not compensate each other it is suspected that this

combination will have the same protective effect together as separately (2).

While patients have developed DTG resistance mutations on DTG monotherapy (18), clinical studies suggest that resistance does not develop if DTG is paired with even an inactive backbone. DTG with 3TC as dual therapy was found to be non-inferior to triple ART and no resistance was found (GEMINI 1 and 2 trials), showing that even if TDF is not active, the regimen is efficacious (20). Post-hoc analysis of the SAILING study found that in patients with resistance to at least two classes, those receiving DTG with two NRTIs did not develop DTG resistance, even when both NRTIs were inactive (27).

Multiple small studies have also supported this finding: the DOLULAM switch trial found that none of the 27 patients switched to DTG/3TC dual therapy developed virological failure by 96 weeks, despite 37% having the M184V mutation (28). A French study that switched 239 virally suppressed patients to a DTG-based regimen, found that regardless of the genotypic susceptibility score, only one patient (who had a history of raltegravir use) developed virological failure (29,30). This suggests that the crippling effect of the NRTIs translates to protection from the development of second-line resistance in vivo and that a second-line TXD regimen could be effective.

There are two ongoing studies investigating the recycling of the TDF/XTC backbone. The DTG and Darunavir Evaluation in Adults Failing Therapy (D²EFT) is an ongoing non-inferiority trial to compare TDF/XTC/DTG, DTG/DRV/r and the WHO standard of care NRTI/PI (DRV/r) combination in HIV-1 patients failing first-line ARVs in predominantly LMICs. The backbone in the standard of care arm will be based on clinical judgement and may be guided by resistance testing if available, whereas the backbone in the experimental NRTI-DTG arm is pre-specified as TDF/XTC (31). This study is expected to be completed in December 2021 (31).

The NADIA study is a phase 3 trial to investigate DTG and DRV/r with TDF/XTC compared to an AZT backbone as a second-line option for 420 patients failing EFV-based first-line treatment. It is at the stage of finalisation of the protocol (32). While D²EFT and NADIA are conducted, our study aims to investigate the recycling of the TDF/XTC backbone with DTG (TXD) and provide evidence in the interim to address this important public health question.

1.3 Dosing

EFV induces enzymes and transporters involved with DTG absorption and metabolism, especially UGT1A1 and CYP3A4, which reduce plasma DTG concentrations at the end of the dosing interval up to 75% (33,34). In a study assessing a DTG/EFV combination, DTG required twice daily dosing when co-administered with EFV (33). However, simulations of switching from EFV to DTG based regimens done by Generaux et al. suggest that EFV concentration remains above the minimum effective concentration (MEC) up to 3 days after discontinuation, and DTG trough concentrations reach MEC 3 days after switch. In CYP2B6 poor metabolisers, this is extended for DTG to 6 days post switch, however the EFV concentrations take 8 days to drop below the MEC (34).

Generaux et al. thus predict that no DTG dose adjustment is required when switching from an EFV-based regimen. A pharmacokinetic sub-study of the STRIIVING study confirmed this in patients, finding that

DTG concentrations were maintained above the IC90 (concentration required for 90% inhibition) at all times after switch from an EFV-based regimen, and that there was no point post-switch at which both EFV and DTG concentrations were below their respective IC90 concentrations (35).

However, this study was conducted in virally suppressed individuals (35). Our study population will be switched with a raised viral load and a high likelihood of NRTI resistance mutations, in which case exposure to sub-therapeutic levels of DTG could drive the development of resistance mutations. Thus in this study, the initial group of patients will be initiated on a supplemented regimen of TXD with 50mg DTG for the first 14 days, after which they will receive TXD once daily. If adequate virological suppression is demonstrated in this group, we will then move forward to evaluate TXD without the supplemental DTG dose.

1.4 Importance

There are already 500 000 people using DTG worldwide, with South Africa lagging behind Botswana, Kenya and Brazil who have already started using DTG as the first-choice first-line (12). Many of these countries are switching patients on a TDF/XTC/EFV blindly to TXD in a setting where VL monitoring is not readily available (<50% of patients in LMICs have access to regular VL testing (23)). As of July 2018, there is no clinical data to support switching patients from TDF/XTC/EFV directly to TXD without a known, suppressed VL (23). Evidence on viral suppression and the development of DTG resistance mutations in the presence or absence of resistance to the backbone drugs would be invaluable in informing this strategy further and in interpreting patient outcomes. The ongoing studies, such as D²EFT and NADIA will have results available from 2021, thus interim answers to the question of a TDF/3TC or FTC backbone with DTG in second-line are urgently needed.

Furthermore, patients who struggle with adherence and engagement are a vulnerable group of patients who need better second-line options as part of a strategy to support their care. Dolutegravir has already proven an attractive second-line option, and a regimen with a recycled TDF/XTC backbone addresses many of the problems with the current second-line options, affording a unique opportunity to test a second-line regimen that could potentially be better than our current first-line option.

2. Problem statement

In order to increase retention on second-line regimens as well as increase the availability of treatment to a growing population in need of second-line options, more efficacious, cheaper regimens with better tolerability and a lower pill burden are required. DTG fulfils the WHO recommended criteria and overcomes most of the issues associated with current second-line options.

The question of which backbone to use is still open and results of the D²EFT and NADIA studies will not be available until 2021 at least. We hypothesise that when DTG is used with TDF and 3TC or FTC, even if both are compromised by resistance mutations, the residual activity and crippling will result in an effective second-line regimen that has good tolerability, a low pill burden, low monitoring requirements

and low costs.

As TDF/XTC in second-line is not an established second-line NRTI backbone, we will do frequent viral load testing as well as genotypes (at baseline and in the event of failure) to clarify the impact that the combination has on outcomes in the presence or absence of K65R and M184I/V mutations. The WHO-recommended second-line of AXD is not widely prescribed yet, and thus extensive data on viral suppression on this regimen is not available from routine programmatic settings. An assessment of impact on viral suppression and retention in care of a TXD regimen in second-line patients who have failed TXE can only be undertaken as research with close monitoring, and most suitably as a randomised controlled trial.

3. Research aims and objectives

3.1. Research aims

The aim of this study is to determine the proportion of patients achieving virological suppression when recycling the NRTI backbone (TXD combination) as a second-line regimen and using the WHP-recommended second-line AXD for patients failing a TXE first-line regimen.

