D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

A phase IIIB/IV randomised open-label trial to compare dolutegravir with pharmaco-enhanced darunavir versus dolutegravir with predetermined nucleosides versus recommended standard of care antiretroviral regimens in patients with HIV-1 infection who have failed recommended first line therapy.

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PROTOCOL AMENDMENT LIST
Original protocol date: 31 January 2017
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Please find below the list of amendments that have been made to the D²EFT protocol Version 2.0 to create the current version, Version 3.0

Chapter/Section	Page #	Comments
Cover page	1	Updated protocol version number and date.
Protocol synopsis	7-8	Background and rationale updated and incudes clarification that NRTIs in the third arm are fixed.
Protocol synopsis	9	Secondary endpoint for safety updated to include AEs ≥ grade 3
Protocol synopsis	11	Clarification added that NRTIs in the third arm are fixed.
Protocol synopsis	12	Clarification that clinical judgment regarding the participants response to assigned therapy will be used to guide the composition of post week 96 study-provided ART if the week 48 study results are not available.
Protocol synopsis	13	Study procedures section revised to remove week 12 visit.
Protocol synopsis	14	Statistical considerations section revised with outcome of DSMB review included for weeks 12 and 24 analyses.
Study flow chart	15	Week 12 visit removed and visit windows adjusted back to v1.1 spacing. Adjustment of reporting requirement for low grade AEs added (grade 1 and 2 adverse events not related to study drug, COVID-19, SAEs/SNAEs or ADIs will not be reported).
3.4	20	Adverse event(s) (AEs) in the secondary endpoint for safety revised to the total number of participants with AEs grade 3 and above and the cumulative incidence of AEs ≥ grade 3.
5.0	22	Study schematic revised to clarify that NRTIs in the third arm are fixed.
6.1	22	Clarifying comment added that NRTIs in the third arm are fixed.
6.2	23	Clarifying comment added that NRTIs in the third arm are fixed.
6.2	23	Clarification that clinical judgment regarding the participants response to assigned therapy will be used to guide the composition of post week 96 study-provided ART if the week 48 study results are not available.
6.3	24	Clarifying comment added that NRTIs in the third arm are fixed.
7.3	27	Correction to confirm the data collection follow-up schedule is the same in all arms.
7.3.1.1	27	Adjustment of low-grade AE reporting requirements such that only those above grade 2 or those related to study drug, COVID-19, SAEs/SNAEs or ADIs require recording.
7.3.2	28	Removal of week 12 visit
8.5.2	32	Reference to liver chemistry threshold stopping criteria added.
8.6	33	Note added that TB of any site occurring on study must always be reported as a SAE.
8.8	33-34	Updated with new information on dolutegravir in conception and pregnancy
8.9	34	Removal of adherence assessment at week 12
8.10	34-35	Prohibited and restricted therapies table updated in line with product information
8.10	35	Qualification made that investigational drugs other than those included in the assigned regimens are prohibited in this protocol *except for*

		intercurrent life-threatening illnesses, where participation can be considered by the study PI on request.
9.0	35	Adjustment of low-grade AE reporting requirements such that only those above grade 2 or those related to study drug, COVID-19, SAEs/SNAEs or ADIs require recording.
9.1.1	36	Adjustment of low-grade AE reporting requirements such that only those above grade 2 or those related to study drug, COVID-19, SAEs/SNAEs or ADIs require recording.
9.2	36-37	Clarification that possible DILIs relate to participants on DTG and mandatory reporting of overdose on study is in relation to study drug. Acronym for Serious Adverse Drug Reactions included.
9.2.1	37	Change of SAE summary distribution frequency to sites revised from 6 to 12 months unless an SAE results in a protocol change.
9.6	40	Clarification that mandatory reporting of overdose on study is in relation to study drugs
10.5	41	Clarification that clinical judgment regarding the participants response to assigned therapy will be used to guide the composition of post week 96 study-provided ART if the week 48 study results are not available.
11.3	42	Clarification that support for transport vials and grid boxes will be in kind.
12.2.4	45	All grade adverse events removed from safety analyses, focusing on AEs ≥ grade 3.
12.3	45	Schedule of analyses updated to account for week 12 and 24 analyses already performed. Outcome of DSMB reviews already conducted are included.
13.0	46	DSMB section updated to account for week 12 and 24 reviews already performed
17.1	51	US National Institutes of Health added as PSC representative.
List of references	54-55	References for updated pregnancy information added
PICF section 4	60-61	Week 12 visit removed from table
PICF section 9	63	Number of participant visits to clinic revised to 6
Investigator agreement and sign-off page	73	Updated protocol version number and date.

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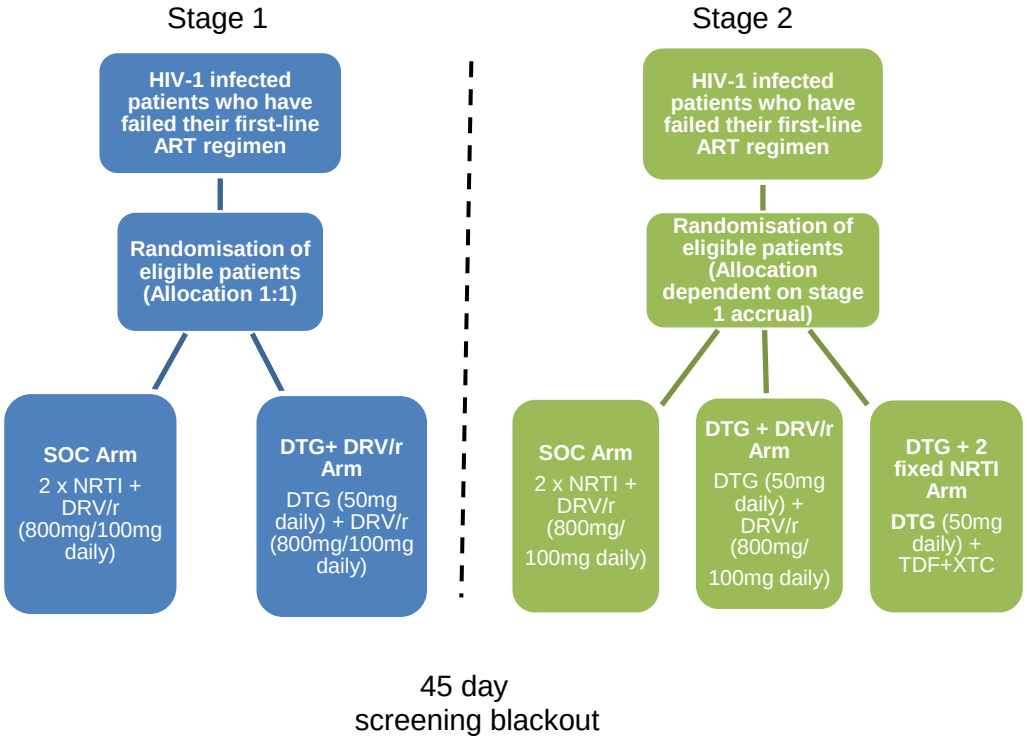
PROTOCOL SYNOPSIS

Title	A phase IIIB/IV randomised open-label trial to compare dolutegravir with pharmaco-enhanced darunavir *versus* dolutegravir with predetermined nucleosides *versus* recommended standard of care antiretroviral regimens in patients with HIV-1 infection who have failed recommended first line therapy (the D^2EFT study)
Protocol registration number	NCT03017872
Background and rationale	When this study was conceived there is an urgent unmet need for a simple and cost-effective regimen of combination antiretroviral therapy (ART) for use in second-line therapy for the treatment of people with HIV-1 infection (HIV) in resource-limited settings. With a projected 30 million people around the world taking first-line therapy by 2020 and an anticipated failure rate of 15% per annum, the WHO recommended approach of switching to recycled nucleos(t)ide reverse transcriptase inhibitors (NRTIs) in combination with a ritonavir-boosted protease inhibitor (standard of care, SOC) was neither simple nor sustainable. The ideal combination second-line ART regimen in a resource limited setting would satisfy 2 sets of criteria: • primary criteria - include agents with: o high potency, o high genetic barriers to resistance o established safety profiles o good tolerance • secondary criteria: o able to be administered once-daily with no impact on the activities of daily living o able to be co-formulated Two major approaches to simplifying second line ART regimens were identified for evaluation: first, simplified therapy with boosted protease inhibitor and an integrase inhibitor (derived from SECOND-LINE), and secondly dolutegravir with fixed nucleosides (tenofovir and lamivudine/emtricitabine, 3TC/FTC). This trial commenced with comparison of the first simplification approach with SOC (stage 1) and expanded to allow comparison of both simplification approaches with each other and SOC (stage 2). The SECOND-LINE study provided proof of principle that a regimen of combination antiretroviral therapy (ART) comprising raltegravir (integrase inhibitor) and lopinavir/r (a pharmaco-enhanced or 'boosted' protease inhibitor (b/PI)) provided non-inferior suppression of HIV replication over a 96 week period compared to applicable WHO-recommended therapy. In addition, evidence of better safety and tolerability was observed for the experimental regimen. This work was subsequently confirmed by others. This study will build on that earlier work and examine the safety and efficacy of an innovative ART regimen as second-line therapy for HIV infection in low and middle income countries. The experimental regimen in the SECOND-LINE study satisfied the primary criteria but not the necessary secondary criteria. The development of new drugs in the intervening period has allowed us to identify boosted darunavir (b/PI) and dolutegravir (DTG, an HIV integrase inhibitor) as an attractive combination satisfying all of the selection criteria. Both drugs are licensed for the treatment of HIV infection.

	Since this trial was designed, emerging data from DAWNING and a changing treatment and funding landscape created an emerging imperative to consider an additional approach in second line: dolutegravir with two nucleosides (DTG+tenofovir (TDF)+lamivudine (3TC) or emtricitabine (FTC)), with or without resistance testing. DAWNING compared DTG with two nuclesoides versus a boosted protease inhibitor (lopinavir) with two nucleosides. Notably all subjects had resistance testing and required one active nucleoside, a contrast to this study and an important consideration in resource limited settings where access to resistance testing is limited. The intervention arm of DTG+nucleosides (DTG+2NRTI) showed superior efficacy measured by viral suppression at week 24, with a margin of superiority of 13.8% (95% CI: 7.3% to 20.3%, P<0.001). The intervention arm of DTG+2NRTI also had a favourable safety profile. The study was terminated early by the DSMB as a result. In parallel with the results of DAWNING, the availability of dolutegravir coformulated with TDF+3TC (TLD) in low income counties at a greatly reduced price gave programmatic interest to the exploration of this combination in second line ART, including in the absence of resistance testing. Given this and the programmatic interest in fixed second regimens without the need for resistance testing, the DTG+2NRTI arm was designed with fixed nucleosides regardless of the availability or results of resistance testing. Baseline samples are being stored for later analysis for HIV genotype for all subjects even at non-resistance testing sites to allow for exploratory analysis of the role of baseline resistance on outcomes. Thus, with the addition of stage 2, the DTG+2NRTI third arm, this trial will establish if either of the simple regimens of DTG + DRV/r and DTG+2NRTI is non-inferior to the current WHO standard of care (SOC) ART regimen and with each other. If either regimen is non-inferior then guidelines could change resulting in rapid translation of these findings into the treatment of millions of people in resource-limited settings. The two simplified approaches examined in this trial each offer realistic opportunity for co-formulation into a one pill, once–daily tablet and prescription could be made without the need for HIV drug (genotypic) resistance testing. These characteristics would permit a public health approach (red-pill – first-line, blue-pill – second-line) to the management of HIV disease in resource-limited settings.
Study objectives	The primary objective is to compare the virological efficacy of the three regimens in the intention to treat (ITT) population. Virological efficacy is defined as the proportion of participants with plasma HIV RNA (pVL) <50 copies/mL at 48 weeks. A number of secondary outcomes will be considered in order to compare the performance of the three regimens. Secondary analyses will focus on virological, immunological, safety, antiretroviral treatment change, medication adherence, quality of life, health care utilisation and costs of care. **Primary endpoint** The proportion of participants in each of the three arms whose pVL is <50 copies/mL at 48 weeks by intention to treat (ITT). **Secondary endpoints** A number of secondary endpoints will be examined in this protocol by randomised treatment arm. These will include, but not be limited to the following assessments at weeks 48 and 96: Virological • Proportion with pVL <200 copies/mL • Proportion with pVL<50 copies/mL where those stopping randomised ART for any reason are classified as pVL>50 copies/mL (NC=F)

	Immunological • Mean change in CD4+ cell count from baseline Metabolic • Mean/median changes from baseline in fasted lipids (TC, LDL-c, HDL-c, and TG) Safety • Total number of participants with any serious adverse events (SAEs), adverse event(s) (AEs) grade 3 and above and the cumulative incidence of SAEs and AEs ≥ grade 3. • Total number of opportunistic diseases (AIDS events), deaths and serious non-AIDS defining events and the cumulative incidence of these • Adverse events associated with cessation of randomly assigned therapy • Categorisation of neuropsychological adverse events Antiretroviral treatment • Proportion who stopped randomised therapy by reason for stopping Resistance • Patterns of genotypic HIV resistance associated with virological failure Adherence • Adherence assessment and associations with virological outcomes Quality of life • Quality of life and anxiety and depression assessments Health care utilisation • Health care utilisation assessment Costs of care • Cost of care assessment

Participant population	Eligible participants will satisfy each and all of the following inclusion criteria and none of the exclusion criteria within 45 days prior to randomisation: ***Inclusion criteria*** • HIV-1 positive by licensed diagnostic test • Aged ≥18 years of age (or minimum age as determined by local regulations or as legal requirements dictate) • Failed first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2NRTI combination therapy according to virological criteria, defined as at least two consecutive (≥7 days apart) pVL results >500 copies/mL after a minimum period of exposure to continuous NNRTI + 2NRTI first-line therapy of 24 weeks (only the second pVL needs to be within 45 days of randomisation) • For women of child-bearing potential, willingness to use appropriate contraception • Able to provide written informed consent ***Exclusion criteria*** • The following laboratory variables: a. absolute neutrophil count <500 cells/μL b. haemoglobin <7.0 g/dL c. platelet count <50,000 cells/μL d. AST and/or ALT ≥5xULN OR ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) • Change in antiretroviral therapy within 12 weeks prior to randomisation • Prior exposure to HIV protease inhibitors and/or HIV integrase inhibitors • Patients with chronic viral hepatitis B infection defined by positive serum hepatitis B surface antigen • Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy (INR >2.3), hypoalbuminemia (serum albumin <2.8g/dL), esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) • Anticipated need for Hepatitis C virus (HCV) therapy during the study • Subject has creatinine clearance of <50 mL/min via CKD-EPI equation • Current use of rifampicin or rifabutin • Use of any contraindicated medications (as specified by product information sheets) • Intercurrent illness requiring hospitalization • An active opportunistic disease not under adequate control in the opinion of the investigator • Pregnant or nursing mothers • Patients with current alcohol or illicit substance use that in the opinion of the site investigator might adversely affect participation in the study • Patients deemed unlikely by the site investigator to be able to remain in follow-up for the protocol-defined period

Study design	This is a phase IIIB/IV, multinational, multicentre, randomised, open-label study in HIV-1 infected patients who have failed their first-line ART regimen. In stage 1 of the study, patients will be randomly allocated to either SOC or DTG+DRV/r in a ratio of 1:1. Following progression to stage 2 with three arms including DTG+2NRTI, patients will be randomly allocated to receive one of the three study regimens in an allocation to be determined by accrual to that point. The study will run for 96-weeks with the primary analysis taking place at the week 48 time point. Up to 1,010 patients will be recruited from approximately 23-28 study centres in Latin America, Africa and Asia. **Study schematic**  45 day screening blackout Randomisation will be stratified by recruitment centre, by screening pVL (< or ≥ 100,000 copies/mL) and by prior use of tenofovir (yes or no). Only contemporaneously randomised subjects will be compared for the primary endpoints (i.e. subjects enrolled in stage 1 will not contribute to the comparison with the DTG+2NRTI arm).
Treatment of participants	Eligible, consenting participants will be randomly allocated to receive either standard of care or one of the simplified regimens. In stage 1 allocation will be equal between the SOC and DTG+DRV/r arms. In stage 2, adding the DTG+2NRTI arm, patients will be randomly allocated to receive one of the three study regimens. All participants will be followed to completion of their week 96 visit. Treatment adherence will be assessed on study using a 7 day recall adherence questionnaire. The protocol mandates that at randomisation participants will receive one of the following regimens: **SOC arm:** 2 x NRTIs and DRV/r for 96 weeks **DTG+DRV/r arm:** DTG and DRV/r for 96 weeks **DTG+2NRTI arm:** DTG and fixed NRTIs (TDF and 3TC or FTC for 96 weeks)

	At the end of 96 weeks (completion of the protocol) study-provided ART can be offered to all participants for a further 48 weeks as informed by the 48-week study results, if available, or by clinical judgment regarding the participants response to assigned therapy. Therefore, if non-inferiority of one of the simplified arms is established, all participants can be offered this (or either simplified regimen, should both be non-inferior) for final 48 weeks. If both intervention arms are found to be inferior then participants can be offered SOC for this final 48 weeks. Treatment choice after 96 weeks will continue to be informed by clinical judgement. After 144 weeks study drug will no longer be available, and composition of the participant's post-study regimen will be the clinician's decision.
Study procedures	**Screening, Randomisation and Follow-up:** All consenting participants will have data collected at their screening visit (within 45 days prior to randomisation). Clinical assessments with uniform laboratory testing and safety assessments will be scheduled at screening, randomisation (week 0), and weeks 4, 24, 48, and 96. The follow-up schedule for data collection is the same in all study groups. Procedures include: *At screening only* • Informed consent • Medical and HIV history *At all study visits unless stated otherwise* • Vital Signs: height (week 0 only), weight, hip and waist circumference and resting blood pressure (weeks 0, 48 & 96) • Symptom directed physical exam, • Updated medical history • Blood sample collection for local laboratory analysis: • Haematology: full blood counts with differential • Serum Biochemistry: urea, electrolytes, creatinine, liver function tests (only creatinine, total bilirubin, albumin, ALT & AST at screening) • Prothrombin time (INR) (screening only, if there is a clinical suspicion of coagulopathy) • Immunology: CD4+, CD8+ T cell count (except screening) • Virology: HIV-1 RNA measured using assays with lower limit of detection of at least 50 copies/mL • Fasted lipids (weeks 0, 24, 48 and 96) • If the participant is female and of child-bearing potential, a urine or blood sample pregnancy test • Blood sample collection for stored plasma/sera (weeks 0, 48 and 96) • Buffy coat collected for future pharmacogenomic (PG) testing (week 0 only) • Blood sample collection for pharmacokinetic (PK) testing (week 4 only) • Blood sample collection for future genotypic resistance testing (only at confirmation of virological failure from ≥ 24 weeks on randomised therapy • Collection of AEs (including SAEs regardless of relationship to study drug), AIDS and serious non-AIDS events and all-cause mortality

	• Collection of concomitant medications in the event of an SAE • Changes in randomly assigned therapy (all reasons, individually and on aggregate) • Adherence assessment (week 4) • Quality of life assessment (weeks 0, 48 and 96) • Health-care utilisation questionnaire (weeks 0, 48 and 96) • Hospital Anxiety and Depression Scale (HADS) (weeks 0, 4, 48 & 96) The week 12 visit was added to protocol v2.0 as a limited safety visit due to concerns about recycling NRTIs in the new third arm. Data from this visit was reviewed by the Data Safety Monitoring Board in January 2020, as specified in protocol v2.0. Their recommendation was to continue the study without modification. In March 2020, the D²EFT Protocol Steering Committee (PSC), concerned about participant and site staff safety related to COVID-19, recommended that week 12 visits be suspended as the safety of the third arm had been established. The PSC further determined in July 2020 that the suspension of week 12 visits be formalised, sanctioning its removal from protocol v3.0. This action was supported by the DSMB. **ART selection:** Prior to randomisation clinicians will be asked to identify, record and report the ART regimen that would be given to each participant based on treatment history and current clinical practice. Participants will then be randomised to one of the available study arms. Choice of NRTI backbone in the SOC arm *only* can be guided by genotypic resistance testing if locally available. (The NRTI backbone in the DTG+2NRTI arm is predetermined for all participants randomised to that arm regardless of the availability or results of resistance testing at site.) The pre-specified ART regimen should be identified and recorded before reviewing the resistance test results. If the site is not using resistance testing, then an algorithm will be applied for selection of the SOC NRTI backbone. ART will be dispensed at time of randomisation, at the week 4 visit and approximately three-monthly intervals thereafter. **Estimating cost-effectiveness:** A comparison of costs and estimates of cost-effectiveness for the randomised comparison will be a critical component of this study. Combination ART costs will be assessed in the three study arms. Health-care utilisation (including hospitalisation, clinic visits, nursing home care and home care) will be self-reported and then used to estimate costs. Indirect costs of medical illness will be estimated from the number of days the participant was unable to carry out routine activities using the quality of life questionnaire.

Statistical considerations	**Statistical and economic analyses** The primary endpoint is the comparison of proportions of participants in each study arm whose pVL is <50 copies/mL at 48 weeks by intention to treat (ITT). Demonstration of non-inferiority will require that the definition of non-inferiority be met in analyses of both the ITT and per-protocol (PP) populations. Non-inferiority is defined as the lower 95% confidence limit for the difference in proportions with undetectable viral load lying above -12% (i.e. a non-inferiority margin of 12%). This value of delta is selected on the basis of US FDA guidance. Treatment estimates and 95% confidence intervals will be calculated and used to assess primary and secondary efficacy endpoints. If non-inferiority is established for the primary comparison (ITT and subsequent PP analyses) further analyses to assess for superiority will be undertaken. As accrual into stage 1 commenced with two study arms prior to stage 2 opening with the third arm, comparisons for the primary endpoint will be staged. All participants accrued to the SOC and DTG+DRV/r arms throughout the trial are contemporaneous and can be compared to each other, while the subjects accrued to the DTG+2NRTI arm will be compared only to their contemporaries accrued to the SOC and DTG+DRV/r arms after stage 2 opens. Binary endpoints will be analysed using chi-square tests or logistic regression. Continuous endpoints will be analysed using ANOVA methods or non-parametric equivalents. Time to event endpoints will be analysed using survival analysis methods. For all endpoints and analysis populations, the primary treatment comparisons will be simple, unadjusted, two-group comparisons. If there are important imbalances in baseline characteristics, then adjusted analyses will also be performed and presented in addition to unadjusted analyses. The primary comparisons will be of each of the simplified regimens with the SOC arm. A subsequent exploratory comparison of the two simplified regimens will also be performed. There will be no adjustment of analyses for multiple comparisons. Statistical analyses to be conducted during this protocol: one interim analysis of data sets at week 24 (complete), a primary analysis (week 48) and an extended follow-up analysis (week 96). In addition, a limited analysis of subjects at week 12 was performed for safety. Data Safety Monitoring Board recommendations from review of both the week 12 and week 24 analyses were to continue the study without modification. Variables required for economic analyses will be collected during conduct of the study. Milestone results will be presented close to parallel with the primary analyses arising from the trial. **Sample size** Under the null hypothesis of no difference between randomised treatment policies and a suppression rate of 75%, to have 90% power to demonstrate non-inferiority in the ITT analysis using a 12% margin will require 288 participants to be randomised into each of the two initial arms (SOC and DTG+DRV/r) (2-sided α=5%) making a total of 576 participants. Adjusting for the anticipated low rates of losses to follow-up (approximately 5%) yields a required sample size for the original two arms 610 participants. Power for the third arm (DTG+2NRTI) to be added in stage 2 depends on the number of subjects accrued in stage 1. In the likely scenario of 100 subjects to each arm in stage 1, randomising 400 subjects to the third arm gives 88% power for comparisons involving DTG+2NRTI, for a total sample size of 1,010 participants.

STUDY FLOW CHART: TIME AND EVENTS SCHEDULE

Visit and week Number[a]	Screening Visit 1	Randomisation[b] Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	≤45 days prior to week 0	Week0	Week 4	Week 24	Week 48	Week 96
Window periods			-2 weeks to +8 weeks	-12 weeks to +12 weeks	-12 weeks to +12 weeks	-36 weeks to +8 weeks
Clinical assessments						
Informed consent	X					
Review eligibility[c]	X	X				
Medical & HIV history	X					
Interim history and adverse events[d]		X	X	X	X	X
Assessment of disease status	X	X	X	X	X	X
Symptom directed physical exam	X	X	X	X	X	X
Vital signs[e]		X			X	X
Real time local laboratory assessments						
Hepatitis B surface antigen	X[f]					
Haematology[g]	X	X	X	X	X	X
Serum Biochemistry[h]	X	X	X	X	X	X
Prothrombin time[i]	X					
Immunology[j]		X	X	X	X	X
Virology[k]	X	X	X	X	X	X
Fasted lipids[l]		X		X	X	X
Pregnancy testing[m]	X	X	X	X	X	X
Storage samples for central laboratory analysis						
Plasma & sera[n]		X			X	X
PG[o]		X				
PK[p]			X			
VF[q]				Only at confirmation of virological failure		
Other assessments						
Quality of life assessment		X			X	X
Adherence assessment			X			
Health-care utilisation		X			X	X
Hospital anxiety and depression scale		X	X		X	X
Antiretroviral therapy						
Pre-specify ART regimen[r]	X					

a Visit and week number: all efforts should be made to schedule visits in keeping with the proposed week numbers. Visit windows are continuous after week 4.

b All randomisation (week 0) assessments should be completed before the participant commences their new ART regimen. The new regimen should be commenced within 1 week of randomisation.

c Eligibility to be reviewed at screening and confirmed prior to randomisation.

d From protocol v3.0, grade 1 and 2 adverse events not related to study drug, COVID-19, SAEs/SNAEs or ADIs will not be reported.

e Vital Signs: height (week 0 only), weight, hip and waist circumference and resting blood pressure (weeks 0, 48 and 96 only).

f Hepatitis B surface antigen test must be done at screening unless a positive result within the previous 6 months is available. If available participant is ineligible.

g Haematology: full blood count with differential (haemoglobin, white cells, neutrophils, lymphocytes, platelets).

h Biochemistry: At screening only creatinine, total bilirubin, albumin, ALT and AST are measured. Thereafter urea, electrolytes (sodium, potassium, bicarbonate, chloride, phosphate), creatinine, liver function tests (ALT, AST, alkaline phosphatase, total bilirubin, albumin).

[i] Prothrombin time (INR) should only be performed if there is a clinical suspicion of coagulopathy

[j] Immunology: CD4+ and CD8+ T cell (absolute and %).

[k] Virology: plasma HIV-1 RNA using assay with lower limit of detection of at least 50 copies/mL plasma.

[l] Fasting (≥8 hours) lipids: total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

[m] Pregnancy test is only relevant for female participants of child-bearing potential and can be tested with either a urine or blood sample.

[n] Stored plasma & sera: for future testing.

[o] Buffy coat collected for pharmacogenomic testing. Genomics requires additional consent.

[p] Plasma sample collected for pharmacokinetic testing. Precise time of last dose of ART therapy and time of blood draw required.

[q] In the case of virological failure from ≥24 weeks on randomised therapy, a plasma sample will be collected at the of confirmatory blood draw for later genotypic resistance testing.

[r] If the site is using resistance testing to guide the choice of NRTIs in the SOC arm, the pre-specified ART regimen must be recorded before the resistance test results are reviewed.

1.0 BACKGROUND AND RATIONALE

1.1 Background

Combination antiretroviral therapy (ART) for the treatment of HIV-1 infection (HIV) prevents morbidity and mortality among individuals and reduces transmission within communities[1-3]. The combinations require life-long administration coupled with good adherence. In low and middle-income countries around the world, life-saving ART is provided through donor agency programs. By 2015 these programs delivered care to 13 million people with ambitious projections to increase this to 30 million people by 2020. Funds available to the current programs and their future objectives are not increasing. As such the community must find creative ways to support and sustain life saving treatment initiatives in resource-limited settings. The success of current programs owes much to the development of standardised treatment regimens that use coformulated drugs in easy to administer pills, coupled with reduced clinical monitoring schedules and task-shifting to allied health professionals. Extending these practical and pragmatic solutions for program delivery to many more millions of people for longer periods of time requires robust new data. New data must address the time-limited effectiveness of antiretroviral therapy ART regimens.

Evidence indicates that annual rates of ART failure around 15% can be anticipated with either acquired or emergent drug resistance. The revised WHO treatment guidelines recommending commencement of ART at any CD4 count and the scale-up of pre-exposure prophylaxis will see more people initiate therapy. It is recognised that this may increase the global risk of HIV drug resistance which will require monitoring and addressing to avoid potentially jeopardising the 90-90-90 targets[4-5]. Failure of an initial treatment regimen typically results in switching of patients to a more expensive second-line ART regimen (US$465 py versus US$146 py), increasing the probability of subsequent failure and limiting future treatment options[6-8]. Moreover, there is no convenient, co-formulated regimen of ART available for second-line therapy that is consistent with a public health approach.

Until recently World Health Organisation (WHO) treatment guidelines relied entirely on expert opinion to guide recommendations for second-line therapy[9], although evidence is growing to support the recommendations[10]. These recommend that patients commence a regimen that consists of a pharmaco-enhanced or 'boosted' HIV protease inhibitor (b/PI) in combination with 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs). Selection of the NRTI component was ideally based on the use of genotypic resistance testing, despite this sophisticated technology being beyond the scope of most in a resource-limited setting. Moreover, there are concerns regarding differences in interpreting resistance genotypes in countries where different HIV-1 clades are prevalent. In southern Africa and India HIV subtype C predominates and is associated with an increased risk of selection of the K65R mutation[11]. Failure of a tenofovir-based regimen is significantly correlated with this mutation[12, 13].

The SECOND-LINE study directly compared opinion-based treatment recommendations with an experimental second-line treatment regimen[14, 15]. This 'proof of principle' study showed that a regimen of ART comprising raltegravir (integrase inhibitor) and lopinavir/r (a b/PI) provided non-inferior suppression of HIV replication over a 96-week period compared to applicable WHO-recommended therapy. In addition, evidence of better safety and tolerability was observed for the experimental regimen[16, 17]. This work was subsequently confirmed by others[18, 19].

1.2 Simplified regimens

The current recommended approach of switching to recycled NRTIs in combination with a b/PI is neither simple nor sustainable. There is an urgent unmet need for a more compact and simple second-line ART regimen for the treatment of people with HIV infection in resource-limited settings. The ideal second-line regimen in these settings would satisfy 2 sets of criteria:

- primary criteria - include agents with:
    - high potency,
    - high genetic barriers to resistance
    - established safety profiles
    - good tolerance

- secondary criteria:
    - able to be administered once-daily with no impact on the activities of daily living
    - able to be co-formulated

In the SECOND-LINE study the experimental regimen satisfied the primary criteria but not the necessary secondary criteria. A ART regimen comprising **dolutegravir (HIV integrase inhibitor) and darunavir/ritonavir (b/PI)** is an attractive combination satisfying all of the selection criteria. Both drugs are licensed for the treatment of HIV infection. They are recommended treatment options for use in first-line and second-line therapy in high-income countries and possess well-defined safety and tolerability profiles. Neither drug is used widely in resource-limited settings because of commercial limitations. They each possess a moderate to high barrier to drug resistance and importantly, are fully active against virus that harbours drug resistance mutations to ART used in recommended first-line treatment. They are administered once-daily with no impact on the activities of daily life. Unit doses are low enough to be attractive for co-formulation.

An alternative simplified regimen was incorporated as a third arm to this study. Since this trial was designed, emerging data from DAWNING and a changing treatment and funding landscape have created an emerging imperative to consider an additional approach in second line: dolutegravir with two nucleosides (DTG+tenofovir (TDF)+lamivudine (3TC) or emtricitabine (FTC)), with or without resistance testing. DAWNING compared DTG with two nuclesoides versus a boosted protease inhibitor (lopinavir) with two nucleosides. Notably all subjects had resistance testing and required one active nucleoside, a contrast to this study and an important consideration in resource limited settings where access to resistance testing is limited. DAWNING enrolled 627 subjects in 11 countries, predominantly in South Africa but ranging across Europe, South America and Asia. The intervention arm of DTG+2NRTI showed superior efficacy measured by viral suppression at week 24, with a margin of superiority of 13.8% (95% CI: 7.3% to 20.3%, P<0.001). The intervention arm of DTG+2NRTI also had a favourable safety profile. The study was terminated early by the DSMB as a result. Formal presentation of week 48 results to assess the durability of the apparent superior outcomes are awaited.

In parallel with the results of DAWNING, the availability of dolutegravir coformulated with TDF+3TC (TLD) in low income counties at a greatly reduced price has given programmatic interest to the exploration of this combination in second line ART, including in the absence of resistance testing. Given this and the programmatic interest in fixed second regimens without the need for resistance testing, the DTG+2NRTI arm is designed with fixed nucleosides regardless of the availability or results of resistance testing. Baseline samples will be stored for later analysis for HIV genotype for all subjects even at non-resistance testing sites to allow for exploratory analysis of the role of baseline resistance on outcomes.

1.3 Advantages of an evidence base for simplified regimens

If either or both novel regimens are found to be non-inferior to the current WHO treatment guidelines for second-line therapy the immediate advantages of this evidence-based alternative would be:

1. For most adolescents and adults with HIV infection the sequence of treatment would be a single regimen of one pill, once-daily ART for both first- and second-line therapy – this has acquired the term ‘red-pill, blue-pill’;
2. Clinical care in a task-shifted environment would be simplified beyond first-line therapy. The successful escalation in numbers of people treated with first-line therapy has been achieved by having most prescriptions made by clinical nurses or physician assistants. With the current guidelines this task-shifting is not possible once the effectiveness of first-line therapy has waned;
3. Decisions regarding second-line treatment would not require access to drug resistance testing technologies or the expertise with which that platform is operated. This would reduce costs and complexity;
4. Supply-chain issues and distribution would be simplified. Pharmacies and the personnel working on the supply side of healthcare would manage far less complex stocks. This would

reduce costs but also improve the durability of supply to avoid stock-outs of life-saving medications;

5. Overcome the current commercial limitations for these drugs in resource-limited settings;
6. Create a commercial incentive for co-formulations to be developed at favourable price-point for public sector ART programs;
7. Inform treatment guidelines, resulting in rapid translation of findings into the treatment of millions of people in resource-limited settings.

A conservative estimate of first-line treatment failure (10% per annum) would result in approximately 10 million people requiring second-line therapy by end of 2020. A regimen of ART with these advantageous characteristics would translate into more achievable and sustainable treatment programs.

Building on earlier work, this study will examine the safety and efficacy of two innovative simplified ART regimens as second-line therapy for HIV infection in predominantly low and middle income countries: dolutegravir with ritonavir boosted darunavir; and dolutegravir with tenofovir and emtricitabine or lamivudine.

2.0 HYPOTHESIS

In HIV-infected patients who have virologically failed first-line ART a regimen of second-line ART incorporating ritonavir boosted darunavir (DRV/r) with dolutegravir (DTG) *or* dolutegravir with tenofovir and emtricitabine or lamivudine (DTG+2NRTI) will provide non-inferior antiretroviral efficacy over 48 weeks compared with WHO-recommended standard of care (SOC) therapy of 2NRTIs plus a ritonavir-boosted PI.

3.0 STUDY OBJECTIVES

To provide robust and generalizable data to inform international treatment guidelines and public sector programs that provide life-saving ART to millions of people in resource-limited settings.

3.1 Primary objective

To compare the virological efficacy of the three regimens in the intention to treat (ITT) population. Virological efficacy is defined as the proportion of participants with plasma HIV RNA (pVL) <50 copies/mL at 48 weeks.

3.2 Secondary objectives

A number of secondary outcomes will be addressed which are of relevance and interest in the assessment of the performance of the three study treatment regimens. Secondary analyses will focus on virological, immunological, metabolic, safety, antiretroviral treatment change, genotypic HIV resistance, medication adherence, quality of life, health care utilisation and costs of care.