3.2. Research objectives

Primary objectives

1. Stage 1: to describe the proportion of patients achieving an HIV VL < 50 copies/ml at 24 weeks on TXD (with supplemental DTG dose for 14 days) as a second-line regimen in patients who have failed first line TXE
 - a. Overall
 - b. Stratified by the presence or absence of resistance to both TDF and 3TC on initiation of the second-line regimen
2. Stage 2: to describe the proportion of patients achieving an HIV VL < 50 copies/ml at 24 weeks on TXD (without supplemental DTG dose) and on AXD, as a second-line regimen in patients who have failed first line TXE.
 - a. Overall
 - b. Stratified by the presence or absence of resistance to both TDF and 3TC on initiation of the second-line regimen

Secondary objectives

3. To determine the proportion of patients who develop DTG resistance mutations and new NRTI on second-line TXD
 - a. To determine whether the development of DTG resistance mutations is associated with the presence or absence of resistance to both TDF and 3TC on initiation of the second-line regimen
4. To describe the resistance profile of patients failing first-line TXE in this setting

5. To evaluate the trough concentrations of DTG when switching from an EFV based first-line regimen, and to assess the requirement for a lead-in supplemental dose of DTG
6. To describe markers of adherence between those failing TXD at 24 and 48 weeks and to compare to a group of matched controls.
7. To describe other clinical characteristics, adverse events and all-cause mortality among the study cohort in stage one and in stage two in the TXD and AXD arms

4. Hypotheses

1. TXD (with supplemented DTG dose) will produce acceptable viral suppression as a second-line regimen in patients failing TXE, as judged in comparison to an 82% suppression rate of AXD in the DAWNING study (16). This viral suppression will be achieved in the presence or absence of K65R and M184V/I mutations.
2. TXD (without supplemented DTG dose) will produce acceptable viral suppression as a second-line regimen in patients failing TXE, as compared to an AXD control arm. This viral suppression will be achieved in the presence or absence of K65R and M184V/I mutations.
3. A maximum of one case of DTG resistance will develop among all patients in the study who receive TXD.
4. The inducing effect of EFV on the exposure of DTG does not result in a significant period of time where DTG trough concentrations are below the protein-adjusted IC_{90} ; thus a lead-in supplemental dose of DTG is not necessary when switching from TXE to TXD in patients with an unsuppressed VL.

5. Methodology

5.1. Study design

This study will be a randomised, open-label, active-controlled trial to determine the proportion of patients achieving viral suppression on TXD as second-line and the WHO standard of care AXD. Given that these patients will all have elevated viral loads, the high baseline risk of NRTI resistance these patients are at and the inducing effect of efavirenz on dolutegravir metabolism that persists after efavirenz is stopped, we propose two stages:

- Stage 1: patients will be initiated on TXD with a supplementary dose of 50mg DTG for 14 days (to make the dose 50mg twice daily), with continuation of 50mg once a day thereafter for the duration of the study as part of a fixed dose combination with TDF and 3TC.
- Stage 2: will describe the VL suppression in the intervention and control arms, but will not be powered for a formal non-inferiority comparison between the two:
 - **Intervention arm:** patients initiated on DTG at 50mg once a day as part of a fixed dose

combination with TDF and 3TC (no supplementary DTG dose)

- **Control arm:** patients initiated on AXD (AZT and 3TC twice daily, with DTG once daily)

A Pharmacokinetic sub-study will be conducted on 12 participants in stage 1 and in 12 patients in stage 2 who are randomised to the TXD arm (the first 12 participants in both stages who consent to also take part in the pharmacokinetic sub-study), to assess the trough concentrations of DTG and off-treatment concentrations of EFV at day 3, 7, 14, and 28. Eligibility criteria are the not different from eligibility for the parent study, with the only additional inclusion criterion being willingness to participate.

Progression from stage 1 to stage 2 will be based on the lower bound of the 95% CI for the primary endpoint (VL suppression at 24 weeks) in a subset of the first 23 patients being $\geq 65.0\%$. This proportion will be determined in participants who have an HIV VL done at 24 weeks, have had a pharmacy refill collected at the prior visit and who are still on TXD (i.e. per protocol analysis to decide on progression to stage 2).

If the lower bound of the 95% CI for the primary endpoint of the first 23 patients is $< 65.0\%$, the enrolment for stage 2 will not commence but the follow up of patients in stage 1 will continue to 24 weeks. If it is $\geq 65.0\%$, the enrolment of patients for stage 2 will commence alongside the follow up of stage 1 patients.

Whether stage 2 enrolment has commenced or not, the results will be re-evaluated after the full cohort of 65 patients reaches 24 weeks.

1. If the lower bound of the 95% CI is $\geq 65.0\%$, enrolment for stage 2 can proceed if it has not already after the interim analysis of 23 patients.
2. If the lower bound remains below 65.0% or is now $< 65\%$ after enrolment for stage 2 has already started, we will refer to the drug safety monitoring board for a decision on whether to not progress to stage 2 or continue stage 2 enrolment and on the further follow up of stage 1 patients, with the option of discontinuing the trial and transferring patients back into clinic care (as outlined in the safety section of the protocol).

This study is not powered for formal statistical comparison between the intervention and control arms in stage two yet informal comparison of virologic suppression (point estimates and 95% confidence intervals) achieved in the two arms will be possible. The inclusion of a control arm is considered to be important for the interpretation of the viral load suppression achieved at the primary and secondary endpoints, as it accounts for clinic-specific factors that may influence adherence and subsequent suppression achieved. AXD is recommended by the WHO as the first option for second-line treatment in patients failing a TDF-based regimen (12) but it is not yet standard of care in practice in South Africa (patients are still prescribed a PI-based regimen) and has not yet been widely prescribed outside of trial

settings. Thus there is little data on the programmatic use of AXD, and none in the context that this study will take place in, to inform the interpretation of the virological suppression of patients on TXD. However, comparing TXD to AXD will yield more relevant insights than comparing TXD to the current a PI-based second-line regimen, as this is set to be phased out and replaced by AXD in the near future (planned in mid-2019). Given that there are not currently widely available data on the virologic outcomes of AXD as second-line ART in ART programmes outside clinical trials, we consider it important to include this arm to benchmark our TXD findings against. It will allow us to make an informal comparison of the point estimates (and 95% confidence intervals) for the primary and secondary endpoints comparing TXD with AXD within our trial.

There are precedents for conducting non-comparative trials with active controls arms to evaluate virologic suppression endpoints with integrase inhibitor ART regimens. The INSPIRING study was also a non-comparative, active-control, randomised, open-label study with two arms randomising patients on tuberculosis treatment to DTG or EFV-based treatment. It was designed to describe the primary outcomes at 48 weeks with 95% CI without making claims on the statistical significance of comparisons (36). The REFLATE (Raltegravir for the treatment of patients co-infected with HIV and tuberculosis) study randomised patients on tuberculosis treatment to three non-comparative ART arms and describes the virologic suppression at 24 weeks in each arm without statistically comparing them (37). In the same way, our study will describe the outcomes in each arm without making statistical claims of significance in a comparison between the two arms.

5.2. Study area and setting

The study will be conducted through the ART clinic, Welcome Service and Risk of Treatment Failure (ROTF) programmes at Michael Mapongwana Community Health Centre (CHC) and Ubuntu Antiretroviral Clinic at Site B CHC in Khayelitsha.

Khayelitsha is a large, peri-urban informal settlement outside of Cape Town, South Africa. It is home to approximately 500 000 people, most of whom speak isiXhosa as their first language. It has a large population of people living with HIV (43 281 patients on antiretrovirals in 2018).

The Welcome Service is a Medecins Sans Frontieres (MSF) intervention for patients who have disengaged with care or who are intermittently engaging with services. It links these patients to the clinic and provides a package of medical and psychosocial support over nine visits, with the aim of improving retention in care and preventing treatment failure. It is suspected that many of these patients already harbour resistant mutations and will require switch to second-line treatment. It is provided only at Michael Mapongwana CHC currently, but will be implemented at Ubuntu Clinic from mid 2019.

The ROTF programme is a four-visit series of nurse-led enhanced adherence settings for patients identified with a high VL. It was implemented by MSF and is now run by the clinic staff and supported by other NGOs. We also suspect that this population already harbour resistant mutations as many patients do not suppress even after the enhanced adherence support and require switch to second-line. This service

is provided at Michael Mapongwana CHC and Ubuntu Clinic.