3.3 Primary endpoint

The proportion of participants in each arm whose pVL is <50 copies/mL at 48 weeks by intention to treat (ITT).

*See definition of the ITT and other analysis populations in the analysis plan (section 12.2 of this protocol).

3.4 Secondary endpoints

A number of secondary endpoints will be examined in this protocol by randomised treatment arm. These will include, but not be limited to the following:

Virological

- Proportion with pVL <200 copies/mL

- Proportion with pVL<50 copies/mL where those stopping randomised ART for any reason are classified as pVL≥50 copies/mL (NC=F)

Immunological

- Mean change in CD4+ cell count from baseline

Fasted lipids

- Mean/median changes from baseline in fasted lipids (TC, LDL-c, HDL-c, and TG)

Safety

- Total number of participants with any serious adverse events (SAEs), adverse event(s) (AEs) grade 3 and above and the cumulative incidence of SAEs and AEs ≥ grade 3.
- Total number of opportunistic diseases (AIDS events), deaths and serious non-AIDS defining events and the cumulative incidence of these
- Adverse events associated with cessation of randomly assigned therapy
- Categorisation of neuropsychological adverse events

Antiretroviral treatment

- Proportion who stopped randomised therapy by reason for stopping

Resistance

- Patterns of genotypic HIV resistance associated with virological failure

Adherence

- Adherence assessment and associations with virological outcomes

Quality of life

- Quality of life and anxiety and depression assessments

Health care utilisation

- Health care utilisation assessment

Costs of care

- Cost of care assessment

4.0 PARTICIPANT POPULATION

This study will be conducted in an international clinical research network with the majority of participants coming from low and middle income countries.

4.1 Eligibility criteria

Eligible participants will satisfy each and all of the following inclusion and none of the exclusion criteria within 45 days prior to randomisation:

Inclusion criteria

1. HIV-1 positive by licensed diagnostic test
2. Aged ≥18 years of age (or minimum age as determined by local regulations or as legal requirements dictate)
3. Failed first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2NRTI combination therapy according to virological criteria, defined as at least two consecutive (≥7 days apart) pVL results >500 copies/mL after a minimum period of exposure to continuous NNRTI + 2NRTI first-line therapy of 24 weeks (only the second pVL result needs to be within 45 days of randomisation)
4. For women of child-bearing potential, willingness to use appropriate contraception
5. Able to provide written informed consent

Exclusion criteria

1. The following laboratory variables:
    a) absolute neutrophil count (ANC) <500 cells/μL
    b) haemoglobin <7.0 g/dL
    c) platelet count <50,000 cells/μL
    d) AST and/or ALT ≥5xULN OR ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin)
2. Change in antiretroviral therapy within 12 weeks prior to randomisation
3. Prior exposure to HIV protease inhibitors and/or HIV integrase inhibitors
4. Patients with chronic viral hepatitis B infection defined by positive serum hepatitis B surface antigen
5. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy (INR >2.3), hypoalbuminemia (serum albumin <2.8g/dL), esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
6. Anticipated need for Hepatitis C virus (HCV) therapy during the study
7. Subject has creatinine clearance of <50 mL/min via CKD-EPI equation
8. Current use of rifabutin or rifampicin
9. Use of any contraindicated medications (as specified by product information sheets)
10. Intercurrent illness requiring hospitalization
11. An active opportunistic disease not under adequate control in the opinion of the investigator
12. Pregnant or nursing mothers
13. Patients with current alcohol or illicit substance use that in the opinion of the investigator might adversely affect participation in the study
14. Patients deemed unlikely by the investigator to be able to remain in follow-up for the protocol-defined period

5.0 STUDY DESIGN

This is a phase IIIB/IV, multinational, multicentre, randomised, open-label study in HIV infected patients who have failed their first-line ART regimen. Patients will initially be randomly allocated to either SOC or DTG+DRV/r in a ratio of 1:1 (stage 1). Following the opening of stage 2 (protocol version 2.0) with three arms including DTG+2NRTI, patients will be randomly allocated to receive one of the three study regimens in an allocation to be determined by accrual to that point.

The study will run for 96-weeks with the primary analysis taking place at the week 48 time point.

Up to 1,010 patients will be recruited from approximately 23-28 study centres, mostly recruited from countries in Latin America, Africa and Asia. The study design is summarised in figure 1.

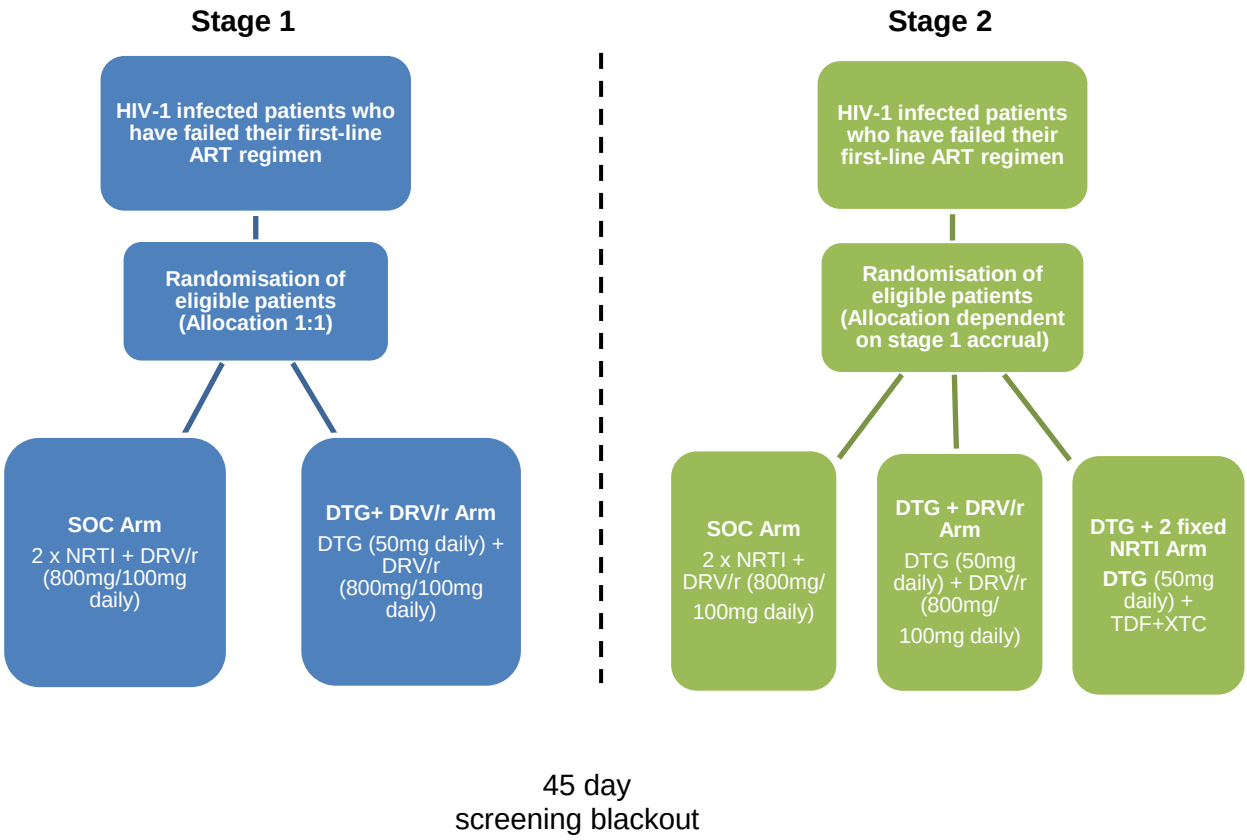


Figure 1. D²EFT study schematic

Randomisation will be stratified by recruitment centre, by screening pVL (< or ≥ 100,000 copies/mL) and by prior use of tenofovir (yes or no). Only contemporaneously randomised subjects will be compared for the primary endpoints (i.e. subjects enrolled in stage 1 will not contribute to the comparison with the DTG+2NRTI arm).

6.0 TREATMENT OF PARTICIPANTS

6.1 Treatment group assignment

Eligible, consenting participants will be randomly allocated to receive either standard of care or one of the simplified regimens. In stage 1 allocation will be between SOC and DTG+DRV/r. Following progression to stage 2 with three arms including DTG+2NRTI, patients will be randomly allocated to receive one of the three study regimens.

Standard of care (SOC) arm: 2 x NRTI + DRV/r (800mg/100mg daily)

Dolutegravir with darunavir (DTG+DRV/r) arm: DTG (50mg daily) + DRV/r (800mg/100mg daily)

Dolutegravir with nucleosides arm (DTG+2NRTI): DTG (50mg daily) + 2 fixed NRTIs (tenofovir (TDF, 300mg daily) and *either* emtricitabine (FTC, 200mg daily) *or* lamivudine (3TC, 300mg daily) (Note the option of FTC or 3TC is referred to as XTC. These agents are equivalent.))

The SOC arm corresponds to a currently recommended WHO regimen for second-line therapy; the DTG+DRV/r arm is an innovative combination regimen comprising two antiretroviral drug classes to which a participant's virus has not previously been exposed; and the DTG+2NRTI arm is an innovative potentially fixed combination regimen including one drug class (integrase inhibitors) to which a participant's virus has not previously been exposed.

The diversity of possible NRTI combinations precludes any blinding between treatment arms in this trial.

Participants will be followed until completion of their week 96 visit. Treatment adherence will be assessed on study using a 7-day recall adherence questionnaire.

6.2 Study supplied drugs

The protocol mandates that at randomisation participants will receive the following:

SOC arm: 2 x NRTIs and DRV/r for 96 weeks

DTG+DRV/r arm: DTG and DRV/r for 96 weeks

DTG+2NRTI arm: DTG and 2 fixed NRTIs (TDF/XTC) for 96 weeks

At the end of 96 weeks (completion of the protocol) study-provided ART can be offered to all participants for a further 48 weeks as informed by the 48-week study results, if available, or by clinical judgment regarding the participants response to assigned therapy. Therefore, if non-inferiority of one of the simplified arms is established, all participants can be offered this (or either simplified regimen, should both be non-inferior) for final 48 weeks. If both intervention arms are found to be inferior, then participants can be offered SOC for this final 48 weeks. Treatment choice after 96 weeks will continue to be informed by clinical judgement.

After 144 weeks study supplied drug will no longer be available and composition of the participant's post-study regimen will be the clinician's decision.

The study supplied drugs are listed below. They are each indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents:

Darunavir (DRV)

Darunavir is an HIV protease inhibitor (PI) which must be co-administered with ritonavir. Darunavir 800 mg tablets are dark red, oval-shaped, film-coated and debossed with "800" on one side and "T" on the other side. One 800mg tablet is taken orally with ritonavir 100mg as a pharmacokinetic enhancer, once daily and with food. Bottles contain 30 tablets and must be stored at 15-30°C (59-86°F).

Dolutegravir (DTG)

Dolutegravir is an HIV integrase strand transfer inhibitor (ISTI). Dolutegravir 50mg tablets are yellow, round, film-coated, biconvex and debossed with "SV 572" on one side and "50" on the other side. One tablet is taken orally, once daily with or without food. Bottles contain 30 tablets and must be stored at 15-30°C (59-86°F).

Ritonavir

Ritonavir is an HIV PI used to enhance the action of other PIs in the ART regimen. Ritonavir 100mg tablets are white, ovaloid, film-coated and debossed with an "a" logo and the code NK. One tablet is taken orally, once daily with food. Tablets should be swallowed whole, and not chewed, broken or crushed. Bottles contain 30 tablets and must be stored at or below 30°C (86°F). **Only proprietary or FDA/WHO prequalified equivalent heat stable ritonavir may be used on study.** Adherence to this requirement will be monitored.

Warnings and precautions regarding contraindicated medications for ART can be found in their respective product information or refer to www.HIV-druginteractions.org.

6.3 ART selection

Prior to randomisation clinicians will be asked to identify the ART regimen that would be given to each participant based on treatment history and current clinical practice. This selection will be recorded and reported. Sites using genotypic resistance testing to guide their selection of the NRTI backbone for SOC arm participants must identify, record and report the pre-specified ART regimen before reviewing the resistance test results.

Participants will then be randomised to one of the three study arms:

SOC arm (2 x NRTI + DRV/r):

A WHO-recommended regimen whose composition requires clinical judgement. Where the site has local access to genotypic resistance testing, the choice to use it to guide NRTI selection is optional (see section 6.5 of this protocol). For sites not using genotyping the following algorithm will be applied for selection of the NRTI backbone of the ART regimen:

- Participants previously treated with a thymidine analogue [zidovudine (AZT) or stavudine (d4T)] should be switched to a tenofovir (TDF) based NRTI backbone.
- Participants previously treated with a TDF based regimen should be switched to an AZT based regimen.
- Continued use of a cytidine analogue [lamivudine (3TC) or emtricitabine (FTC)] in a second-line ART regimen will be at the discretion of the treating clinician.

Compliance with this algorithm will be monitored as well as the composition of all antiretroviral drugs used by participants randomised to the SOC arm of the trial.

DTG+DRV/r arm:

A single, protocol defined treatment regimen.

DTG+2NRTI arm:

A single, protocol defined treatment regimen where either 3TC or FTC may be used with TDF as the fixed NRTI component. Where the site has local access to genotypic resistance testing, results of genotype testing will *not* affect selection of NRTIs for this arm.

6.4 Prior and concomitant medications

Use of rifampicin or rifabutin at screening is an exclusion criterion for this study. Please see section 8.6 for treating incident TB on study. Information regarding use of other concomitant medications will only be collected if a serious adverse event occurs (including SNAEs and ADIs meeting the definition of an SAE).

6.5 Genotypic resistance testing

This trial will be conducted primarily in low and middle-income settings where the availability of genotyping is variable. As such genotyping is permitted on study but is optional. Sites wishing to guide the selection of the NRTI backbone in the SOC arm according to genotypic resistance testing must have local access to the technology and specify its use to construct the NRTI backbone before the study is implemented. *Once a site elects to conduct genotypic HIV drug resistance testing, it must do so for all participants enrolled.*

A plasma sample will be collected any time from ≥ 24 weeks on randomised therapy where there is a pVL > 500 copies/mL on 2 consecutive occasions >7days apart. These samples will be stored and used for central resistance testing after the study. This information will then be used in a pre-specified analysis of responses according to genotype.

6.6 Laboratory studies

Plasma and sera samples will be collected at weeks 0, 48 & 96 and cryopreserved in a central repository (if allowed by local laws and Ethics Committee approval) or else, if this is not allowable, stored in country. This repository will be used for central baseline resistance testing and has inherent value for later studies of HIV pathogenesis. Consent to release and use these samples for future research will be sought from Ethics Committees. They will determine whether or not a participant's consent should be obtained for use of their samples in a particular research project.

For participants who consent to future central pharmacogenomic testing to assist in the evaluation of HIV disease, buffy coat will be collected from the same EDTA tube as the week 0 plasma.

A one-time plasma sample will be collected at week 4 for pharmacokinetic testing of study drug. The exact time of the last ART dose prior to the sample being collected must be noted by the participant and recorded with the blood draw time by the site staff. The PK sample will support clinical data and help describe the relationship between the pharmacokinetic outcome and virological efficacy.

We will use measures of pVL reported by local pathology laboratories for analysis of the study primary endpoint. Centralised testing will not be undertaken since no meaningful differences between local versus central testing of this parameter in the setting of large multicentre, multinational clinical trials has previously been shown[20].

6.7 Estimating cost-effectiveness

A comparison of costs and estimates of cost-effectiveness for the randomised comparison will be a critical component of this study. It is possible that the ultimate implications of the trial may rest on interpretations of cost-effectiveness. Paradoxically, the diversity of healthcare settings that will participate in the trial argues against a single standard analysis of cost-effectiveness. Moreover, the costs of ART are subject to volatility, are different throughout the world and subject to a variety of unpredictable influences. As such we will adopt a pragmatic approach to this important aspect of the study with the intent of informing country or region-specific guidance for the use of study results to determine cost-effectiveness[21]. Please refer to section 12.2.5 for details of economic analyses and data collection tools.

7.0 STUDY PROCEDURES

7.1 Initial screening period

Potentially eligible individuals will have data collected at their screening visit consistent with eligibility assessment and the collection of variables and data to support study analyses within 45 days before the randomisation visit. All results from screening must be available before randomisation. All prospective participants must be given adequate information about the trial, including the Participant Information Sheet, and be given an opportunity to ask questions about the trial. Voluntary written consent for the trial must be obtained at the screening visit before any protocol specified assessments are performed. The following will be performed within 45 days prior to randomisation:

7.1.1 Clinical assessments during screening

- Informed consent
- Demographics: year of birth, race and gender at birth
- HIV history to include: mode of transmission, estimated duration of HIV infection, prior AIDS (CDC stage-3-defining and additionally listed opportunistic illnesses - see section 9.4), ART history and current ART regimen
- Complete medical history to include: non-HIV related diagnoses including liver disease, renal disease, cardiovascular disease, non-AIDS defining cancers, diabetes, hypertension, hepatitis C
- Symptom directed physical examination (to include assessment of unstable liver disease)
- Smoking history and current status
- Pre-specify ART regimen (for sites using genotypic resistance testing, this must be done prior to reviewing the patient's resistance test results)

7.1.2 Laboratory assessments during screening

- Haematology: full blood count with differential (haemoglobin, white cells, neutrophils, lymphocytes, platelets)
- Serum chemistries and liver function tests: creatinine, total bilirubin, albumin, ALT and AST only

- Plasma HIV-RNA analysis using assays with lower limit of detection of ≤ 50 copies/mL
- Hepatitis B surface antigen (if no positive test result in the last 6 months)
- Prothrombin time (INR) should be measured if there is a clinical suspicion of coagulopathy
- If the participant is female and of child-bearing potential, a urine or blood sample pregnancy test

7.1.3 Rescreening

Rescreening is not permitted in this study. All screening failures must be documented on the site screening and randomisation log.