Patients will be enrolled at both sites through the ART clinic, ROTF and the Welcome Service.

5.3. Study population and sampling

5.3.1 Eligibility

5.3.1.1 Inclusion criteria

HIV positive patients over 18 years old, who have failed their TXE first-line ART regimen, are able to attend the study clinic for one year of scheduled visits and who have given written, informed consent will be enrolled in this study. In female patients of child-bearing potential, those willing to use effective and reliable contraception for the duration of the study will be eligible (see ‘Management of women of child bearing age in both phases’)

Failure of a first-line regimen is defined as:

- A VL of >1000 copies/ml (within the previous two months) and an immediately prior VL >1000 copies/ml, taken 2-24 months prior (based on data captured by National Health Laboratory Service)

5.3.1.2 Exclusion criteria

- If the patient has two VL 2-3 months apart: > 2 log drop in VL between the most recent VL (within the previous two months) and the immediately prior VL (taken 2-3 months prior)
- CD4 count < 100 cells/ μ l
- Renal impairment (estimated Cr Cl < 50ml/min using the MDRD formula)
- Haemoglobin < 7.5
- ALT > 100 or total bilirubin > twice the upper limit of normal
- Pregnant or desire to become pregnant during the study period (48 weeks)
- Breastfeeding
- Being treated for active tuberculosis (TB) or concern that patient has undiagnosed active TB (based on symptom screening) as rifampicin reduces the concentrations of DTG and thus requires dose adjustments (10).
- Any previous or current diagnosis of malignancy
- Allergy or intolerance to one of the drugs in regimen
- Active psychiatric disease or intermediate (score 8-15) or high risk (score>15) substance abuse on the Alcohol Consumption Questions (Audit C) screening (38)
- On treatment for AIDS-defining condition (not including secondary prophylaxis maintenance therapy)
- Any other clinical condition that in the opinion of an investigator puts the patient at increased risk if participating in the study.

5.3.3. Management of women of child bearing age in both phases

Women of child-bearing age will not be excluded from this study, but their reproductive health needs will be actively managed as pregnancy and the intention to become pregnant within the 48 weeks of the study are exclusion criteria. This is because of an identified signal indicating a potential increase in risk of neural tube defects in infants born to women taking DTG at conception (39). Since August 2014, the Botswana Harvard AIDS Institute Partnership has monitored birth outcomes at eight government hospitals in Botswana to evaluate the prevalence of neural-tube defects associated with ART exposure at the time of conception, alongside Botswana's implementation of DTG as the first-option first-line ART across the country from 2016. As of May 2018, four infants born to women taking DTG at the time of conception had been found to have a neural-tube defect, equating to a 0.94% prevalence compared to 0.12% in the infants born to mothers taking a non-DTG ART at conception (39).

The WHO recommends a woman-centred approach to the management of this risk, empowering women to make informed decisions about their health. There are no reported or expected drug-drug interactions between DTG and hormonal contraception, thus the WHO recommends providing women of childbearing potential with reliable contraception alongside DTG (12).

Women of child-bearing potential consenting to take part in this study will be required to commit to the use of effective and reliable contraception, including IUCDs, injectable, implantable or oral hormonal contraception, for the duration of the study. The study will facilitate their access to these through government services and study doctors will be required to frequently check that this is maintained. We will also implement additional counselling about the potential risks associated with the use of dolutegravir and conception so that fully informed consent to participate is obtained.

Pregnancy tests will be done at baseline and regularly throughout the study. If a woman is found to be pregnant on the DTG arm during the study or expresses the wish to become pregnant, she will be switched to a standard PI-based second-line. If a woman becomes pregnant during the study period, she will be followed up throughout the pregnancy. We will refer the mother and infant pair to a paediatric colleague at Red Cross Childrens Hospital for a formal assessment for foetal anomalies in the first 4 weeks of the post-partum period. Outcomes will be reported to the ethics committees and DSMB. Any pregnancy complication that results in a non-viable pregnancy outcome (eg. miscarriage) will be investigated in partnership with gynaecology and obstetric colleagues and reported to the ethics committees and DSMB.

5.3.4. Sample size

Assuming VL suppression (HIV RNA <50 copies/ml at week 24) of 82% (as achieved by the DTG arm at 24 weeks in the DAWNING trial (16)) is achieved at the modified intention to treat (mITT) analysis at 24 weeks, a sample size of 57 will produce a 95% CI of 72-92%. To account for patients discontinuing the regimen or dropping out (e.g. stopping contraception), 65 patients will be enrolled into stage 1 and into each arm of stage 2 (total of 195 patients).

Sample size for the Pharmacokinetic study

We used SAS Programmer 9.4 (SAS Institute, Cary, NC, USA) to calculate the sample size. Based on a PK study of patients switching from EFV to DTG, we expect the geometric mean ratio (GMR) of the DTG trough concentrations of day 7/day 28 to be 0.66 in stage 2 (40). Based on an expected coefficient of variance of 55%, power of 80%, and 10% level of significance a sample of 10 participants is sufficient to determine a difference of this magnitude in the GMR. Based on an assumed withdrawal rate of 20% we

will enrol 12 participants.

In stage 1 it is unclear what the GMR will be of double dose DTG, but it is likely that the GMR will exceed 1; a GMR of 1.22 was reported in a study of 12 participants that assessed the interaction between rifampicin and DTG (41). Given that EFV is a weaker inducer than rifampicin it is not unreasonable to assume that the GMR will be higher than 1.22. Therefore we will enrol 12 participants using the same assumptions as above for stage 2.

Sample size for the analysis to progress from stage 1 to stage 2

Assuming a VL suppression (HIV RNA <50 copies/ml at week 24) rate of 82% is achieved at the mITT analysis at 24 weeks, a sample size of 23 will produce a 95% CI of 66-98%. Thus the decision to progress from stage 1 to stage 2 will be taken after 23 participants have completed 24 week assessment and who have an HIV VL done at 24 week who have had a pharmacy refill collected at the prior visit and who are still on TXD.

5.4 Study procedure

5.4.1. Recruitment & pre-screening

Patients will be recruited from the clinic, the Welcome Services and ROTF at both study sites. The clinician at their routine visit will identify eligible patients from their routine VL, explain the purpose of the study and make clear that the patient's routine care is in no way contingent on participation in the study. If the patient agrees, they will be referred to the study for screening and enrolment.

MSF has played a key role in the Ubuntu Site B and Michael Mapongwana ART clinics since 2002. MSF initially established these clinics in partnership with the provincial government and after handing over the running of these clinics to the province, has continued to play a strategic role in supporting key initiatives aimed at enhancing quality of care and outcomes of patients on ART with a focus on patients with specific challenges. Presently, MSF is supporting initiatives aimed at enhancing retention in care and reducing delays in switches to second line ART in clinics in Khayelitsha. As part of this MSF has permission to access electronic data systems which flag patients who have had repeated high HIV viral loads and are eligible for switch to second line. We propose that MSF staff will work with provincial staff at the clinic to flag such patients and ask them to attend the clinic for a discussion regarding switching to second line with clinic staff. As part of this discussion the option of enrolling in the ARTIST trial will be discussed. If they are interested they will be referred to the study staff. If patients do not wish to enrol in the ARTIST trial but are eligible for second line switch this will be done within the ART clinic according to state protocols and separate from the trial.

5.4.2. Informed consent

After referral from the Welcome Service/ROTF clinician, the patient will be contacted by the study staff. They will be taken through the process of informed consent and will have the study explained in detail by the counsellor, with the study nurse and doctor available to answer any questions. If they agree, informed

consent will be taken.

5.4.3. Screening & enrolment

Screening

The patients will be seen by the study nurse and doctor who will perform an assessment for eligibility, perform all blood tests and manage the collected specimens.

The bloods taken on the screening visit will be sent for a CD4 count, creatinine, full blood count and differential count, and ALT. A urine dipstick pregnancy test will be performed if the participant is female, unless the patient is post-menopausal.

Clinical status (history and examination), mental health status (history), substance abuse risk (Audit C questions completed), tuberculosis status (symptom screening and history) and the patient's desire to fall pregnant will also be assessed.

Enrolment

Enrolment (week 0 visit) will take place within 3 months of the screening visit. If a patient returns after this time they will require re-screening.

On enrolment, the first 65 patients will receive TXD with supplemental DTG 50mg for the first 14 days. The subsequent 130 patients will be randomised to the AXD or TXD arm (65 per arm) and informed of the arm and started on treatment at the week 0 visit. A baseline VL (and a urine pregnancy test in female participants) will be performed on week 0. The patient will be examined and contraception use and desire to fall pregnant checked. Blood for genotypic resistance testing will be taken and stored for testing at the end of the study. In stage one, dried blood spots (DBS) will be taken for storage to test levels of tenofovir-diphosphate (TVF-DP) after analysis of VL suppression, in order to assess adherence. Samples will be securely stored under appropriate conditions at the CIDRI-Africa lab until analysed.

Randomisation

The participants enrolled in Stage 1 will not be randomised. Randomisation will occur in Stage 2 to either the AXD or TXD regimens. The purpose of the Stage 1 is to provide initial data regarding the safety of the strategy. The purpose of Stage 2 is to evaluate the strategy without the lead-in dose and allow informal comparison of that TXD arm to the AXD arm. After the initial 65 patients are enrolled in stage 1, subsequent patients in stage 2 will be randomized in a 1:1 ratio to receive AXD or TXD. A randomisation sequence will be prepared by an independent statistician before Stage 2 commences using block randomisation (block sizes alternating between 4 and 8). Randomisation allocation will be concealed from the study staff until after the informed consent has been signed and the patient is formally enrolled in the study. The independent statistician will prepare opaque sealed envelopes labelled 1 to 130 containing the allocation assignment for the sequentially enrolled participants.

5.4.4. Follow-up Visits

Patients will be followed up at weeks 4, 8, 12, 16, 20, 24, 36, 48 and 52 weeks after enrolment.

A doctor or nurse will perform the clinical consultation, ARV prescription and subsequent follow up assessment. The study nurse will perform all blood tests and manage the collected specimens, as well as

provide standardised enhanced adherence counselling along with the counsellor for all patients in the study. This will be based on the enhanced adherence counselling that was developed for patients in the Welcome Service.

Contraception use and pregnancy wishes will be checked at each visit (for female participants), as well as the physical status of the patient. Self-reported adherence will also be determined by the study nurse.

Patients will be given a window period of 7 days to attend the scheduled appointment, and may also attend up to 7 days before the scheduled visit. A text message will be sent to the patient the day before the appointment to remind them. If a patient misses an appointment a text message will be sent the next day to follow up, and if they do not return or make contact by day 3 after the scheduled appointment date, they will be called. Consent for text messaging and calls will be specifically obtained.

If a patient misses three consecutive visits they will be considered lost to follow up (LTFU) by the study definition and traced by routine clinic procedures (counsellor phone calls and community care worker home visits) in order to assess their clinical status and adverse events and to encourage their return to care. This is both to ensure complete data collection and ensure continuity of care for the patient. If they return to care, the patient will continue to be seen by the study staff for the remainder of their 48 weeks after enrolment to ensure full follow up. If the LTFU was triggered by an adverse event or other outcome which may have implications for the research, as judged by the PIs, this will be reported to the Drug Safety Monitoring Board (DSMB) and ethics committees. This information will be gathered either by phone or at home visit or when they return to care.

5.4.5. Monitoring

HIV VL will be performed at weeks 0, 4, 8, 12, 16, 20, 24, 36, and 48. If any of the VL after week 12 are >50 copies/ml, or if there is <1 log decline in HIV VL at any visit from week 4 onward, enhanced adherence support will be given and the VL repeated after two weeks. If there is no decline, genotypic resistance testing will be performed to assess for DTG resistance, and the case reviewed by the trial steering committee to decide on further management.

Patients will have a repeat CD4 count at week 48, and a repeat Creatinine at weeks 4, 16 and 48 and repeat full blood count and differential count at weeks 4, 8, 12 and 24 in stage 2. Urine pregnancy tests will be performed in female participants at every visit, unless postmenopausal. In stage one, DBS will be taken and stored for TFV-DP levels at weeks 0,12, 24, 36 and 48 in order to assess adherence in those who do not virologically suppress. In stage two, plasma will be taken from patients in both arms and stored for DTG levels as an objective measure of short-term adherence at weeks 4, 8, 12, 16, 20, 24, 36 and 48. These will be analysed in a case control sub-study (cases will be participants who do not achieve virologic suppression at weeks 24 and 48).

Blood samples will be taken by the study nurse and sent to the NHLS laboratory as study specimens.

5.4.5.1 Pharmacokinetic component

Twelve participants from stage 1 and 12 from stage 2 will be invited to participate in the PK sub-study.

DTG trough concentrations (taken prior to the DTG dose) will be taken on day 3, 7, 14, and 28. Residual EFV plasma concentration levels will be taken at the same time as the DTG trough dose on day 3, 7, 14, and 28.

We will do limited genetic tests in all participants in the PK sub-study to determine EFV metaboliser genotype as it has been shown that the induction effect of EFV is greater in slow metabolizers (42), which would result in lower DTG trough concentrations when switching from EFV. The following nucleotide polymorphisms will allow categorisation of participants into slow, intermediate, and extensive metabolisers: *CYP2B6* 516G→T (rs3745274), 983T→C (rs28399499), 15582C→T (rs4803419), and *CYP2A6* 48A→C (rs28399433) (43).

PK blood samples will be taken by the study nurse. The patient will not need to see the clinician for a consultation, but has the opportunity to ask questions or bring up issues, upon which the nurse taking the blood will assess whether the patient requires an ad hoc consultation that day.

The drug assays will be done at the Division of Clinical Pharmacology laboratory, University of Cape Town, which has developed validated assays for DTG and EFV in plasma and TFV-DP on dried blood spots using liquid chromatography-tandem mass spectrometry. Whole blood will be used for DNA extraction by Qiasymphony[®] according to manufacturer's instructions. Targeted genotyping will be done with Taqman[®] assays for selected single nucleotide polymorphisms that determine EFV metaboliser status.