7.2 Randomisation (week 0) visit

To proceed to the randomisation visit, all participants must have fulfilled the eligibility criteria by the results of evaluations at screening. All randomisation evaluations must be completed prior to commencement of the new ART regimen.

Prior to randomisation clinicians must identify, record and report the ART regimen that would be given to each participant based on treatment history and current clinical practice. Sites using genotypic resistance testing to guide their selection of the NRTI backbone for SOC arm participants should identify, record and report the pre-specified ART regimen prior to reviewing the resistance test results.

7.2.1 Clinical assessments

- Targeted physical examination (symptom directed). Symptoms reported by the participant will be reviewed by the clinician and recorded on the electronic case report form (eCRF). Serious adverse events are reported any time they occur after the participant has consented to the study (see section 9.2.1 for serious event reporting requirements)
- Vital Signs: height, weight, hip and waist circumference & resting blood pressure
- Updated medical history including changes or additions to diagnoses, diseases, any change in antiretroviral drugs or use of contraindicated medications
- Complete quality of life questionnaire
- Complete health care utilisation questionnaire
- Complete Hospital Anxiety and Depression Scale (HADS)

7.2.2 Laboratory assessments

- Haematology: full blood count with differential (haemoglobin, white cells, neutrophils, lymphocytes, platelets)
- Serum chemistries and liver function tests: electrolytes (sodium, potassium, bicarbonate, chloride, phosphate), urea, creatinine, LFTs (total bilirubin, ALT and AST, alkaline phosphatase, albumin)
- Plasma HIV-RNA levels using assays with lower limit of detection of ≤50 copies/mL
- Immunology: CD4 and CD8 (% and absolute)
- Fasted lipids (minimum 8 hours): total cholesterol, HDL cholesterol, LDL cholesterol & triglycerides
- Blood sample collection for plasma, serum & buffy coat storage (see section 6.6 of this protocol)
- If the participant is female and of child-bearing potential, a negative urine or blood sample pregnancy test is required within 14 days before randomisation.

7.2.3 Randomisation and Drug Supply

After eligibility has been confirmed and all week 0 study visit assessments are completed the participant will be randomised online via the web based CRF. The participant will be automatically randomised to commence one of the available study arms: in the first stage to one of two arms; and following opening of stage 2 (protocol version 2.0 and later) to one of three arms. A Participant Identification (PID) number will be provided.

The investigator will complete a prescription for 1 month's supply of the randomised regimen and the participant should commence treatment within 1 week of randomisation. If safe and well tolerated further ART can be prescribed and dispensed approximately 3-monthly thereafter from the week 4 visit.

7.3 Follow Up Visits

For protocol mandated clinical assessments, the target date of study visits and their window periods will be calculated from the date of randomisation (day 0, week 0). A schedule of the dates for study visits will be provided for each participant once randomisation has been completed. These should be time points for dispensing but may not always be so. Drugs will be prescribed to prevent/avoid drug holidays. Guidance for site staff will also be detailed in the Manual of Operations (MOOP).

After the randomisation visit, window periods will be continuous meaning that the day after one visit window closes the next visit window opens. The follow-up schedule for data collection is the same in all arms. More frequent clinical visits may be conducted to ensure participant safety or for the purposes of providing routine care. The sponsor will monitor visit frequencies between treatment arms to ensure this open-label study is not affected by ascertainment bias.

Serious events (including serious non-AIDS events and AIDS defining illnesses meeting the requirements for serious event reporting), an overdose of study drug(s) and pregnancies resulting in congenital anomalies/birth defects and/or spontaneous/induced abortions must be reported within 24 hours of site awareness of them.

7.3.1 Comprehensive Visits

7.3.1.1 Clinical assessments at weeks 4, 24, 48, 96

- Targeted physical examination (symptom directed) [every study visit]
- Symptoms reported by the participant or symptoms identified after examination will be reviewed by the clinician at each visit and recorded on the eCRF as adverse events if they are above grade 2 or are related to study drug, COVID-19, are serious (SAE or SNAE) or are an ADI. [every study visit]
- Updated medical history including changes or additions to diagnoses, diseases, or any change in antiretroviral drugs or use of contraindicated medications [every study visit]
- Vital signs: weight, hip and waist circumference and resting blood pressure [weeks 48 and 96 only]
- Complete adherence assessment [week 4 only]
- Complete quality of life questionnaire [weeks 48 and 96 only]
- Complete health care utilisation questionnaire [weeks 48 and 96 only]
- Complete Hospital Anxiety and Depression Scale (HADS) (weeks 0, 4, 48 & 96 only)
- Dispense study medication [approximately 3 monthly]

7.3.1.2 Laboratory assessments at weeks 4, 24, 48, 96

- Haematology: full blood count with differential (haemoglobin, white cells, neutrophils, lymphocytes, platelets) [every study visit]

- Serum chemistries and liver function tests: electrolytes (sodium, potassium, bicarbonate, chloride, phosphate), urea, creatinine, LFTs (total bilirubin, ALT and AST, alkaline phosphatase, albumin) [every study visit]
- Plasma HIV-RNA levels using assays with lower limit of detection of ≤50 copies/mL [every study visit]
- Immunology: CD4 and CD8 (% and absolute) [every study visit]
- Fasted lipids (minimum 8 hours): total cholesterol, HDL cholesterol, LDL cholesterol & triglycerides [weeks 24, 48 & 96 only]
- Blood sample collection for plasma & serum storage [weeks 48 & 96 only]
- Blood sample for pharmacokinetics of study drugs (refer to MOOP for strict requirements) [week 4 only]
- If the participant is female and of child-bearing potential, she must have a urine or blood sample pregnancy test [every study visit]
- In the event of a plasma viral load >500 copies/mL an additional blood sample should be taken (>7 days later) to confirm virological failure and store plasma for future resistance testing (see section 8.1 of this protocol) [from ≥ 24 weeks on randomised therapy].

7.3.2 Limited safety visit

The week 12 visit was added to protocol v2.0 as a limited safety visit due to concerns about recycling NRTIs in the new third arm. Data from this visit was reviewed by the Data Safety Monitoring Board in January 2020, as specified in protocol v2.0. Their recommendation was to continue the study without modification. In March 2020, the D²EFT Protocol Steering Committee (PSC), concerned about participant and site staff safety related to COVID-19, recommended that week 12 visits be suspended as the safety of the third arm had been established. The PSC further determined in July 2020 that the suspension of week 12 visits be formalised, sanctioning its removal from protocol v3.0. This action was supported by the DSMB.

7.4 Missed visits and missed assessments

Every effort should be made to schedule visits in keeping with the visit schedule and to carry out all required assessments at these visits. Any missed study visits or missed assessments should be indicated as such on the eCRF. If a scheduled visit is conducted after the window period has closed for that specific visit, it will be counted as the next window period. *Do not* conduct a second routine visit in the same window period.

7.5 Withdrawal of study participants

Randomised study participants should be strongly encouraged to remain in follow-up for the duration of the trial, regardless of whether or not they continue to take the randomly assigned therapy. All study participants should continue to attend all study visits and complete all study-mandated assessments as per protocol. No participants will be replaced if there is a withdrawal.

Rarely there may be reasons for premature study discontinuation and withdrawal of participants from the study. These include the following criteria:

- Withdrawal of consent - participants may revoke consent for follow-up without jeopardising their relationship with either their doctor or the Sponsor. If a participant revokes consent then, if possible, all assessments scheduled for the final visit should be completed. The date and reason of the withdrawal of consent must be documented in the participant's medical notes. See MOOP for more details.
- Termination of the study by the Protocol Steering Committee.

Should a participant reconsider their decision to withdraw, they may be re-consented. Re-consent should explicitly state the period the participant agrees to have their data collected from.

8.0 CLINICAL & TOXICITY MANAGEMENT GUIDELINES

8.1 Guidelines for clinical management of ART regimen failure on study

This section deals with the clinical management of a series of clinical scenarios which may arise during the course of the study and which require a clinical response. It is emphasised that these scenarios and suggested responses relate to clinical management issues and **ARE INDEPENDENT** of the analyses of the primary and secondary study endpoints.

Failure of the regimens in this study from the perspective of clinical management (independent of the study endpoints) will be defined as any (one or more) of the following:

1. failure to attain a pVL <500 copies/mL **within the first 24-weeks** following commencement of randomised therapy
2. recrudescence of pVL to ≥500 copies/mL on 2 consecutive occasions ≥7 days apart, after having attained a pVL <500 copies/mL
3. CDC stage-3-defining and additionally listed opportunistic illnesses (see section 9.4). The investigator must not deem these to be a result of immune restoration disease (IRD) – see section 8.6 for IRD definition.
4. Failure of the absolute CD4 T-cell count to rise from baseline value following 24 weeks of continuous randomised therapy
5. Adverse events experienced that result in discontinuation of study drug (see section 8.7 for further details).

Participants failing the regimen according to any of the above criteria must:

- be managed as considered clinically appropriate,
- be encouraged to remain in clinical follow-up,
- have blood drawn per protocol (including a blood sample taken for additional resistance testing).

The following recommendations are guidelines that do not override sound and qualified clinical judgement.

From the point of view of individual participant management investigators may elect to continue participants on the same regimen if, in their judgement, the participant continues to benefit on virological and/or immunological and/or clinical grounds.

Virological failure of SOC arm:

In this scenario it is likely that the DRV/r will retain activity and therefore participants will be allowed to replace the 2 x NRTI component with dolutegravir and continue the DRV/r component.

Virological failure of either intervention arm (DTG+DRV/r or DTG+2NRTI)

In this scenario management will be at the discretion of the investigator but may include continuation of the same regimen, partial or complete regimen change. The use of resistance genotypic testing is advised if local testing is available. For sites not using resistance testing, reference to section 6.3 of this protocol is recommended for selection of a suitable NRTI combination.

Where possible, results of site clinical resistance testing at failure will be captured in real time in addition to batched resistance testing for all participants, with particular intention to emergent integrase resistance in Arm 3. It is intended that characteristics of virological failures be captured in a substudy.

8.2 Management of ART intolerance

Management of intolerance to one or more of the antiretrovirals will be at the discretion of the investigator and will depend upon the availability of local alternatives. In the case of intolerance

attributed to DRV/r a switch to an alternative b/PI is advised. If intolerance is thought to be due to one of the NRTIs, an alternative NRTI is recommended (e.g. AZT to d4T for anaemia, TDF to ddI for renal toxicity, d4T to AZT for peripheral neuropathy).

8.3 Dose modifications

No dose modifications should be made in response to observed toxicities or failure to achieve or maintain a clinical response. Toxicities and unacceptable treatment responses should be managed as guided in sections 8.4 to 8.7.

8.4 Toxicity management

Limited pathology will be collected for analysis as part of this protocol. Each investigator must ensure that safety pathology is collected and reviewed, in keeping with local standards of care.

For the purposes of uniform assessment of adverse events (including toxicities) this protocol employs the current DAIDS Common Toxicity Grading Scale (see MOOP). Please refer to section 9 of this protocol for adverse event reporting requirements.

8.4.1 Drug induced liver injury (DILI)

In the event of a discontinuation of DTG for suspected DILI, other clinically significant liver chemistry elevations (see criteria listed below), severe skin reaction or hypersensitivity reaction, participants should not restart DTG due to the risk of a recurrent reaction. Participants should instead be switched to a SoC regimen and continue to be followed on study.

Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology during administration of DTG and the follow-up period. DTG will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin; bilirubin fractionation required)
- ALT ≥8xULN;
- ALT ≥3xULN (if baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;
- ALT ≥3x baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8xULN that persists > 2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks;

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

If any liver chemistry stopping criteria are met immediately discontinue DTG and switch the participant to a SoC regimen. Participants should not restart DTG due to the risk of a recurrent reaction. Refer to the MOOP for additional follow-up instructions.

8.4.2 Allergic Reaction

Participants may continue investigational product(s) for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the investigational product(s) should permanently discontinue the investigational product regimen and the participant should be switched to a SoC regimen. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

8.4.3 Rash

Mild to moderate rash is an expected adverse reaction for both DRV and DTG. Episodes can occur within the first four to ten weeks of treatment for DRV and DTG respectively and tend to resolve without interruptions or discontinuations of therapy.

The product information provides extensive information regarding each drug.

The participant should be advised to contact the Investigator immediately if a rash develops or worsens; if any systemic signs or symptoms worsen; or if mucosal involvement develops.

8.4.4 Toxicity management guidelines

8.4.4.1 DAIDS Grade 1 or 2 adverse events

Participants who develop a Grade 1 or 2 adverse event or toxicity may continue the study drugs without modification. Participants experiencing Grade 1 or 2 adverse events who choose to discontinue the study drug(s) should remain on study and continue to undergo protocol-mandated evaluations and assessments.

8.4.4.2 DAIDS Grade 3 adverse events

If the investigator has compelling evidence that the adverse event has *not* been caused by the study drug(s), dosing may continue. Participants who develop a Grade 3 adverse event or toxicity considered to be possibly, probably or definitely related to the study drug should have study drug(s) withheld, at the investigator's discretion in accordance with the product information. The participant should be re-evaluated regularly until the adverse event returns to Grade ≤2, at which time the study drug(s) may be reintroduced at the discretion of the investigator or according to standard practice.

If the same Grade 3 adverse event recurs within four weeks, study drug(s) must be permanently discontinued if the investigator considers the adverse event related to study drug(s). However, if the same Grade 3 adverse event recurs after four weeks, the management scheme outlined above may be repeated.

Participants experiencing Grade 3 adverse events requiring permanent discontinuation of study drug therapy should be followed regularly (weekly is suggested) until resolution of the adverse event. Participants should remain in follow-up and continue to attend for protocol-mandated assessments and evaluations.

8.4.4.3 8.4.3 DAIDS Grade 4 adverse events

Participants who develop a Grade 4 adverse event or toxicity considered to be possibly, probably or definitely related to the study drug(s) will have the study drug(s) temporarily discontinued (except for those abnormalities described in sections 8.5.1 – 8.5.3 inclusive). The AE should be resolved before any decision is made in accordance with the product information to rechallenge the participant with the study drug(s). Participants experiencing Grade 4 AEs requiring permanent discontinuation of study drug therapy should be followed regularly (weekly is suggested) until resolution of the adverse event. The participant should remain on study and continue to undergo protocol-specified evaluations and assessments.

Participants with Grade 4 asymptomatic or non-significant laboratory abnormalities may continue study drug therapy if the investigator has compelling evidence that the toxicity is NOT related to the study drug(s).

8.5 Protocol-specific toxicity management guidelines

Certain clinical and laboratory abnormalities will be subject to the following guidelines under this protocol. These guidelines are provided to encourage uniformity of participant management in light of observed clinical and/or laboratory abnormalities that are well documented as expected adverse experiences following administration of study drugs. Departure from these guidelines is discouraged.

8.5.1 Hypertriglyceridaemia/Hyperlipidaemia

If elevated triglyceride or lipid levels are from a non-fasting blood draw, the test should be repeated on a specimen drawn after a minimum eight hour fast. Only levels done in a fasting state (8-hour minimum) should be graded for toxicity.

Participants with asymptomatic Grade ≥3 triglyceride, total cholesterol, or LDL elevations may continue study medications at the discretion of the investigator. Appropriate dietary modification and lipid lowering therapy should be considered. Thought should also be given to modification of other existent cardiovascular disease (CVD) risk factors (e.g. sedentariness, overweight/obese, tobacco smoking).

8.5.2 Hepatitis/Hepatotoxicity

For Grade 3 elevation in AST or ALT (5.1-10.0xULN), study medications may be continued at the discretion of the site investigator, taking into account the liver chemistry threshold stopping criteria in section 8.4. Careful assessments should be performed to rule out alcohol-related hepatitis, non-study medication-related drug toxicity, or viral hepatitis (e.g. flare of disease activity, acute infection, super-infection or IRD) as the cause of the Grade 3 elevation. The possibility of mitochondrial toxicity/hepatic steatosis/lactic acidosis syndrome should also be explored in participants in the SOC arm receiving NRTIs.

For Grade 4 elevations (>10xULN) in AST or ALT, all study medications should be withheld until the toxicity grade returns to Grade ≤2.

8.5.3 Renal toxicity

Routine assessment of renal function will be undertaken with derivation of creatinine clearance calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation[22]:

Estimated GFR =

$$141 \times \min(SCR/\kappa,1)^{\alpha} \times \max(SCR/\kappa,1)^{-1.209} \times 0.993^{Age} \times (1.018 \text{ if female} \times (1.159 \text{ if black})$$

$\kappa = 0.7$ if female	$\alpha = -0.329$ if female	min = the minimum of Scr/κ or 1
$\kappa = 0.9$ if male	$\alpha = -0.411$ if male	max = the maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

Dosing of all medications in a participant's regimen should be critically reviewed if the eGFR falls below 60ml/min/1.73m^2. It is recommended that Investigators follow the current local guidelines for the management of renal impairment in HIV-1-infected participants and/or reference clinical guidelines from the New York State Department of Health AIDS Institute at: (http://www.hivguidelines.org/clinical-guidelines/adults/kidney-disease-in-hiv-infected-patients/).

8.6 Management of AIDS Defining Illnesses (ADI) and Immune Restoration Disease (IRD)

In general, management will follow relevant local and international guidelines. Any episode of an ADI on study will be regarded as a study failure according to CDC criteria (see section 9.4 of this

protocol), unless the episode is thought to represent immune restoration disease (IRD). The protocol and MOOP will contain guidelines for the differentiation of ADI and IRD.

Mycobacterium tuberculosis of any site is considered an ADI and must always be reported as a serious adverse event when occurring on study. Pulmonary TB treatment will be according to standard recommendations with the following adaptations according to the treatment arm of the subjects:

1. **Arm 1 and 2:** Wherever possible, participants in Arms 1 and 2 (with DRV/r) will have access to rifabutin under the auspices of the study in place of rifampicin for inclusion in combination anti-TB therapy. Rifabutin will be dose-reduced in the presence of a protease inhibitor according to guidelines. In this instance, participants may remain on their randomised regimen.
2. **Arm 3:** Participants in Arm 3 may be treated with standard regimens including rifampicin where appropriate, in which case may remain on their randomised regimen with a dose adjustment to the dolutegravir (twice daily dosing). Alternatively if clinically appropriate and possible they may be treated with rifabutin in place of rifampicin as in Arm 1 and 2.