5.4.6. Post-trial access to the study drug

At the end of 48 weeks, patients will exit the study and resume per guideline follow up in the government ART clinic. On their week 48 visit an appointment will be made for the following month in the ART clinic for the patient to transition back to provincial care. The decision on further treatment will be made according to the findings of the study, the availability of the study drug in the public sector at that point and the discretion of the treating clinician. Available options include AXD, the WHO recommended second line (10,12) and AZT/3TC/LPV/r, the current Western Cape recommended second-line (6). If the patient has virologically failed at the end of the study, darunavir, rilpivirine or raltegravir could also be incorporated into the regimen depending on genotypic resistance results. The patient's results and progress will be communicated in writing to their chosen clinic.

Figure 1. Study Procedure

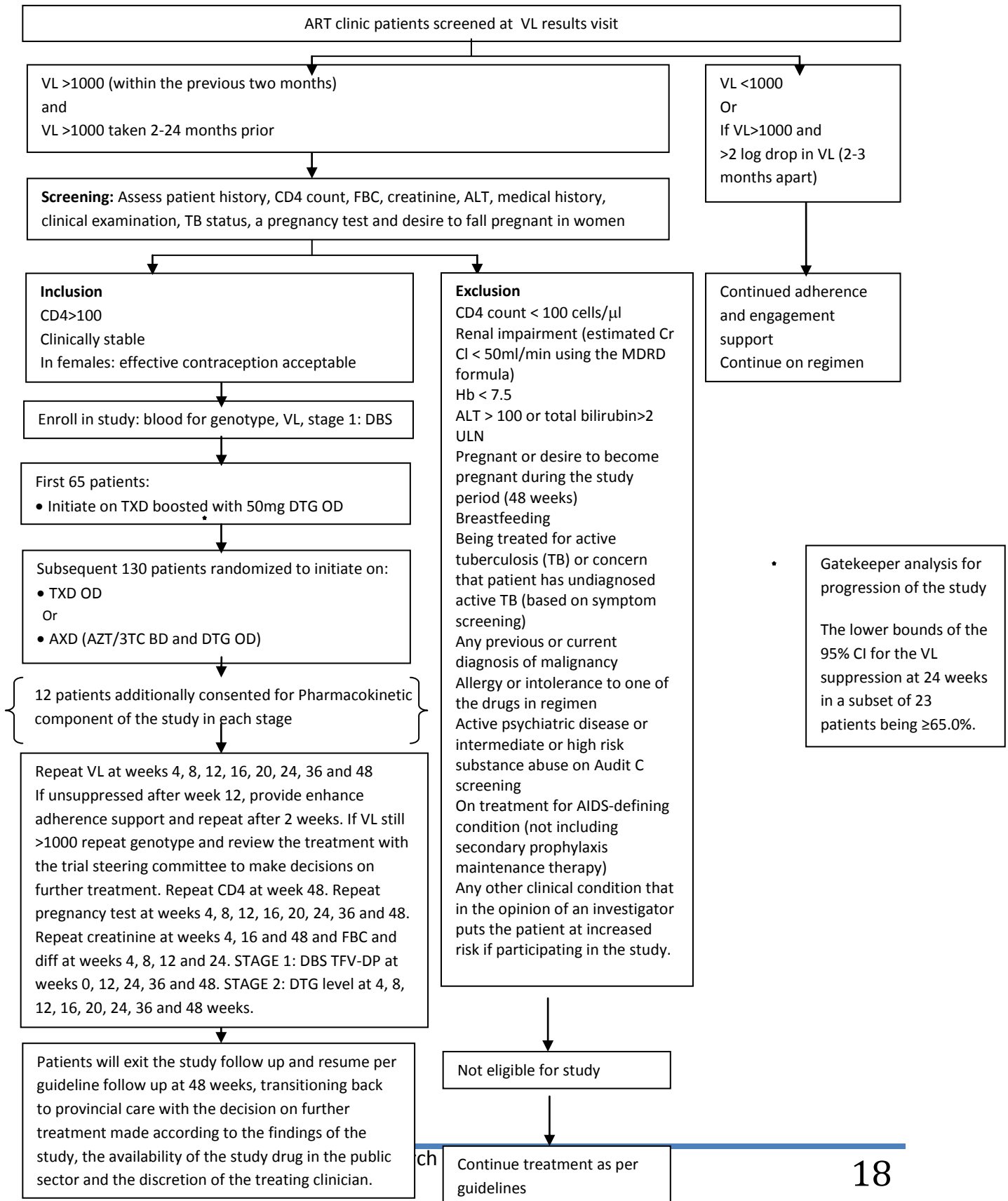


Table 1. Schedule of events

Visit	Screening	Week									
		0	4	8	12	16	20	24	36	48	52
Informed consent	X										
Inclusions & exclusions	X	X									
Medical history	X										
Confirm use of acceptable contraception	X	X	X	X	X	X	X	X	X	X	X
Physical exam if symptoms	X	X	X	X	X	X	X	X	X	X	X
Adverse event screening		X (Baseline)	X	X	X	X	X	X	X	X	X
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X		X			X				X	
ALT	X										
Full blood count and differential count	X		X	X	X			X			
HIV VL	(performed before screening visit)	X	X	X	X	X	X	X	X	X	
CD4 count	X									X	
Genotype		X									
DTG trough and EFV		First month									
DTG level (Stage 2)			X	X	X	X	X	X	X	X	
TFV-DP DBS (Stage 1)		X			X			X	X	X	

6. Data management and analysis

6.1 Data collection

6.1.1 Data to be collected

Demographics

- Age
- Gender
- Address

Baseline clinical information

- Medical history
 - VL history
 - CD4 history
 - ART history: ART regimens and start dates
 - Encounter history
 - Appointment/engagement history
 - Tuberculosis history
 - Obstetric history
 - Mental health history
 - Substance use screening
 - Other comorbidities
- Clinical examination findings

Follow up visit information

- Symptoms and clinical examination findings
- Barriers to adherence as recorded in the counselling notes

Laboratory values

- VL at weeks 0, 4, 8, 12, 16, 20, 24, 36 and 48
- CD4 at week 0 and at 48 weeks
- Residual EFV levels in 12 patients in each stage
- DTG trough levels in 12 patients in each stage
- EFV metaboliser genotype in 12 patients in each stage
- Genotypic resistance results
 - Baseline
 - Repeat results in those with virologic failure
- Creatinine at weeks 4, 16 and 48
- FBC and differential at weeks 4, 8, 12 and 24

- Pregnancy test results
- Stage 1: DBS for TFV-DP levels at weeks 0, 12, 24, 36 and 48 (case-control)
- Stage 2: Plasma for DTG level at 4,8, 12, 16, 20, 24, 36 and 48 weeks (case-control)

Clinical Outcomes

- Adverse events
 - Grade 3 or 4
 - Serious
 - Requiring discontinuation of any of the ARVs in the regimen
- Mortality (all-cause) with causality assessment
- Appointments and attendance

6.1.2 Method of collection

All data will be recorded by the clinicians, nurses and counsellors on the case report forms (CRFs). Data will be captured from the CRFs on a weekly basis and uploaded into a study database (RedCap) by dual capturing.

Background information will be collected from provincial Single Patient Viewer.

6.2 Storage

Patient data will be stored on a password-encrypted hard drive, kept off the clinic premises at UCT.

6.3 Analysis

Analysis will be performed in Stata Version 14 (44). Descriptive statistics will be presented with 95% confidence intervals. The detailed analysis plan will be described in a Statistical Analysis Plan which will be written before the first participant is enrolled.

Unless otherwise specified, we will use the modified intention to treat analysis (mITT) according to the FDA snapshot analysis algorithm for analysing virological failure. The FDA snapshot algorithm regards those with measured HIV RNA ≥ 50 copies/ml, those with missing HIV RNA within the visit window, intolerance or adverse event due to any drug in the regimen requiring switch, and those with drug substitution not permitted by the protocol as failures (45). LTFU will be considered failure. Stopping or switching due to DTG or NRTI intolerance or adverse events will be regarded as failure. Switching for reasons of stopping contraception or wish to become pregnant, or becoming pregnant, transfer out for non-clinical reasons and death from non-HIV and non-drug causes (as assessed by the study doctor) will not be regarded as failure.

6.3.1 Primary outcome:

VL suppression of HIV RNA < 50 copies/ml at 24 weeks is the primary end point. The proportion (with 95% CI) of patients achieving an HIV VL < 50 copies/ml at 24 weeks will be assessed, in stage 1 and stage 2

- a. Overall

- b. Stratified by the presence or absence of resistance to both TDF and 3TC on initiation of the second-line regimen
- c. Stage 2: TXD and AXD arms

6.3.2 Secondary outcomes:

1. Resistance
 - a. Resistance profile at enrolment (NRTI and NNRTI resistance)
 - b. DTG and NRTI resistance in those who experience virologic failure
2. Pharmacokinetics
 - a. Residual EFV concentrations in the first 28 days
 - b. GMR (with 90% confidence intervals) of DTG trough concentrations for day 7 to 28 and day 14 to 28; as well as proportion of patients with DTG trough concentrations above the PA-IC₉₀ value at all PK timepoints and classification by EFV metaboliser genotype
 - c. Adherence to treatment (as indicated by self-reporting, DBS TFV-DP levels at weeks 0, 12, 24 and 48 in stage one and DTG levels at weeks 4, 8, 12, 16, 20, 24, 36 and 48 for both arms in stage two) in those who experience virological failure and matched controls from among those who are suppressed at 24 and 48 weeks
3. Other clinical outcomes
 - a. Number of adverse events:
 - i. Grade 3 or 4
 - ii. Serious
 - iii. Requiring discontinuation of any of the ARVs in the regimen
 - iv. Mortality (all-cause)
 - b. CD4 counts: median (IQR) at week 48 and change from week 0
 - c. Virological suppression
 - i. Modified intention to treat at 12 and 48 weeks
 - ii. Per protocol at 12, 24 and 48 weeks
 1. In addition, a sensitivity analysis will be performed where those patients who met the definition of failure at 24 and 48 weeks but who had no TFV-DP levels (stage one) or DTG levels (stage two) at 24 and 48 weeks, indicating poor adherence, will be removed from analysis
 - iii. Overall and stratified by baseline resistance with both K65R and M184I/V mutations

6. Ethical considerations

7.1 Confidentiality

All patient interactions will maintain strict confidentiality and names will be removed from the datasets for analysis. Patient identifiers (including study numbers linked to patient name) will be stored in one patient log file that will be locked in a cabinet. All other study documents will use the study number only.

7.2 Autonomy

Informed consent will be obtained from every participant for screening and for the study in advance of enrolment into the study. Patients will be assessed by the counsellor or study nurse taking consent for their capacity to consent. All patients providing consent will be >18 years old, with no clinical reason to suspect that they are not of sufficient capacity to consent.

Additional consent will also be taken for pharmacogenomics analyses.

Consent will be explained verbally and in a written form. isiXhosa speaking patients will have the option of a translated consent form in isiXhosa, with explanation by an isiXhosa-speaking healthcare worker.

The explanation will include information to inform the participant of:

1. The nature of the research study
2. The voluntary nature of their participation
3. The aims of the study
4. The duration of the participant's involvement
5. The expected benefits to the participant and to others
6. The expected nature of the drugs being tested
7. The procedures involved in participation, including text messaging and calls to remind the patient of their appointment
8. The alternative standard of care medical therapy
9. The risks, inconvenience, discomfort and distress that may reasonably be anticipated by participating in the study
10. The potential for unforeseen risks
11. Their ability to refuse to participate and withdraw their consent at any time without reason, and that this will not affect their care
12. That the participant may be withdrawn from the study if the investigating physician considers this is necessary in the best interests of the participant
13. That personal information may be scrutinised during audit by competent authorities and properly authorised people, but all personal information will be treated as strictly confidential and will not be made publicly available
14. That information generated by the study may be published but that no details will be divulged from which the participant could be identified
15. That their samples will be stored and kept secure and confidential, but that they may be used for further testing for future studies outside the scope of this study
16. That study information will be retained for a period after the end of the trial
17. The compensation arrangements that are available
18. Contact details for emergencies

7.3 Beneficence

Depending on the results of this study, the evidence could be used to advocate for the use of fixed-dose TLD formulations as second-line, which could benefit future patients by providing them with an efficacious regimen that is more tolerable, has low monitoring requirements and has a low pill burden.

7.4 Non-maleficence

The potential for the development of DTG resistance is considered low (2,9,24,27–29,31) but we will monitor for virologic failure at frequent intervals (0, 4, 8, 12, 16, 20, 24, 36, and 48 weeks). Virologic suppression will be monitored by the DSMB who will convene at two monthly intervals during the study to review data with a pre-defined stopping rule based on failure to achieve a threshold of virologic suppression. Resistance testing will be performed on those participants who develop virologic failure and an alternative ART regimen will be available (through public sector access that would include a boosted PI) should DTG resistance develop.

In order to address the potential risk for neural tube defects if taking DTG peri-conception, women of child-bearing potential will be offered reliable and consistent contraception as recommended by the WHO (12) and only those for whom this is an acceptable option will be eligible for the study.

Fair monetary compensation will be provided to participants for attending study visits, in line with the National Health Research Ethics Council (NHREC) guidance in order to compensate them for their time and inconvenience and to reimburse them for their expenses (46).

7.5 Justice

This study has potential applicability to other populations

1. In the coming years DTG will become widely available in lower resource settings and 70 low and middle income countries have already included or are planning to include DTG in national guidelines (12). The knowledge gap on the safety of transitioning patients from EFV to DTG if they are not known to be virologically suppressed forms a barrier to expanding DTG access in countries where VL monitoring is not routinely available. VL testing is currently only available on a national level in South Africa, Namibia and Botswana, covering less than 50% of patients in LMICs (23). There is a need for clinical data to support switching patients from TXE to TLD with a detectable or unknown VL (23). If the TLD regimen proves robust in the face of NRTI resistance mutations, there is potential for mass transfer from TXE to TLD without the requirement for a VL to guide the decision. Maintaining the same backbone and removing the need to perform a VL would simplify implementation and reduce the cost of transition. TLD in a generic fixed dose combination will also already be procured for first-line ART programmes so would be readily available at a low cost. This study could contribute evidence to inform this strategy and facilitate this programmatic transition.
2. Children have even fewer second-line options than adults, especially if they were initiated on a PI-based regimen. The use of DTG is supported by the FDA for children over six years of age and >30kg and the WHO recommends its use for all HIV positive individuals older than 6 years and >15kg (12). Thus there is the potential for expansion of TLD to younger populations in whom TDF is already recommended (>15 years and ≥ 40 kg (6)).
3. Evidence on the use of DTG in second-line regimens can help to advocate for access to DTG as a

valuable second-line option that is efficacious, tolerable and has a low pill burden.