It is intended that outcomes of incident TB will be captured in an associated sub-study, including treatment choices.

For the purposes of this study the definition of IRD will follow a modification of the proposed criteria suggested by French, Price and Stone as follows[23]:

A. Atypical presentation of opportunistic infections or tumours in participants responding to antiretroviral therapy (ART)

I. Localised disease

II. Exaggerated inflammatory reaction

III. Atypical inflammatory response in affected tissues

IV. Progression of organ dysfunction or pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to commencement of ART and exclusion of treatment toxicity and new diagnoses.

B. Decrease in pVL by >1$\log_{10}$copies/mL

To qualify for a diagnosis of IRD participants would be required to demonstrate at least one of criterion A (AI – AIV) and criterion B.

8.7 Discontinuation of therapy

In general, all randomised study participants should be encouraged to take the study treatment as per protocol. However, study therapy MUST be immediately discontinued for the following reasons:

- Any clinical adverse event, laboratory abnormality or intercurrent illness that, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the participant
- Termination of the study by the Protocol Steering Committee
- Withdrawal of consent by the participant

Additional reasons for either temporarily or permanently ceasing study treatment include:

- Disease progression requiring medical intervention
- Administration of prohibited therapy
- Investigator or participant wish to stop therapy

Participants discontinuing their study drugs should remain in follow-up and be encouraged to continue protocol-mandated evaluations and assessments.

8.8 Pregnancy on study

Pregnancy is an exclusion criterion for this study. Women of child-bearing potential must be willing to use contraception and will undergo a urine or serum pregnancy test at each visit. If pregnancy is

detected during follow-up the participant should be managed in keeping with prevailing national and international guidelines.

In January 2017, when version 1.0 of this protocol was finalised, there was insufficient data to allow dolutegravir to be used widely in pregnancy. Interim results from one small study[24] found four infant congenital anomalies across 21 pregnancies. With the WHO guidelines[25] in 2019 updated to recommend dolutegravir for adults and adolescents, the question of its safety during conception and pregnancy is being scrutinised in terms of pharmacokinetics in pregnant women[26,27] and neural tube defects in infants. Neural tube defects are being analysed through pharmacovigilance databases[28,29] and a large birth-outcome surveillance survey, Tsepamo[30]. Updated data[31] from Tsepamo are reassuring with a rate of neural tube defects not significantly higher with dolutegravir (0.19% when dolutegravir is begun at the time of conception and 0.04% when started during pregnancy) than with other antiretrovirals (0.11% when begun at the time of conception). With these studies ongoing there is still insufficient data to allow dolutegravir to be used widely in pregnancy.

If a woman is found to be pregnant during follow-up the following management is recommended:

- SOC arm - continue their randomised ART regimen. If a participant becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator, and continuation of study drug can be considered if the potential benefit justifies the potential risk.
- DTG arm - as there are limited data available for the safety of DTG in pregnancy this protocol recommends switching to the SOC regimen for the duration of the pregnancy and reverting to the DTG arm thereafter.

Pregnancy outcomes on study will be captured in a prospective pregnancy substudy.

Refer to section 9.7 of this protocol for requirements of pregnancy reporting.

8.9 Treatment adherence

Adherence will be assessed using a self-reported 7-day recall adherence questionnaire. For full details on adherence assessment please refer to the MOOP. The SECOND-LINE study found that less than complete adherence at weeks 4 and 48 were significantly associated with virological failure[32]. This study will require an adherence assessment to be completed at weeks 4. All participants should be counselled regularly on the need for maintaining strict adherence with the allocated study regimens. The objective is 100% adherence at all times during follow-up. The site Principal Investigator is responsible for assessing adherence with all aspects of the study including use of ATV therapy and attendance at protocol-mandated clinical visits and assessments.

8.10 Prohibited and restricted therapies during the study

Use of the following are either contraindicated or cautioned due to direct interactions with study drugs:

Drug name	Interacts with **dolutegravir**	Interacts with **darunavir**	Interacts with **both**
carbamazepine	X		
dofetilide	X		
dalfampridine / fampridine	X		
metformin	X		
oxcarbazepine	X		
phenobarbital	X		
phenytoin	X		
rifampicin			X*
St. John's Wort			X
medications containing polyvalent cations (refer to product information)	X		
alfuzosin		X	
cisapride		X	

Drug name	Interacts with **dolutegravir**	Interacts with **darunavir**	Interacts with **both**
colchicine (in participants with renal and/or hepatic impairment)		X	
dihydroergotamine		X	
dronedarone		X	
elbasvir/grazoprevir		X	
ergotamine		X	
lomitapide		X	
lovastatin		X	
lurasidone		X	
methylergonovine		X	
oral midazolam		X	
pimozide		X	
ranolazine		X	
sildenafil (for treatment of pulmonary arterial hypertension)		X	
simvastatin		X	
triazolam		X	

*****See section 8.6 for treatment of TB with rifampicin on study

Rifampin should not be co-administered with darunavir. For management of pulmonary TB on study please refer to section 8.6.

For a comprehensive list of prohibited and restricted therapies, and for significant drug interactions requiring dosage alteration or alterative drugs, please refer to the current product information of each ART drug used.

Investigational drugs other than those included in the assigned regimens are prohibited in this protocol except for intercurrent life-threatening illnesses, where participation can be considered by the study PI on request.

8.11 Concomitant Medication

For this study we will only be collecting information on concomitant medications when a serious adverse event occurs (including SNAEs and ADIs meeting the definition of a SAE) (see MOOP for details).

9.0 ADVERSE EVENT RECORDING AND REPORTING

Adverse events and adverse drug reactions may occur in the course of this study and within the specified follow-up period. These events may also occur during the screening period prior to randomization as a result of protocol-specified interventions.

From protocol v3.0 of this study, reporting of grade 1 and 2 clinical adverse events is only required if related to study drug (adverse drug reaction), COVID-19, are serious (SAE/SNAE) or are an ADI. This is due to large variability in reporting of low-grade AEs across sites resulting in an incomplete data set. In addition, the study drugs have been widely used over a number of years and their side effects are well characterised. All clinical adverse events grade 3 and above must be reported. As a general rule, isolated laboratory abnormalities in the absence of clinical symptoms and/or signs should not be captured as adverse events unless they reach grade 4 status or become clinically significant. At that time the grade 4 laboratory abnormality and/or resulting clinical event should be reported as an adverse event (e.g. low haemoglobin should be reported as anaemia).

9.1 Adverse Events (AEs)

An adverse event is any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease occurring in a participant administered with a pharmaceutical product which does not necessarily have a causal relationship with the product. Where adverse events are related to the drug, they may be referred to as Adverse Drug Reactions (ADRs).

Pre-existing conditions or diseases that occur during the study (e.g. seasonal allergies, asthma or recurrent headaches) should not be considered as adverse events unless they change in frequency or severity.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time.

9.1.1 Reporting of Adverse Events

Timely and complete reporting of all AEs assists in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study participants; (2) a greater understanding of the overall safety profile of the study drugs; (3) recognition of dose-related study drug toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

The collection of non-serious AE information should begin at initiation of new ART regimen. AEs may be either spontaneously reported or elicited during questioning and examination of a participant. All identified AEs must be recorded and described in the participant's medical notes immediately. Grade 1 and 2 clinical adverse events related to study drug, COVID-19, SAEs/SNAEs or ADIs and all grade 3, 4 and 5 AEs, must be entered on the AE page of the eCRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual signs or symptoms.

Participants experiencing AEs that cause interruption or discontinuation of study drugs, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE was considered by the investigator to be certainly, probably, or possibly related to the study drugs.

Non-serious AEs should be followed to resolution or stabilisation until the end of the study and reported as SAEs should they become serious.

9.2 Serious Adverse Events (SAEs)

The definition of a SAE is any untoward medical occurrence that at <u>any dose</u>:

- results in death;
- is life-threatening (Note: the term "life-threatening" in the definition of "serious" refers to an event/reaction in which the participant was at risk of death at the time of event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires in-patient hospitalisation (hospital admission of ≥24 hours) or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a medically important event or reaction that may not be immediately life-threatening or result in death or hospitalisation but, in the judgement of the investigator, may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition above (e.g. intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalization, or development of drug dependency or drug abuse);
- All events of possible drug induced liver injury with hyperbilirubinemia defined as ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) in participants taking dolutegravir.

  (NOTE: bilirubin fractionation is 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 ≥2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.);

- Grade 4 events (not limited to a laboratory abnormality) not already reportable in one of the above categories;
- Is a cancer (a pre-existing cancer should only be reported if it worsens after study entry);
- Is an overdose of either study drug (whether accidental or intentional).

Where SAEs are related to the drug, they may be referred to as Serious Adverse Drug Reactions (SADRs).

9.2.1 Serious Adverse Event Reporting

SAEs should be collected following the participant's written consent to participate in the study. SAEs and SADRs must be reported for the entire period the participant is taking study-supplied ART. All serious adverse events must be reported within 24 hours (1 working day) of the site first becoming aware of the SAE, whether or not there is a suspected causal relationship to the study drug.

SAEs must be reported to The Kirby Institute by email or fax using the paper Serious Event Report form. Prior to submission of the initial SAE report the Principal Investigator/designee shall assign causality regarding the drug. The causality may be amended upon further clarification of the event. Initial reports should be followed promptly by detailed, written follow-up reports when all information is not included in the initial report (refer to MOOP). The final report should always be signed-off by the Principal Investigator. Any concomitant medications the participant was taking within 30 days of the SAE must also be reported.

For deaths, the Principal Investigator/designee will supply the sponsor and the IRB/IEC with any additional requested information (e.g. death certificate, autopsy reports and medical reports).

Serious event summaries of SAEs occurring during the study will be distributed to all sites by The Kirby Institute. Unless the SAE requires a protocol amendment, line listings will be provided to each site annually for submission to ethics with their annual review. Study treatment group will not be provided.

The investigator must comply with all applicable ethical and regulatory requirement/s relating to the reporting of serious adverse events.

Any serious adverse event that is ongoing at the week 96 visit must be followed until resolution or until the event stabilizes (for those events that will not resolve).

9.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse event which satisfies all of the following:

- Suspected as being related to study drug (i.e. has a reasonable suspected causal relationship),
- Unexpected in relation to study drug
- Where the nature and severity of the event is not consistent with known information about the study drug (e.g. the Investigator's Brochure for an unapproved investigational product).

9.3.1 Reporting of SUSARs

The Project Team in collaboration with the Medical Officer will review all serious events to identify any which fit the criteria of a SUSAR and therefore require expedited reporting to relevant parties. The event will be designated as unexpected if it is not reported in the Product Information or if the event is of greater frequency, specificity or severity.

The Sponsor must expedite the reporting of all serious adverse reactions which are suspected, unexpected and certainly, probably, possibly or of undetermined relationship to the study drug to all site Principal Investigators/institutions, using the Council for International Organizations of Medical Sciences (CIOMS) form. It is the responsibility of the site Principal Investigator or their

designee to report SUSARs to their appropriate IRB/IEC/s (in line with IRB/IEC requirements) and regulatory authorities in accordance with any local requirements and ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

As for SAEs, all SUSARs occurring on study will have a corresponding serious event summary. These will be distributed to all sites by The Kirby Institute on a 6-monthly basis. Study treatment group will not be provided.

Researchers must inform the IRB/IEC and regulatory authorities of all serious or unexpected AEs that occur during the study which may affect the conduct of the study or the safety of the participants and/or their willingness to continue participation in the study.

9.4 Serious Non-AIDS events (SNAEs) and AIDS defining events

SNAEs are defined as fatal and non-fatal diagnoses in the following categories (see MOOP Appendix 2 for details):

- Acute myocardial infarction
- Congestive heart failure
- Coronary artery disease requiring drug treatment
- Coronary revascularisation
- Decompensated liver disease
- Deep vein thrombosis
- Diabetes mellitus
- End stage renal disease
- Non-AIDS defining malignancy (except non-invasive basal cell carcinoma or squamous cell carcinoma)
- Peripheral arterial disease
- Pulmonary embolism
- Stroke

AIDS events (CDC revised surveillance case definition for HIV infection, 2014: stage-3-defining opportunistic illnesses in HIV infection – see MOOP Appendix 3):

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)

- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site*, pulmonary, disseminated, or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (previously known as "*Pneumocystis carinii*") pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

Additions to CDC definition which are considered AIDS-defining for the purpose of this study:

- Aspergillosis, invasive
- Bartonellosis
- Chagas disease (American trypanosomiasis) of the CNS
- Herpes zoster, multi-dermatomal (≥10 lesions in a non-contiguous site)
- Leishmaniasis, visceral (kala-azar)
- Lymphoma, Hodgkin's
- Lymphoma, non-Hodgkin's, all cell types
- Microsporidiosis (> 1 month's duration)
- Nocardiosis
- Penicillium marneffii, disseminated
- Pneumocystis carinii (jiroveci), extrapulmonary
- Rhodococcus equi disease

***TB must always be reported as a SAE on study.**

9.4.1 Reporting of SNAEs and AIDS defining illnesses

All SNAEs and AIDS defining illnesses meeting the definition of an SAE must be reported to The Kirby Institute as per SAE reporting requirements outlined in section 9.2.1. Details of how to report these are outlined in the MOOP.

9.5 Suicidal ideation or behaviours

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor subjects for suicidality before and during treatment. Depression will be monitored using the Hospital Anxiety and Depression Scale (HADS).

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour.

If any participant experiences a possible suicidality-related adverse event (PSRAE) while participating in this study that is considered by the Investigator to meet International Conference on Harmonization (ICH)-E2A[33] definitions for seriousness, the Investigator will collect information using a paper PSRAE CRF form in addition to reporting the event on a SAE CRF form. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to Sponsor within one week of the investigator diagnosing a possible suicidality-related adverse event.

9.6 Definition and reporting of an overdose of study drug

Overdose of either study drug, whether or not associated with an adverse reaction, must be reported within 24 hours on the paper SAE form to The Kirby Institute and the participant monitored closely for signs and symptoms of adverse reactions and appropriate clinical care given. An overdose is either study drug taken in excess of that recommended in the product information. As the study drugs are highly protein bound, they are unlikely to be significantly removed by dialysis.

9.7 Reporting of pregnancy

It is the responsibility of investigators or their designees to report any pregnancy in a participant which occurs while the participant is taking study-supplied drug. All pregnancies must be advised to the project team within 7 days of site awareness via the pregnancy page of the eCRF. Pregnancies resulting in a congenital anomaly/birth defect and/or spontaneous/induced abortions are subject to expedited reporting and therefore the serious event form will need to be completed and submitted to The Kirby Institute within 24 hours (one working day) of site awareness of the event. All participants who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to The Kirby Institute.

Anonymised data from eCRF pregnancy forms will be transmitted by The Kirby Institute to the Antiretroviral Pregnancy Register, an international register making a systematic attempt to collect data on pregnancy, ART and outcomes. Submission of data to the registry is encouraged, but not mandated by the study and a participant may choose not to have their data submitted. The scientific conduct and analysis of the Registry are overseen by an Advisory Committee consisting of members from the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), the National Institutes of Health (NIH) as well as the private sector (http://www.apregistry.com/).

10.0 PACKAGING, LABELING, STORAGE AND ACCOUNTABILITY OF CLINICAL TRIAL SUPPLIES

10.1 Drug packaging, labelling and distribution

Dolutegravir is provided by ViiV Healthcare and darunavir is provided by Janssen Pharmaceutica NV. These study drugs will be distributed to participating sites by ALMAC clinical services.

DTG and DRV will be packaged (if required) and labelled prior to distribution to study sites/pharmacies. Each bottle will be labeled with a booklet label containing required languages. Distribution and receipt of these drugs will be at no cost to study sites.

Dolutegravir and darunavir are the only study drugs to be provided centrally in this protocol. Support for the procurement of ritonavir* will be provided by the Sponsor as outlined in the site's clinical trial agreement. There will be no material support for the provision or cost of the NRTI component of the non-study drugs.

Refer to section 6.2 for a description of study drugs.

Please refer to the pharmacy MOOP for all information regarding study drug management.

** Must use only proprietary or FDA/WHO prequalified equivalent heat stable ritonavir on study.*

10.2 Handling and dispensing of study drugs

Study drugs must only be dispensed according to the MOOP. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study participants. The study drugs must be dispensed only from official study sites by suitably trained, authorised personnel according to local regulations.

Study drugs will be dispensed from site supplies in accordance with the random allocation following receipt of prescriptions from recognised study investigators. This prescription must contain the unique participant identification number. After randomisation, study drugs will be dispensed at week 0, week 4 and approximately every 3 months thereafter until the end of the study. Refer to section 10.5 of this protocol for details of post-study drug supply.

The ART should be handled in keeping with normal procedures for licensed products.

10.3 Study drug accountability records at investigational site(s)

It is the responsibility of the Principal Investigator to ensure that a current record of study provided ART accountability is maintained at each site where they are inventoried, dispensed and disposed for the duration of the study. Records and/or logs must comply with applicable regulations and guidelines.

10.4 Destruction of study provided drug

Expired or returned study provided drug will be destroyed in line with local procedures and recorded on a drug destruction log. For further details of destruction of study medications, please refer to the MOOP.

10.5 Post study drug supply

At the end of 96 weeks (completion of the protocol) study-provided ART can be offered to all participants for a further 48 weeks as informed by the 48-week study results, if available, or by clinical judgment regarding the participants response to assigned therapy. Therefore, if non-inferiority of one of the simplified arms is established, all participants can be offered this (or either simplified regimen, should both be non-inferior) for final 48 weeks. If both intervention arms are found to be inferior then participants can be offered SOC for this final 48 weeks. Treatment choice after 96 weeks will continue to be informed by clinical judgement.

After 144 weeks study drug will no longer be available and composition of the participant's post-study regimen will be the clinician's decision.

Note: SAEs, ADRs, pregnancies and drug accountability must be reported to ViiV Healthcare and Janssen Pharmaceutica NV *for the entire period participants at a site are taking study supplied drug*.

11.0 BIOLOGICAL SAMPLES

11.1 Blood collection

It is important that the handling of blood samples is undertaken according to local guidelines and regulations for handling infectious substances. The blood tubes required to be used for each test should be as per local laboratory guidelines. Laboratory supplies should be sourced locally, in line with recommendations in the D^{2}EFT laboratory manual. Only laboratory supplies outlined in the clinical trial agreement with sites will have their procurement funded by the Sponsor.

All blood samples for eligibility purposes must be taken during screening. For follow-up visits, it is strongly recommended that the blood is collected on the date of the actual study visit. If this cannot occur, blood must be collected as close to the visit date as possible and within the correct visit window. Refer to the laboratory MOOP for details on specimen collection.

Plasma and sera for storage will be collected prior to randomisation and at the week 48 and 96 visits. Buffy coat will be collected for pharmacogenomic testing prior to randomisation from consenting participants (see section 6.6 of this protocol). Plasma for pharmacokinetic testing will be collected at week 4. From ≥ 24 weeks on randomised therapy, if there is a pVL > 500 copies/mL on 2 consecutive occasions >7days apart a plasma sample will be collected for future central resistance testing.

11.2 Labelling of blood collection tubes

Blood collection tubes should be labelled accurately and legibly as outlined in the MOOP.

11.3 Transportation of samples

It is important that during the transportation of blood samples precaution is taken according to local guidelines and regulations for handling infectious substances.

Sites will be required to set up the procedures for transporting the blood tubes to the local laboratory. It is important that the samples arrive at the laboratory within 3 hours of blood collection (this time frame is determined by need to process the chemistry and lipids within 4 hours of collection).

Staff handling, packaging, and/or shipping biological samples from an interim laboratory to the central laboratory must understand and comply with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods and/or diagnostic specimens. Methods for packaging and shipping biological samples are detailed in the laboratory MOOP.

Transport vials and grid boxes will be provided in kind to the interim laboratories by the Sponsor.

11.4 Storage of samples

Plasma, sera and buffy coat samples will be collected and processed at the local laboratory. The samples will be stored in an interim local laboratory and then sent for central storage to St Vincent's Centre for Applied Medical Research laboratory (AMR) in Sydney (if allowed by local laws and Ethics Committee approval, or else, stored in country). Where samples are stored centrally, they will be shipped at regular intervals throughout the study. Transport to AMR in Sydney will be organised by The Kirby Institute. The cost of processing and storage of bloods will be provided to the sites as per the clinical trial agreement. Please refer to the laboratory section of the MOOP for storage sample requirements.

11.5 Processing of samples

All blood samples for routine clinical care and safety monitoring will be analysed at the local laboratory. It is important that the handling of blood samples is undertaken according to local guidelines and regulations for handling infectious substances. The investigator may be contacted should the technical condition of the sample, absence of information or inconsistencies on the request form be such that the samples cannot be processed.

11.6 Reporting of results

The blood results from routine clinical care and safety monitoring will be reported to the site as per local standard procedures. It is important that once these results are received they are reviewed and entered into the eCRF. The results are to be kept in the medical record (hard copy or electronically) for source data verification.

12.0 STATISTICS

12.1 Sample size determination

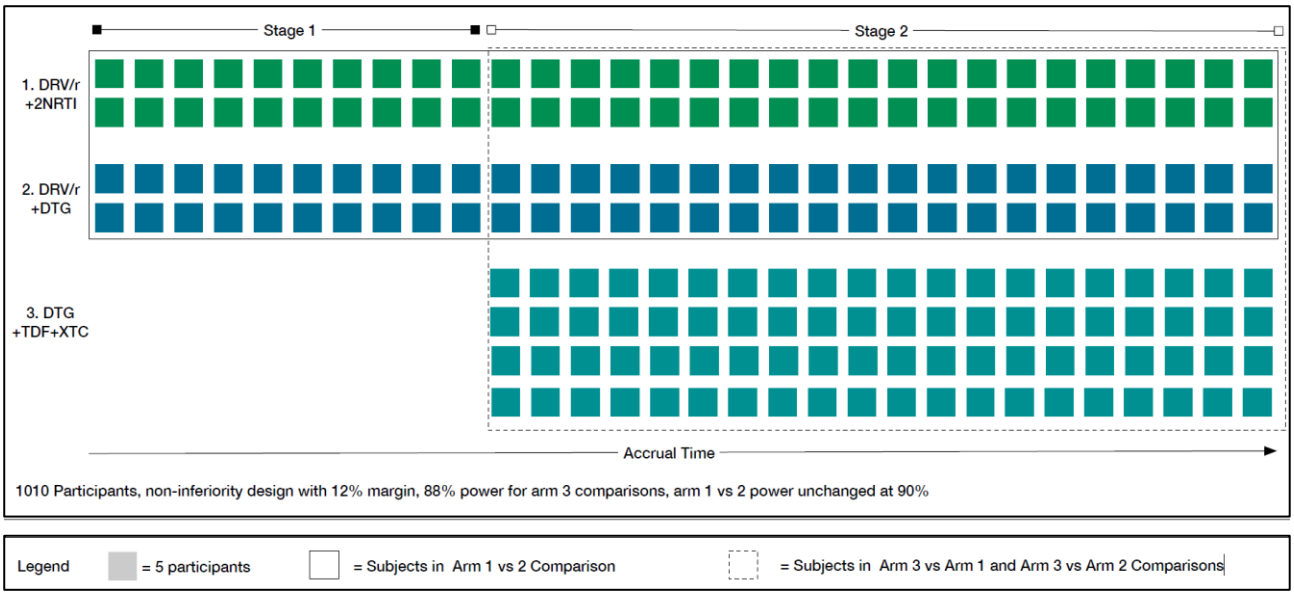
The primary endpoint is the comparison of proportions of participants in each arm whose pVL is <50 copies/mL at 48 weeks by intention to treat (ITT). Recent studies using once daily DRV/r combined with background NRTIs in ART experienced participants suggests that approximately 70% will

achieve pVL <50 copies/mL at 48 weeks, with even greater suppression (82%) among those with no prior PI exposure[34]. We expect response rates within this range.

Non-inferiority is defined as the lower 95% confidence limit on the difference in proportions with undetectable viral load lying above -12% (i.e. a non-inferiority margin of 12%). This value of delta is selected on the basis of US FDA guidance that specifies the non-inferiority margin for antiretroviral drugs is required to be less than the lower bound of treatment effect for the regimen under investigation[35].

As stage 1 accrual commenced with two study arms prior to stage 2 with the third arm opening, comparisons for the primary endpoint will be staged. All participants accrued to SOC and DTG+DRV/r throughout the trial are contemporaneous and can be compared to each other, while the subjects accrued to DTG+2NRTI once stage 2 opens will be compared only to their contemporaries accrued to SOC and DTG+DRV/r after stage 2 opens:

Stage 2



Under the null hypothesis of no difference between randomised treatment policies and a suppression rate of 75%, to have 90% power to demonstrate non-inferiority in the ITT analysis using a 12% margin will require 288 participants to be randomised into each of the two initial arms (SOC and DTG+DRV/r) (2-sided α=5%) making a total of 576 participants. Adjusting for the anticipated low rates of losses to follow-up (approximately 5%) yields a required sample size for the original two arm comparison of 610 participants. Power for the third arm (DTG+2NRTI) to be added in stage 2 depends on the number of subjects accrued in stage 1. In the likely scenario of 100 subjects to each arm in stage 1, randomising 300 subjects to the third arm in stage 2 gives 84% power for comparisons involving DTG+2NRTI with the same 12% non-inferiority margin, while randomising 400 subjects to the third arm gives 88% power for comparisons involving DTG+2NRTI.

12.2 Analysis Plan

12.2.1 The intention to treat (ITT) population

The ITT population is defined as all participants who undergo randomisation and who receive at least one dose of study medication and attend at least one follow up visit. Participants will be compared as randomised regardless of the treatment received.

During follow-up it is anticipated that a proportion of participants will experience various events which may result in different exposures to ART.

The following describes a framework for the analysis of the primary endpoint based on a particular handling of anticipated events:

I. in the event of the participant dying or becoming lost to follow-up the participant will be considered to have failed randomised treatment

II. in the event that ART is changed because of pVL ≥50 copies/mL the participant will be considered to have failed randomised treatment

III. ART changes for any other reason (other than II) do not constitute failure in the ITT population

This analysis corresponds to a comparison of the randomised treatment strategies, including all changes to ART regimens that occur subsequent to randomisation and will constitute the primary analysis.

A secondary analysis of this population but using a virological threshold of 200 copies/mL will also be undertaken.

12.2.2 The per protocol (PP) population

The PP population is defined as all participants as defined in the ITT population excluding those who changed randomly assigned ART for any reason other than pVL ≥50 copies/mL and for whom virologic data is missing for week 48.

This approach corresponds to a comparison of the effectiveness of the two randomised ART regimens as if participants had adhered to their randomly allocated ART and completed all protocol mandated assessments.

12.2.3 Statistical analyses

Analysis of the primary endpoint will be performed by ITT missing=failure (non-suppression). Since ITT analyses are known to slightly underestimate treatment effects (thus making noninferiority less demanding) demonstration of non-inferiority will require that the definition of noninferiority be met in analyses of *both* the ITT and per-protocol (PP) populations. Non-inferiority of ART regimens will first be assessed using ITT. If the treatment strategies are found to be equivalent under ITT, then they will be assessed for non-inferiority under PP. The primary endpoint for assessment of non-inferiority is the proportion of participants with pVL <50 copies/mL after 48 weeks. For secondary endpoints comparing ART regimens, the ITT population will be primary, although analyses of the PP population will also be performed. This approach is consistent with current US FDA guidelines for comparative studies of ART[36]. Safety endpoints will all be analysed according to randomised arm on available data with no imputations.

Treatment estimates and 95% confidence intervals will be calculated and will be used to assess primary and secondary ART regimen efficacy endpoints. If non-inferiority is established for the primary comparison (ITT and subsequent PP analyses) further analyses to assess for superiority will be undertaken. The effect of randomised ART regimen on the primary endpoint will also be assessed, stratified by TDF use and baseline pVL and by site availability of genotypic resistance testing. In these subgroup analyses, treatment estimates and 95% confidence intervals will be calculated within each subgroup. Consistency of treatment estimates across subgroups will be assessed using tests for interaction between treatment effect and subgroup.

Binary endpoints will be analysed using chi-square tests or logistic regression. Continuous endpoints will be analysed using ANOVA methods or non-parametric equivalents. Time to event endpoints will be analysed using survival analysis methods. Interaction will be assessed using logistic regression.

For all endpoints and analysis populations, the primary treatment comparisons will be simple, unadjusted, two-group comparisons. If there are important imbalances in baseline characteristics, then adjusted analyses will also be performed and presented in addition to unadjusted analyses. The primary comparisons will be of each of the simplified regimens with the SOC arm. A subsequent exploratory comparison of the two simplified regimens will also be performed. There will be no adjustment of analyses for multiple comparisons.

Because the third arm DTG+2NRTI has been added after trial recruitment started, all pairwise randomised comparisons will only include patients that have been randomised to both treatment

options being compared. This means that patients randomised in the first phase of the trial, that is only randomised to either SOC or DTG+DRV/r, will not be included in comparisons with the DTG+2NRTI arm.

12.2.4 Safety analyses

The proportion of participants with grade 3/4 adverse events will be summarised by randomised treatment group, by severity and by relation to study drug for all participants treated with study drug. Serious adverse events will be summarised for all enrolled participants. The incidence rate of adverse events ≥ grade 3 will also be calculated. The analysis of safety variables will be done according to a per protocol approach.

12.2.5 Economic analyses

Antiretroviral therapy costs will be assessed across study arms and can be compared in a number of sensitivity analyses using different pricing systems (Average Wholesale Price (AWP), Public Health Service (PHS) price and Generic Price (GP)). Health-care utilisation (including hospitalisation, clinic visits, nursing home care and home care) will be self-reported and then used to estimate costs. Indirect costs of medical illness will be estimated from the number of days the participant was unable to carry out routine activities. Quality of Life will be measured using the SF-12v2 questionnaire. Safety data, viral loads and quality of life data will also be analysed.

12.3 Schedule of Analyses

Formal analyses to be conducted during this protocol are: one interim analysis of data sets at week 24 (complete), a primary analysis (week 48) and an extended follow-up analysis (week 96). In addition, a limited analysis of subjects at week 12 was performed for safety. Detailed analysis plans (statistical, safety and economic) describing all proposed analyses will be prepared by the study biostatistician and health economist in advance of database lock for each defined interim and final analysis. These will be reviewed by the PSC prior to implementation.

An early safety analysis was conducted once the first 100 participants randomised to the DTG+2NRTI arm had reached 12 weeks. This early analysis compared virological response between the DTG+2NRTI and DRV+2NRTI (SOC) arms. This was reviewed in closed session by an independent Data Safety Monitoring Board (DSMB) that reported to the study Protocol Steering Committee (PSC). The DSMB recommended continuation of the study without modification.

The week 24 interim analysis summarised study variables when 50% of enrolled participants in the original two study arms had completed 24 weeks of follow-up and included all stated primary and secondary measures of interest. This was reviewed in closed session by an independent Data Safety Monitoring Board (DSMB) that reported to the study Protocol Steering Committee (PSC). The rationale for timing the interim analysis in this way was that the number of participants in the added DTG+2NRTI arm may be lower than the original two arms, but it was difficult to predict accurately. The DSMB, on review of the interim data, was charged with making a recommendation as to the need for, and timing of, a further interim analysis. The DSMB again recommended continuation of the study without modification.

The primary analysis will summarise study variables when the last participant randomised has completed 48 weeks of follow-up. This analysis will be reviewed firstly by the PSC and then presented publicly with treatment arms identified. This constitutes the final analysis of week 48 data (the primary analysis point) and decisions regarding the future conduct of the trial will be made based on statistical significance and clinical relevance. Arrangements have been included to switch all participants to the other treatment arm if necessary.

Economic analyses will be undertaken as soon as follow-up milestones are completed with results to be presented in parallel or as close to parallel with the primary analyses arising from the trial.

The follow-up analysis of all data up to week 96 provides an opportunity to examine longer term durability and safety data. An analysis plan for the week 96 data will be finalised and approved by the PSC prior to the final data lock. In the setting of life-long therapy these outcomes are of considerable importance.

13.0 DATA SAFETY AND MONITORING BOARD (DSMB)

A DSMB has been established and is composed of individuals independent of the study i.e. not a member of the PSC or a study site investigator. The study biostatistician has an ex officio role in the DSMB. The study biostatistician is responsible for selection of the DSMB and coordination of its activities. The DSMB will be accountable to the PSC and will undertake independent review of protocol-specified and ad hoc interim analyses if required.

Given concerns about potency and/or resistance in the third arm (DTG+2NRTI), an early DSMB analysis occurred when 100 participants randomised to DTG+2NRTI reached 12 weeks. It was calculated that approximately 150 participants randomised to the first two arms would have reached 12 weeks by this stage.

This early analysis focused on a comparison of DTG+2NRTI with DRV+2NRTI (SOC).

Assuming around 75% of participants allocated DRV+2NRTI have undetectable viral load (<200 copies/mL) at 12 weeks (as seen in the SECOND-LINE study), then this comparison would have 80% power to detect 57% of participants allocated DTG+2NRTI having undetectable viral load (2-alpha=5%).

We also compared mean changes in log10 viral load at week 4 from week 0 to assess very early potency. Assuming variability in this endpoint corresponds to a standard deviation of 0.9logs (also seen in the SECOND-LINE study), then this comparison would have over 95% power to detect differences of 0.5logs.

Given that the final analysis is for noninferiority, we did not propose stopping rules based on stricter type 1 error rates. As no substantial difference between arms was seen at this early interim, the early analysis does not affect the conclusions regarding noninferiority. However, stopping rules at this early interim analysis were only based around DTG+2NRTI having poorer virological outcomes compared with DRV+2NRTI. There was no consideration of stopping at this time for better efficacy.

An interim analysis summarised study variables when 50% of enrolled participants in the original two arms completed 24 weeks of follow-up and included all measures identified *a priori* in the DSMB terms of reference. The interim analysis reviewed by the independent DSMB recommended to the PSC that the study should continue unchanged. Randomised arms were masked for this review.

By originally timing the interim analysis in this way, it was acknowledged that the number of participants in the added DTG+2NRTI arm may be lower than the original two arms, but it was difficult to predict accurately. The DSMB, on review of the interim data, were charged with making a recommendation as to the need for, and timing of, a further interim analysis. The DSMB had no safety concerns with the study, however, they recognized that the COVID-19 pandemic has the potential to affect both study accrual and the assessment of safety (adverse events, deaths). They therefore recommended a subsequent DSMB review of the study when a total of 500 participants have had their week 24 visit.

The DSMB, in agreement with the PSC, was able to require implementation of stopping rules that required changes in the conduct of the study should concerns surrounding the safety of participants arise from review of the week 24 results. A conservative Peto-Prentice-type stopping rule ($p<0.001$) was used to judge whether one arm should be ceased for inferiority. The advantage of this very conservative stopping rule was that statistical significance at the final week 48 analysis can be left unadjusted at $p<0.05$.

In addition, the DSMB were -provided with information relating to the conduct and management of the study. Datasets (blinded or un-blinded) have not been made available for review outside of the DSMB and relevant project biostatistician.

The terms of reference and operating guidelines of the DSMB will be drafted by the study biostatistician (as documents separate to the Protocol) and finalised in collaboration with the DSMB prior to the commencement of the study.

14.0 DATA COLLECTION, SOURCE DOCUMENTS AND RECORD RETENTION

14.1 Data collection and source documents

The Principal Investigator or designee is responsible for preparing and maintaining adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the study.