8. Safety

1. Intense monitoring of HIV VL (0, 4, 8, 12, 16, 20, 24, 36, and 48 weeks) allows for a change in regimen if virologic suppression is not achieved or maintained
 - a. If a patient experiences virologic failure, a second genotype will be performed and the resistance results of the genotype on initiation and on failure will be discussed by the trial steering committee and used to inform the design of a new regimen that could include standard of care PIs, darunavir, rilpivirine and/or raltegravir.
 - b. We anticipate that such events, if they do occur, will be infrequent (around 5% of patients in DTG monotherapy studies, and likely less with two NRTIS added). Furthermore, we anticipate that because no patients will be PI-experienced, a PI-based alternative suppressive regimen will be available in all cases where DTG resistance develops. We will communicate a detailed written ART plan after study completion to the clinic who is taking over care of such a patient and Prof Meintjes will be available to advise on on-going care of such patients after the trial – he has provided patient advice to clinicians in Khayelitsha since 2003. We anticipate that it is very unlikely such mutants would result in onward transmission. The availability of suppressive alternative regimens make this unlikely and the signature DTG mutation (R263K) severely compromises the virus in terms of replicative capacity meaning that viruses carrying the mutation disappear rapidly from the circulating population of viruses when DTG drug pressure is removed.
2. If a participant experiences any new symptom or is concerned, they will be encouraged to make telephonic contact with the clinic regarding any new symptoms by sending a “Please Call Me Message” which is free of charge. We will phone them. If they have symptoms of an SAE or unexpected event they will then be asked to attend the clinic and be reimbursed.
3. An independent DSMB will be established consisting of three independent, experienced HIV clinical researchers (quorum will be two HIV clinical researchers). The study statistician will prepare the report for the DSMB but will not be a voting member of the DSMB. Two-monthly teleconferences will take place after the first patient enrolled reaches 12 weeks in the study, to monitor VL data
 - a. Stopping rule: if <65% of participants fail to achieve HIV RNA <50 copies/ml by week 16 (after a minimum of 10 patients have reached 16 weeks, excluding those who have been transferred out or died from non-HIV related causes). This rule may be modified by the DSMB prior to the trial starting when the Charter is agreed.
 - b. Adverse events or factors with implications for the research or that trigger a patient to become LTFU will be reported to the DSMB.
4. If a patient falls pregnant or expresses the wish to fall pregnant during the trial she will be immediately switched to a PI-based regimen
5. All ARVs will be sourced from quality assured sources and will be WHO pre-qualified and registered for use in South Africa by SAHPRA (South African Health Products Regulatory Authority – SA regulator).

9. Human resources

A nurse study coordinator, two medical officers, two nurses, three counsellors, a pharmacist, a data capturer and a driver will be employed for the specific purpose of implementing this trial and the RADIANT TB trial (MSF ERB approval reference 18109, received 15 February 2019). All research staff will undergo Good Clinical Practice (GCP) training. Study staff will undergo appropriate training (GCP, BLS, ACLS where appropriate and on SOPs) before commencing patient enrolment and receive adequate supervision from the PIs. Staff training will include a 2 day start-up meeting covering all SOPs for both this trial and the other trial (RADIANT TB) which will be supported by the same staff. The external study monitor and PIs will be present at both days of this start-up meeting..

10. Timeline

	2018	2019				2020				2021			
Quarter:	4	1	2	3	4	1	2	3	4	1	2	3	4
Protocol & ethics submission	X	X											
Preparation of CRFs	X	X											
Staff recruitment		X	X										
Enrolment			X	X	X	X	X	X					
Follow up			X	X	X	X	X	X	X	X	X	X	
Analysis						Progress to stage 2	Interim analysis						Complete analysis
Write up													X
Dissemination													X
													X

References

1. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic [Internet]. 2018 [cited 2018 Sep 2]. Available from: <http://www.unaids.org/en/resources/909090>
2. Oliveira M, Ibanescu RI, Pham HT, Brenner B, Mesplede T, Wainberg MA. The M184I / V and K65R nucleoside resistance mutations in HIV-1 prevent the emergence of resistance mutations against dolutegravir. *AIDS*. 2016;30(June):2267–73.
3. Estill J, Ford N, Salazar-Vizcaya L, Haas A, Blaser N, Habiyambere V, et al. Estimating the need of second-line antiretroviral therapy in adults in sub-Saharan Africa up to 2030: a mathematical model. *Lancet HIV*. 2016;3(3):e132–9.
4. Kaplan SR, Oosthuizen C, Stinson K, Little F, Euvrard J, Schomaker M, et al. Contemporary disengagement from antiretroviral therapy in Khayelitsha, South Africa: A cohort study. *PLoS Med*. 2017;14(11):1–24.
5. World Health Organization. Global Action Plan on HIV Drug Resistance 2017-2021: 2018 Progress Report. 2018.
6. Western Cape Government. The Western Cape Consolidated Guidelines for HIV Treatment: Prevention of Mother- to- Child Transmission of HIV (PMTCT), Children, Adolescents and Adults. 2018 (Amended Version). Vol. 2018. 2018.
7. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. *World Heal Organ*. 2016;155 p.
8. Haas A, Keiser O, Balestre E, Brown S, Bissagnene E, Chimbetete C, et al. Monitoring and Switching of First-line Antiretroviral Therapy in sub-Saharan Africa: Collaborative Analysis of Adult Treatment Cohorts. *Lancet HIV*. 2015;2(7):1–21.
9. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV. *N Engl J Med* [Internet]. 2006;354(3):251–60. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa051871>
10. World Health Organization. Technical Update: Transition to new antiretroviral drugs in HIV programmes: clinical and programmatic considerations. 2017.
11. Kandel CE, Walmsley SL. Dolutegravir – a review of the pharmacology , efficacy , and safety in the treatment of HIV. *Drug Des Dev Ther*. 2015;9:3547–55.
12. World Health Organization. Policy Brief Update on Antiretroviral Regimens for Treating and Preventing HIV Infection and Update on early Infant Diagnosis of HIV: July 2018. 2018.