Source documents (the point of the initial recording of data) include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. These include, but are not limited to, participant medical records, laboratory reports, ECG tracings, X-rays, radiologist reports, biopsy reports, ultrasound photographs, participant progress notes, pharmacy records and any other similar reports or records of procedures performed in accordance with the protocol. It is not acceptable for the CRF to be the only record of the participant's study participation and progress must also be recorded in the participant medical record. This is to ensure that anyone accessing the participant's medical record has adequate knowledge of their participation in a clinical study.

Any document that acts as a source document should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Where the source data is stored electronically this requirement will be satisfied in the form of an audit trail. Persons signing the source documents must be listed, on the appropriate study documentation (site delegation log), as a site staff member.

14.2 Submission of data

With limited exceptions, data will be collected for this study on an Electronic Data Capture system using a web-enabled password protected platform. The exceptions include the SAE form and a limited number of paper-based documents. Following each participant visit the designated site staff will complete the visit specific eCRF. The Principal Investigator is responsible for ensuring the data collected are complete, accurate and recorded in a timely manner. Serious events, serious non-AIDS events, AIDS defining illnesses, an overdose of study drug(s) and pregnancies must be reported within 24 hours of site awareness of them, that is, sites should not wait until the next study visit to report them (refer to section 9). The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Once the eCRF is completed Sponsor staff will monitor the data for completeness and accuracy. Any discrepancies either manual or automatic will be notified to the site staff for clarification. Corrections to eCRFs will only be possible by study personnel with sufficient authorisation to make changes. All changes will record time, date, computer ID and the name of the authorised person's access code. Corrections to paper-based forms can only be done by study staff and must be signed and dated.

14.3 Records retention and archiving

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files) and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for 15 years, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If a Principal Investigator withdraws from the study (e.g. relocation, retirement), the records will be transferred to a mutually agreed-upon designee or site (i.e. another Investigator or IRB). Notice of such transfer will be given in writing to the Sponsor.

14.4 Study monitoring

Representatives of The Kirby Institute or their delegates must be allowed to visit all study site locations periodically to assess the data, quality and study integrity.

The Principal Investigator is responsible for retaining all essential documents listed in ICH Good Clinical Practice (GCP) guidelines. These must be organised in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

14.5 Auditing

The study may be subject to audit by The Kirby Institute, UNITAID, ViiV Healthcare, Janssen Pharmaceutica NV, the US National Institutes of Health, the ethics committee, relevant regulatory agencies or the relevant government authorities. Under such circumstances, the investigator must agree to allow access to study documents and relevant hospital/clinic records. Audit reports will be kept confidential between the site and the Sponsor.

The Principal Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities and forward copies of inspection reports to the Sponsor.

15.0 ETHICS COMMITTEE/REGULATORY APPROVAL AND INFORMED CONSENT

15.1 Ethical conduct of the study

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

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

The sponsor is responsible for ensuring regulatory approval for the study is obtained.

The study will be reviewed by the relevant local ethics committees and regulatory authorities, in accordance with current local guidelines. The Sponsor will assist in the process of approval as required by each individual site. Before study commencement at a site, the Investigator must have written and dated approval/favourable opinion from the IRB/IEC and local regulatory authorities for the protocol, consent form, participant recruitment materials/process (e.g. advertisements) and any other written information to be provided to participants. The approval must clearly identify all documents approved by the IRB/EC and regulatory authorities including version number and dates of the protocol and participant information/informed consent form. It should also contain a statement that the IRB/EC is compliant with ICH GCP requirements for composition and procedures. A copy of the approval must be sent to the study Sponsor. The site Principal Investigator must also obtain approval for any amendments to the protocol or participant information and informed consent form.

The Principal Investigator must comply with all IRB/EC, and where relevant regulatory authorities, reporting requirements for all safety reporting, annual updates, end of study reports and any other important information relevant to the conduct of the study. The Principal Investigator must agree to abide by any IRB/EC conditions of approval. Researchers must inform the IRB/IEC, and where relevant regulatory authorities, as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the study or which may indicate the need for amendments to the study protocol. In addition, the Principal Investigator should provide any updates or other information required by relevant parties in accordance with any local regulatory requirements or institution procedures.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g. loss of medical licensure, debarment).

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

15.2 Compliance with the protocol

The study will be conducted as described in this protocol. The Principal Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study participants. Any significant deviation must be documented and notified to the Sponsor.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favourable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favourable opinion;
- The Sponsor;
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to the Sponsor along with other required documentation.

15.3 Protocol amendments

When revisions to the protocol are made by the Sponsor, if the revision is an Administrative Letter, the Principal Investigator must submit this for the information of their IRB/IEC.

When revisions to the protocol are made by the Sponsor, if an Amendment substantially alters the study design or increases the potential risk to the participant:

1. the consent form must be revised and submitted to the IRB/IEC for review and approval/favourable opinion;
2. the revised approved form must be used to obtain consent from participants currently enrolled in the study if they are affected by the Amendment; and
3. the new approved form must be used to obtain consent from prospective participants prior to enrolment.

15.4 Informed consent and procedures

The Project Team will prepare the informed consent which must:

- include all elements required by ICH-GCP;
- include all applicable regulatory requirements;
- adhere to the ethical principles that have their origin in the Declaration of Helsinki;
- include a statement that the sponsor, study drug providers, the ethics committee, and regulatory authorities will have direct access to participant study records (see appendix 1 for participant information and consent form template).

The Principal Investigator must ensure that participants or their legally authorised representative (LAR) are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they participate. Prospective participants or their LAR must understand that their participation in the study is voluntary and should they decline to participate this decision will not affect their relationship with the site or site staff.

The Principal Investigator should provide the patient or LAR with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Principal Investigator should allow time necessary for patient or patient's LAR to inquire about the details of the study. Freely given written informed consent must be obtained from every participant or their LAR prior to any protocol-specific procedures being conducted on that patient. Consent must be confirmed by the patient's or their LAR's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. The patient or LAR should receive a copy of the signed and dated informed consent and any other written information provided prior to the patient's participation in the study.

If the patient is illiterate, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the patient or their LAR must sign and date the informed consent form, if capable. If incapable, agreement of the participant should be indicated by including their thumb print on the ICF. The impartial witness must also sign and date the informed consent form along with the person who conducted the consent discussion.

Should an ethics committee-approved informed consent form not be available in a patient's most proficient language, then a translator should be sought. This translator should act as a witness to the informed consent process and be asked to sign the informed consent form accordingly.

15.5 Updates to the consent form

The informed consent and any other information provided to participants or the participant's LAR should be revised whenever important new information becomes available during the course of the study that is relevant to the participant's consent. This information should receive IRB/IEC approval/favourable opinion prior to use, except if the safety of the participant is compromised by the resulting timelines. The Principal Investigator or their designate should fully inform the participant or the participant's LAR of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented. During participation in the study, any updates to the consent form and/or the written information will be provided to the participant.

16.0 CONFIDENTIALITY OF DATA

16.1 Confidentiality of participant records

By signing the Clinical Trial Agreement, the site Principal Investigator agrees that the sponsor, IRB/EC or regulatory authorities may consult and/or copy study documents to verify information in the CRF. By signing the consent form the participant agrees to these processes.

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

16.2 Confidentiality of study data

By signing the Clinical Trial Agreement, the site Principal Investigator affirms to the sponsor that information provided to them by the sponsor will be maintained in confidence and divulged only as necessary to the ethics committee and institution employees directly involved in the study. Both ethics committee members and employees must also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

17.0 GOVERNANCE

This international research protocol is funded by UNITAID, the US National Institutes of Health, ViiV Healthcare and The National Health Medical & Research Council, Australia. Dolutegravir and darunavir will be provided by ViiV Healthcare and Janssen Pharmaceutica NV respectively. The study is sponsored by the University of New South Wales (UNSW) and coordinated through The Kirby Institute for infection and immunity in society. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

17.1 Protocol Steering Committee (PSC)

There will be a single PSC chaired by Kirby Institute. This group will comprise representatives from:

- each participating site coordinating centre (SCC)
- UNSW (including the study biostatistician)
- ViiV Healthcare
- Janssen Pharmaceutica NV

- US National Institutes of Health

The PSC will seek the expertise of other key opinion leaders as necessary. The PSC will be the primary management entity for the collaborative study group. This group will meet face to face or via teleconference, arranged as required but at least twice per year during the study follow up period. Decisions in this group will be reached by consensus among the designated membership. Routinely the views of other stakeholders will be sought at meetings of the PSC and this will allow others to attend meetings. The PSC, comprised of members from a range of internal and external stakeholders will guide the design, implementation and conduct of the study.

17.2 Project Team

Day-to-day management of the protocol will be undertaken by a dedicated project team based at The Kirby Institute at UNSW and supported as required by contract service organisations. The Project Team is accountable to the PSC.

For contact details on the clinical trial sites, laboratories and pharmacies please refer to the MOOP.

18.0 FINANCING AND INSURANCE

Investigators will be paid according to the separate financial agreement document that must be signed and dated prior to study commencement. The Principal Investigator should provide details of the study budget to the IRB/IEC, as required by the individual committee. In addition, any participant reimbursement of expenses for participation in the study must be clearly stated in the participant information and consent form and must be approved by the IRB/IEC.

18.1 Indemnity and compensation

Indemnification for site personnel, investigators and institutions will be provided as required in keeping with the provisions as determined by the Medicines Australia guidelines through UNSW Australia. Details of this provision will be documented in separate agreements.

No-fault-compensation is available to study participants who experience injury as a result of their participation in this study. Details of the method of compensation will be provided in separate agreements between institutions.

19.0 QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA)

By signing this protocol (Appendix 3), the sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice standards and all applicable local laws and regulations relating to the conduct of a clinical study.

20.0 PUBLICATION POLICY

The primary output of this research project would comprise 1-3 high impact peer review journal publications. In the interests of collegiality and recognising that completion of this study will have resulted from the contribution of many people around the world the masthead authorship for this manuscript will be “The D^{2}EFT Study Group”. The PSC will compose a writing committee for the primary manuscript who will be identified as such in an appendix. In addition, one person from each investigational site will be listed in a separate appendix as being part of the D^{2}EFT Study Group. The PSC will determine if there is a need for additional appendices in which to identify others who have contributed in a significant way to the design AND conduct AND reporting of resultant study data. If the journal will not accept group authorship the writing committee will be listed as authors and be completed with the phrase ‘on behalf of the D^{2}EFT Study Group’.

Additional manuscripts that are expected to report on the findings of any subsequent substudies should have named investigators and be completed with the phrase ‘on behalf of the D^{2}EFT Study Group’. In these circumstances an appendix should contain the names of the PSC.

All proposed manuscripts should be submitted to the PSC 45 days before they are to be submitted to a journal for peer review.

Conference presentations should identify an authorship group consistent with those who have contributed to the data to be reported. All proposed conference presentations should be submitted to the PSC at least 20 days before submission of an abstract.

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ABBREVIATIONS LIST

Abbreviation/ Acronym		Description	Abbreviation/ Acronym		Description
3TC	-	Lamivudine	ISTI	-	integrase strand transfer inhibitor
ADR	-	Adverse drug reaction	ITT	-	Intention to treat
AE	-	Adverse event	LFT	-	Liver function test
AIDS	-	Acquired immune deficiency syndrome	LAR	-	Legally authorised representative
ALT	-	Alanine amino transferase	LPV/r	-	Lopinavir/ritonavir
AST	-	Aspartate amino transferase	MI	-	Myocardial infarction
ART	-	Antiretroviral therapy	MOOP	-	Manual of operations
AZT	-	Zidovudine	NC=F	-	Non-compliance = failure
b/PI	-	Boosted protease inhibitor	NIH	-	National Institutes of Health
CDC	-	Centers for Disease Control	NNRTI	-	Non-nucleoside reverse transcriptase inhibitor
CRF/eCRF	-	Case report form/electronic case report form	NRTI	-	Nucleos(t)ide reverse transcriptase inhibitors
CVD	-	Cardiovascular disease	PI	-	Protease inhibitor
d4T	-	Stavudine	PID	-	Participant identification
ddI	-	Didanosine	PSC	-	Protocol Steering Committee
DILI	-	Drug induced liver injury	PSRAE	-	Possible suicidality-related adverse event
DRV/r	-	Ritonavir-boosted darunavir	PTB	-	Pulmonary tuberculosis
DNA	-	Deoxyribonucleic acid	pVL	-	Plasma viral load = plasma HIV RNA
DSMB	-	Data safety monitoring board	py	-	Per year
DTG	-	Dolutegravir	QA	-	Quality assurance
ECG	-	Electrocardiograph	QC	-	Quality control
eGFR	-	Estimated glomerular filtration rate	RNA	-	Ribonucleic acid
FDA	-	Food and Drug Administration	SADR	-	Serious adverse drug reaction
FTC	-	Emtricitabine	SAE	-	Serious adverse event
GCP	-	Good Clinical Practice	SF-12	-	Study Short-Form 12-item Survey (version 2)
GFR	-	Glomerular Filtration Rate	SNAE	-	Serious non-AIDS defining event
HADS	-	Hospital anxiety and depression scale	SUSAR	-	Suspected unexpected serious adverse reaction
HIV	-	Human Immunodeficiency Virus	TDF	-	Tenofovir disoproxil fumarate
IATA	-	International Air Transport Association	ULN	-	Upper limit of normal
ICH	-	International Conference on Harmonisation	UNSW	-	University of New South Wales
ID	-	Identification	WHO	-	World Health Organisation
IRB/IEC	-	Institutional review board/Institutional ethics committee	XTC	-	Denotes the option of FTC or 3TC use

APPENDIX 1: PARTICIPANT INFORMATION SHEET AND CONSENT FORM (MAIN STUDY)

[Insert institutional logo]
[name of local institution/s where research is being conducted]

PARTICIPANT INFORMATION AND CONSENT FORM

A phase IIIB/IV randomised open-label trial to compare dolutegravir with pharmaco-enhanced darunavir versus dolutegravir with predetermined nucleosides versus recommended standard of care antiretroviral regimens in patients with HIV-1 infection who have failed recommended first line therapy.

D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

Principal Investigator(s): *[insert]*

Site Address: *[insert]*

Invitation

You are invited to take part in the D^{2}EFT research study because you are infected with the HIV virus and your first combination of anti-HIV drug therapy is no longer controlling the HIV infection. It is up to you whether or not you want to join this study. Please ask questions and take as much time as you need to decide.

The study is being done by **[insert local institution name]**. It is part of an international group study supported and run by The Kirby Institute at the University of New South Wales in Sydney, Australia (the Sponsor).

Before you decide whether or not you wish to join in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the purpose of the study?

International health organisations currently recommend the use of combination anti-HIV drugs for treating HIV infection. Once started, most people will need to stay on these drugs life-long. First-line HIV drug therapy is the first combination of anti-HIV drugs you were on. Over time first-line therapy can become less able to control the amount of virus in the blood. If this happens a new combination of HIV treatment is given to bring down the level of HIV virus again (second-line therapy). This study has been set up to investigate the use of two possible simple combinations of anti-HIV drugs to be used as second-line HIV therapy. The first combination being investigated is dolutegravir and darunavir+ritonavir, and the second combination being investigated is dolutegravir and tenofovir with emtricitabine or lamivudine.

There are different types, or classes, of anti-HIV medications which your doctor will discuss with you. Current recommendations for second-line therapy are to switch to 3 new anti-HIV drugs, one from a class that has never been used before and 2 from a class that has. Choosing new drugs from a class that has already been used can be complicated and needs careful thinking as the drugs may not be very effective in controlling the HIV virus. A blood test, called a resistance test, can be used to check which anti-HIV drugs may not control your HIV virus well. The result from the blood test can be used to help guide the decision of which drug to choose but this testing is complicated, expensive and often not available.

The new combination of study drugs for second-line therapy were chosen because at least one drug is from a class you have not used before, and the combinations can be chosen without resistance testing. The new drugs do not easily lose their activity against the HIV virus and are easy to take (3 tablets once a day). There is no need to change the food you eat and your normal daily activities can be continued.

The purpose of this study is to compare if the two possible simple combinations of anti-HIV drugs are as safe and effective over 96 weeks as the currently recommended combination. Participants in the study will receive a second-line combination determined by the study: either the currently recommended treatment combination or one of the new treatment combinations.

2. Why have I been invited to participate in this study?

You are invited to join in this study because you have been taking a combination of anti-HIV drugs for at least 24 weeks and:

- This therapy is no longer working to keep the amount of virus in your blood at very low levels;
- You have not used one of the types of anti-HIV drugs we are looking at in the new combination before;
- There has not been a change in your anti-HIV drugs within the last 12 weeks.

3. What if I don't want to take part in this study or if I want to withdraw later?

You do not have to join this research study if you do not want to. If you choose to volunteer to join the study, you can leave the study at any time. If you choose not to join or to leave the study, it will not affect your regular medical care or your relationship with the staff caring for you.

You will be told about any new information learned during the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results are available and how to learn about them.

If you do not wish to continue in the study once you have joined it, you can leave the study at any time without having to give a reason. However, your information collected during your time on the study will still be used. Also, if you are receiving HIV medicines provided by the study, you will not continue to be given these HIV medicines through the study after you leave. Your doctor or nurse will help you find another way to get HIV medicines.

If you wish, any of your blood collected for the study that can still be identified as yours will be destroyed should you choose to leave the study.

If the study is stopped by the sponsor, or if at any time your study doctor thinks that it is best for you to no longer be in the study, they will explain the reasons and arrange for your care to continue.

4. What does this study involve?

A total of approximately 1,010 people will take part in the study from countries in Africa, Asia, India and Latin America. You will need to come to the clinic for 6 study visits over the 96 weeks of the study.

D^{2}EFT is a randomised open-label study. A study is randomised because sometimes we don't know the best way of treating patients with a particular condition so we need to compare different treatments. To do this, people who join a study are put into groups and each group is given a different treatment. The results are compared to see whether one treatment is better. We need to be sure the groups are similar and the best way to do this is to use a computer to put each person into a group randomly, like the flip of a coin. Neither the doctor nor the person joining the study can decide which treatment the person will receive. Being open-label means that you and the study team will know which treatment you are given.

If you decide to join the study you will be asked to sign this form showing that you agree to join in and you will be given a copy to keep. An ethics committee has looked at this study and given it the go ahead. The committee makes sure that people who join the study will be respected and have their health and rights protected.