13. USAID, PEPFAR. The Dolutegravir Opportunity: Managing supply chain risk for the introduction of a new antiretroviral (ARV) medicine. USAID Glob Heal Supply Chain Progr Procurement Supply Manag. 2017;(September):2017–8.
14. Prabhu VR, Wong C, Jenkins S, Nizami S, Catlin K, Domanico P. New ARVs Could Represent Over USD 3 Billion in Cost Savings Through 2025. In: Conference on retroviruses and Opportunistic Infections. 2016.
15. Dutta A, Barker C, Kallarakal A. The HIV Treatment Gap : Estimates of the Financial Resources Needed versus Available for Scale-Up of Antiretroviral Therapy in 97 Countries from 2015 to 2020. PLoS Med. 2015;5:1–43.
16. Aboud M, Brites C, Lu H, Supparatpinyo K, Hercilla L, Sievers J, et al. DTG Versus LPV/r in Second Line (DAWNING): Outcomes by WHO-Recommended NRTI Backbone. Conf Retroviruses Opportunistic Infect. 2018;2018.
17. Charpentier C, Descamps D. Resistance to HIV integrase inhibitors: About R263K and E157Q mutations. Viruses. 2018;10(1):1–8.
18. Wijting I, Rokx C, Boucher C, Kampen J van, Pas S, Vries-Sluijs T de, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. Lancet HIV. 2017;4:e547-54.
19. Hocqueloux L, Allavena C, Prazuck T, Bernard L, Sunder S, Esnault J-L, et al. Dolutegravir monotherapy versus dolutegravir/abacavir/lamivudine for HIV-1-infected virologically suppressed patients: Results from the randomized non-inferiority MONCAY trial. In: AIDS2018. 2018.
20. Cahn P, Sierra-Madero J, Arrivas J, Antinori A, Ortiz R, Clarke A, et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment-naïve adults with HIV-1 infection - 48-week results from the GEMINI studies. In: AIDS2018. 2018.
21. Fulcher JA, Du Y, Zhang T, Sun R, Landovitz RJ. Emergence of Integrase Resistance Mutations During Initial Therapy Containing Dolutegravir. Clin Infect Dis. 2018;67(5):791–4.
22. Lopez MJP, Chueca N, Hernández-Febles M, Fernandez-Caballero JA, Garcia F, Zarzalejos JM. Virological failure through the R263K pathway to a first line Dolutegravir containing regimen. In: AIDS2018. 2018.
23. Vitoria M, Hill A, Ford N, Doherty M, Clayden P, Venter F, et al. The transition to dolutegravir and other new antiretrovirals in low-income and middle-income countries: what are the issues? AIDS [Internet]. 2018;32(12). Available from: https://journals.lww.com/aidsonline/Fulltext/2018/07310/The_transition_to_dolutegravir_and_other_new.1.aspx
24. Hakim JG, Thompson J, Kityo C, Hoppe A, Kambugu A, Oosterhout JJ Van, et al. Lopinavir plus nucleoside reverse-transcriptase inhibitors , lopinavir plus raltegravir , or lopinavir monotherapy for second-line treatment of HIV (EARNEST): 144-week follow-up results from a randomised

- controlled trial. *Lancet Infect Dis*. 2018;18:47–57.
25. Rosa AM La, Harrison LJ, Taiwo B, Wallis CL, Zheng L, Kim P, et al. Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. *Lancet HIV*. 2016;3(6):PE247-E258.
 26. SECOND-LINE Study Group, Boyd M, Kumarasamy N, Moore C, Nwizu C, Losso M, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND). *Lancet*. 2013;381(9883):2091–9.
 27. Demarest J, Underwood M, St-Clair M, Dorey D, Almond S, Cuffe R, et al. DTG-containing regimens are active in INI-naïve patients with a history of NRTI resistance. In: 20th International AIDS Conference. 2014.
 28. Reynes J, Meftah N, Tuailon E, Charpentier C, Montes B. Dual regimen with dolutegravir and lamivudine maintains virologic suppression even in heavily treatment experienced HIV-infected patients: 96 weeks results from maintenance DOLULAM study. In: International AIDS Society Conference. 2017.
 29. Charpentier C, Peytavin G, Le M, Joly V, Cabras O, Perrier M, et al. High virological suppression rates regardless to the genotypic susceptibility score after switching to a dolutegravir-based regimen: W48 results in a prospective cohort. In: International AIDS Society Conference. 2017.
 30. Charpentier C, Peytavin G, Lê MP, Joly V, Cabras O, Perrier M, et al. High virological suppression regardless of the genotypic susceptibility score after switching to a dolutegravir-based regimen: week 48 results in an observational cohort. *J Antimicrob Chemother* [Internet]. 2018 Jun 1;73(6):1665–71. Available from: <http://dx.doi.org/10.1093/jac/dky062>
 31. Kirby Institute. Protocol for Dolutegravir and Darunavir Evaluation in Adults Failing Therapy (D²EFT) [Internet]. *ClinicalTrials.gov*. 2017 [cited 2018 Sep 2]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03017872>
 32. Clayden P. Fit for purpose: Antiretroviral treatment optimisation [Internet]. 2018 [cited 2018 Nov 15]. Available from: <http://i-base.info/htb/34533>
 33. Song I, Borland J, Chen S, Guta P, Lou Y, Wilfret D, et al. Effects of enzyme inducers efavirenz and tipranavir/ritonavir on the pharmacokinetics of the HIV integrase inhibitor dolutegravir. *Eur J Clin Pharmacol*. 2014;70(10):1173–9.
 34. Generaux G, Song I, Bowers G, Piscitelli S. A Mechanistic SimCYP Simulation Evaluating Dolutegravir and Efavirenz Pharmacokinetics Following a Switch From Once-daily Efavirenz to Once-daily Dolutegravir. In: 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 2014.
 35. DeWet J, DeJesus E, Sloan L, Koteff J, Brennan C, Adkison K, et al. Pharmacokinetics of Dolutegravir After Switching to Abacavir/Dolutegravir/ Lamivudine From an Efavirenz-Based

- Regimen: A PK Sub-Study From STRIIVING. In: 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 2016.
36. ViiV Healthcare. Open-label Study of Dolutegravir (DTG) or Efavirenz (EFV) for Human Immunodeficiency Virus (HIV) - Tuberculosis (TB) Co-infection [Internet]. ClinicalTrials.gov. 2018. Available from: <https://clinicaltrials.gov/ct2/show/NCT02178592>
 37. Grinsztejn B, De Castro N, Arnold V, Veloso VG, Morgado M, Pilotto JH, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis*. 2014 Jun;14(6):459–67.
 38. Bush K, Kivlahan DR, McDonnell MB. The AUDIT Alcohol Consumption Questions (AUDIT-C) An Effective Brief Screening Test for Problem Drinking. *Arch Intern Med*. 1998;158(16):1789–95.
 39. Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. *N Engl J Med* [Internet]. 2018;NEJMc1807653. Available from: <http://www.nejm.org/doi/10.1056/NEJMc1807653>
 40. Wet J de, DeJesus E, Sloan L, Koteff J, Brennan C, Adkison K, et al. Pharmacokinetics of Dolutegravir After Switching to Abacavir/Dolutegravir/ Lamivudine From an Efavirenz-Based Regimen: A PK Sub-Study From STRIIVING. In: 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. Washington DC; 2016.
 41. Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21–7.
 42. Ngaimisi E, Minzi O, Mugusi S, Reidel KD, Suba A, Eueda N. Pharmacokinetic and pharmacogenomic modelling of the CYP3A activity marker 4b-hydroxycholesterol during efavirenz treatment and efavirenz/rifampicin co-treatment. *J Antimicrob Chemother*. 2014;69:3311–9.
 43. Sinxadi PZ, Leger PD, McIlleron HM, Smith PJ, Dave JA, Levitt NS. Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. *Br J Clin Pharmacol*. 2015;80(1):146–56.
 44. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.; 2011.
 45. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and research (CDER). Human Immunodeficiency Virus-1 Infection : Developing Antiretroviral Drugs for Treatment Guidance for Industry Human Immunodeficiency Virus-1 Infection : Developing Antiretroviral Drugs for Treatment Guidance for Industry. 2015.
 46. NHREC. Payment of Trial Participants in South Africa: Ethical Considerations for Research

Ethics Committees. 2012.

47. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. [Internet]. 2017. 1-56 p. Available from:
<http://apps.who.int/iris/bitstream/10665/255884/1/9789241550062-eng.pdf?ua=1>