After the consent form is signed blood will be drawn and tested to make sure you are able to join the study. You will be allocated into one of the following study groups:

- Standard of care group: a World Health Organisation recommended HIV drug regimen including darunavir + ritonavir (to be discussed with your doctor).
- Dolutegravir and darunavir group: dolutegravir and darunavir+ritonavir taken once daily.
- Dolutegravir and nucleosides group: dolutegravir and tenofovir with emtricitabine or lamivudine taken once daily

Darunavir and dolutegravir are being donated by the drug companies. The cost of the ritonavir used with darunavir will be paid for by the study sponsor.

If you agree to join in this trial, you will be asked to have the following:

Screening Visit (to make sure you qualify to enter the study)

At this visit, the following will be done:

- Discuss the study and, if you choose to join in, sign and date the informed consent form;
- Your doctor will review your medical notes including any illnesses, information on your HIV infection and any medicines you are taking;
- You will have an examination which will look at any health issues you may be experiencing;
- Blood tests will be done which need approximately 25mLs or 1¼ tablespoons of your blood to be collected (where 1 tablespoon equals 20 mLs). Blood tests will measure/test for:
    - red and white blood cells and platelets (these help your blood to clot),
    - the amount of HIV virus in your blood,
    - how your liver and kidneys are working,
    - if you are infected with the hepatitis B virus (unless you have had a hepatitis B result in the last six months showing you have this virus).
- If you are a woman who can become pregnant, test your blood or urine to see if you are pregnant (a test must show that a woman is not pregnant in the 2 weeks before joining the study).

Other Visits

If you do not qualify to join the study you will be told of this by the site staff. You will not need to come back to the clinic for this study. If you do qualify you will be asked to come back to the clinic (up to 45 days after your screening visit) to have some baseline tests (these provide us with information to compare your later study information to) and be randomly placed into a study group. This is called week 0. After that the visits are 4, 24, 48 and 96 weeks after week 0.

Each visit you will have an examination. You can discuss any health concerns you may have and you will be asked questions about your health, medicines, and side effects. This information is very important and we ask for it to protect your safety. You will also have the following:

Week 0, 48 and 96 visits	Week 4 visit	Week 24 visit
You should not eat or drink anything except water for 8 hours before these clinic visits.	**It is very important that you know the exact time you took your last dose of Anti-HIV drugs before this visit. You will be asked for this information at the visit so you may wish to write the time down and bring it with you.** **You can eat and drink normally before this visit**	**You should not eat or drink anything except water for 8 hours before this clinic visit.**
Measure your height (at week 0 only), weight, waist, hips and blood pressure	You will be asked to answer questions about taking your anti-HIV drugs	
Approximately 45mLs or 2¼ tablespoons of blood taken to measure: • red and white blood cells and platelets (these help your blood to clot), • the amount of HIV virus in your blood, • CD4+ and CD8+ cell counts (type of blood cells that are affected by HIV),	Approximately 35mLs or 1¾ tablespoons of blood taken to measure: • red and white blood cells and platelets (these help your blood to clot), • the amount of HIV virus in your blood, • CD4+ and CD8+ cell counts (type of blood cells that are affected by HIV), • how your liver and kidneys are working,	Approximately 30mLs or 1½ tablespoons of blood taken to measure: • red and white blood cells and platelets (these help your blood to clot), • the amount of HIV virus in your blood, • CD4+ and CD8+ cell counts (type of blood cells that are affected by HIV), • how your liver and kidneys are working,

• how your liver and kidneys are working, • amount of fats (lipids) in your blood At week 0 only, an additional 10 mLs (1/2 tablespoon) of blood will be taken for future resistance testing.	• how the study drug is absorbed, moves around and is removed from your body	• amount of fats (lipids) in your blood
If you are a woman, test your blood or urine to see if you are pregnant	If you are a woman, test your blood or urine to see if you are pregnant	If you are a woman, test your blood or urine to see if you are pregnant
You will be asked to answer questions about your quality of life, how you have been feeling in the past week, and use of health care facilities (like the number of times you visited your doctor in the last 4 weeks)	You will be asked to answer questions about how you have been feeling in the past week	

One month's supply of anti-HIV drugs will be provided after you have joined the study and been allocated to your study group. You should start taking your new anti-HIV drugs within 1 week of your week 0 visit. At the week 4 visit you will receive approximately 3 months' supply of anti-HIV drugs. You will continue to get anti-HIV drugs approximately 3-monthly after this. This means that sometimes you will need to visit the clinic when you do not have a study visit scheduled to collect more of your anti-HIV drugs.

At any time during the study, if you have a bad effect from the study medications, you will need to advise your doctor. You may be asked to stop the study medication and may need to come to the clinic for extra exams or lab tests.

Blood storage
Some of the blood collected at weeks 0, 4, 48 and 96 will be stored for future testing. The blood will be used for future medical research in the treatment of HIV.

If, from 24 weeks since starting the anti-HIV drugs for this study, a blood test shows that the drugs are no longer working to keep the amount of virus in your blood at very low levels, you will be asked to have a second blood test at least a week later (9mLs or approximately ½ tablespoon of blood will be drawn). This is to confirm the result and store some blood for resistance testing at a later date. Blood stored for future resistance testing will be kept securely at a laboratory in Sydney, Australia.

Most results from tests performed on stored blood cannot be given to you as the tests may not be conducted until years after the end of the study. None of the results from the tests done are part of usual medical care. This means your health is not affected by not knowing the results.

At any time during the study please talk to your study doctor or nurse as soon as possible if:
- You are sick or hurt or in the hospital for any reason.
- You move or transfer your care to another doctor.
- You become pregnant.

5. How is this study being paid for?

This study is being funded by grants to The Kirby Institute at the University of New South Wales from UNITAID (part of the World Health Organization) in Switzerland, the National Institutes of Health in the USA, ViiV Healthcare and the National Health and Medical Research Council of Australia. No money is paid directly to individual researchers.

6. Are there risks to me in taking part in this study?

All HIV medicines may have some side effects. There may also be risks linked with this study that we do not know about or cannot predict.

There is a possibility that you will be allocated to a treatment group which the study results show was less effective than one or both of the other two treatment groups.

Even though great care is taken to avoid them, a medical problem may occur from participating in this study.

The more common or serious side effects of the drugs in the study are listed below. Please note that this list does not include all the side effects. Your study doctor/nurse will discuss all side effects with you.

Frequency	Dolutegravir	Darunavir/ritonavir
Very Rare (<1%)	Unusual dreams; dizziness; rash*	
Rare (≥1% <2%)	Nausea; depression; belly pain or discomfort; flatulence; vomiting; weak and tender muscles; liver problems; decrease in kidney function; itching; suicidal[#] thinking, attempt, behaviour, or completion.	Flatulence; irritation of the stomach lining; liver problems; problems involving the pancreas; muscle pain, weakness and swelling; bone pain; itching; unusual dreams; unusual sensations such as burning or tingling; Stevens-Johnson Syndrome[^].
Uncommon (≥2%<10%)	Difficulty sleeping; headache; tiredness; diarrhoea	Indigestion; nausea; vomiting; tiredness; Lack of appetite; bloating; weakness or lack of energy; fat changes in your body leading to a change in body shape; headache; abdominal pain; rash; diabetes mellitus.
common (>10%)		Diarrhoea

* all types of rash

[#] These events were usually seen in study participants who already have a history of depression or other mental illness.

[^] A serious disorder with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Can include swelling of the face and tongue with a sore mouth and throat.

Please note: it is important to report all side effects to your study doctor or nurse. If you develop a rash you should immediately tell the study doctor or nurse at your site.

Risks of blood drawing

As part of this study, you will have your blood drawn at each visit. This procedure is uncomfortable but rarely results in any major problems. Side effects that have been noted with drawing blood include feeling light-headed or faint, fainting, formation of a blood clot, bruising and/or infection at the site of the needle stick.

Pregnancy and breast feeding (only for women who are able to have children)

Pregnant and nursing mothers are not allowed to join this study. There may be harmful effects to the unborn child which are not yet known and you should speak to your study doctor about the need to avoid pregnancy during this study. If you do become pregnant during the study you should tell your study doctor immediately. They will discuss the options with you at that time and will follow your progress until your pregnancy finishes.

The effects of dolutegravir and darunavir in pregnancy are not well understood.

If you do become pregnant while on study you will be asked for permission to share the information collected about your pregnancy with the Antiretroviral Pregnancy Register. This register collects information on pregnancy, anti-HIV drugs and pregnancy results from all over the world. If you do choose to share your information neither you nor your baby will be identified. You may choose not to share your information with the register and this will not affect your participation in the study or your relationship with your care team.

Interaction with other medications

There can be a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study. You must tell any doctor you see during the study about all of the medications you are taking, especially before starting any new medications. This includes any other prescribed medicines, over-the-counter medicines, herbal medicines or supplements. You must also tell the study doctor or nurse before enrolling in any other clinical trials while participating in this study.

Despite all reasonable care taken to avoid them there may be some risks that are unexpected. Joining a study may affect your employment or health insurance. You should be aware of any possible affect before agreeing to join this study.

7. What happens if I am injured as a result of the study?

If you are injured as a result of this study, you should contact the study doctor as soon as possible, who will help you get the medical care needed.

If you have a bad experience resulting directly from the study drug or a study procedure, compensation (something that is done or given to make up for something bad) will be given for the reasonable costs of medical treatment to the extent such costs are not covered by your medical insurance or government health schemes. Compensation will be provided in accordance with the principles of the national compensation scheme of the country in which the study is performed and the incident occurs. If no national scheme exists, the Clinical Trial Compensation Guidelines issued by Medicines Australia will be adhered to. Please speak to your doctor if this needs to be explained further.

8. Will I benefit from the study?

Information gained from this study may improve future treatment of HIV infection however it may not directly benefit you.

9. Will taking part in this study cost me anything, and will I be paid?

Joining in this study will not cost you anything. You will not be paid or reimbursed for participating in this study.

The only specific cost in this study will be the travel costs for attending the clinic on the 6 occasions for study specific visits. It is hoped you can arrange for most of these visits to tie in with your regular doctor visits.

The study will cover the costs of providing dolutegravir and darunavir+ritonavir.

10. What will happen to my blood sample after it has been used?

You will be asked whether you agree to have some of your blood stored. This will be stored for a short time at a local laboratory in your country and then sent to the central laboratory (St Vincent's Centre for Applied Medical Research (AMR) in Sydney, Australia) if allowed by local laws and Ethics Committee approval. If not allowed, it will be stored in your country.

If you agree to your blood samples being stored after the study, they will be used for this study and future medical research for the treatment of HIV. It is difficult to know in advance what future research would be most useful because it builds on information gathered from other studies in the area which are going on all the time. The Ethics Committee will decide whether or not your consent should be obtained at that time for a particular research project.

Your stored samples will not be used by private or for-profit entities, or for research leading to the development of commercial products.

11. How will my confidentiality be protected?

Of the people treating you, only the study doctor and research team involved in your care will know whether or not you are participating in this study. Any information collected which can identify your connection with this study will be kept confidential and will be shared only with your permission, or except as needed by law. Your health records and any information gathered during the research project may be subject to inspection (to check the procedures and information gathered) by the relevant authorities, authorised representatives of the Sponsor, the US National Institutes of Health, and the institution relevant to this Participant Information Sheet [insert name of site] or as required by law. By signing the Consent Form, you allow release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above. Your study results will be held securely at [insert name of site].

Only information that does not identify you will be sent off site. Your name will not appear on any of the information sent to the sponsor; instead your information will be coded using a 3-letter code and study number which no-one else will share. Your blood samples that are kept in storage will only be labelled with your study number, 3-letter code and year of birth.

12. What happens with the results?

If you give us your permission by signing the consent document, we may discuss/publish the results, for example, with the sponsor and/or the ethics committee for monitoring purposes, peer-reviewed medical and scientific journals, presentation at conferences or other professional forums.

In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

13. What happens to my treatment when the study is finished?

After the study, your doctor will decide on the best combination of anti-HIV drugs for you, which may include either the current standard or one of the new regimens being tested in this study. Your doctor will discuss the options with you.

14. What should I do if I want to discuss this study further before I decide?

When you have read this information, the researcher [insert name] will discuss it with you and answer any queries you may have. If you would like to know more at any stage, please do not hesitate to contact them on [insert number/email/other contact].

15. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by [insert EC name]. If you have any questions or concerns about your rights as a research participant, please contact [insert EC contact details] and quote [insert EC reference number].

Thank you for taking the time to learn about this study.
If you wish to join it, please sign the attached consent form.
This information is for you to keep or dispose of as you see fit.

[Insert institutional logo]
[name of local institution/s where research is being conducted]

CONSENT FORM

To be used in conjunction with Participant Information

D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

1. *I agree to join in as a participant in the study described in the Participant Information attached to this form.*

2. *I confirm that I have read and understood the Participant Information, which explains why I have been selected, why and how the study is being done and the possible risks involved, and the information has been explained to me to my satisfaction.*

3. *Before signing this consent form, I have been given the chance to ask any questions relating to any possible harm I might suffer as a result of joining the study and I am satisfied with the answers.*

4. *I understand that I can withdraw from the study at any time and it will not affect my relationship with my doctor or to the [insert as applicable, e.g. University/Hospital/Research Institute].*

5. *I agree that research information gathered from the results of the study may be published, as long as I cannot be identified.*

6. *I understand that if I have any questions about joining in this research, I may contact [insert name] on telephone number [insert phone number], who will be happy to answer them.*

7. *I agree to have my blood samples stored for future research studies into HIV infection and immunity _____ (Participant initials)*
   OR
   I do not agree to have my blood samples stored for future research studies into HIV infection and immunity _____ (Participant initials)

8. *I understand that some of the exact studies for which my stored samples shall be used are not yet known.*

9. Only for women who can become pregnant:
   If I become pregnant,
   - I agree to have information about the pregnancy submitted to the Antiretroviral Pregnancy Registry _____ (Participant's initial);

   OR
   - I do not agree to have information about the pregnancy submitted to the Antiretroviral Pregnancy Registry _____ (Participant's initial).

10. *I confirm that I have received a copy of this Consent Form and the Participant Information.*

Complaints may be directed to [insert local details]

Signature of participant	**Please PRINT name**	**Date**
[or person responsible (insert or delete as necessary)]		

Signature of witness*[if required]	**Please PRINT name**	**Date**

Signature of investigator	**Please PRINT name**	**Date**

*“By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant’s legally acceptable representative, and that informed consent was freely given by the participant or the participant’s legally acceptable representative” (**ref: ICH GCP 4.8.9**)

[Insert institutional logo]
[name of local institution/s where research is being conducted]

D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to join in the study described above and understand that such withdrawal **WILL NOT** have an effect on any treatment or my relationship with the **[Insert Site Name]** or my medical attendants.

Signature of participant	**Please PRINT name**	**Date**

The section for Revocation of Consent should be forwarded to *[INSERT name and address of Principal Investigator]*

APPENDIX 2: PARTICIPANT INFORMATION SHEET AND CONSENT FORM (GENOMICS)

[Insert institutional letterhead]
[name of local institution/s where research is being conducted]

PARTICIPANT INFORMATION AND CONSENT FORM FOR GENETIC TESTING

A phase IIIB/IV randomised open-label trial to compare dolutegravir + pharmaco-enhanced darunavir versus dolutegravir with predetermined nucleosides versus recommended standard of care antiretroviral regimens in patients with HIV-1 infection who have failed recommended first line therapy.

D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

Principal Investigator(s): *[insert]*

Site Address: *[insert]*

Invitation

You are invited to take part in this research because you have consented to the main D^{2}EFT research study. Before you decide whether or not you wish to join in this genetic testing, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What if I don't want to take part in this genetic testing or if I want to withdraw later?

You do not have to join this research study if you do not want to. If you choose to volunteer to join the study, you can quit at any time. If you choose not to join or to quit, it will not affect your regular medical care or your relationship with the staff caring for you.

If you do not agree to genetic testing, you can still participate in the D^{2}EFT study.

If you do not wish to continue in the genetic testing study once you have joined it, you can quit at any time without having to give a reason. However, your information collected during your time on the study will still be used. If you wish, any samples collected for genetic testing that can still be identified as yours will be destroyed.

2. What does genetic testing involve?

Everyone who joins the D^{2}EFT study will be invited to join in genetic testing (approximately 1,010 people). Those who agree to genetic testing will be asked to sign the Participant Information and Consent Form for Genetic Testing.

If you agree, part of the blood collected at week 0 will be used for future genetic testing.

The genetic testing will be done to look at your DNA and see if you have certain types of genes which guide how your body reacts to HIV, the drugs used to treat HIV or infections that can occur in HIV-infected people. This means the study will only look at those genes that effect how your body will react to HIV or related infections. The exact studies to be done on your genetic sample are not yet known. The information that will be kept include your participant identification number, 3-letter code, year of birth, date of blood collection and type of sample.

Prior to any genetic test being done, approval will be asked of the local Ethics Committee.

By signing this informed consent form, you allow the researchers, authorised personnel from The Kirby Institute, University of New South Wales, the ethics committee and government authorities to access your medical records to obtain information about you that is related to the study.

3. How will my confidentiality be protected?

Of the people treating you, only the study doctor and and research team will know whether or not you are participating in this study. Any information collected which can identify your connection with this study will be kept confidential and will be shared only with your permission, or except as needed by law. Only the researchers named above, the representatives of the Sponsor, the relevant authorities and the US National Institutes of Health will be able to see your details. The results of this study will be held securely by the Sponsor.

Samples selected for genetic testing will not contain your name, but only a study ID code. The study ID code is a combination of one or more of the following identifiers: your participant identification number, year of birth and a 3-letter code. Only qualified and authorised laboratory staff will be able to access your coded stored samples.

Despite all these precautions DNA itself is a unique identifier therefore confidentiality cannot be guaranteed.

4. Are there risks to me in taking part in genetic testing?

As part of this study, you will have your blood drawn. This procedure may be uncomfortable but usually does not lead to any major problems. Side effects that have been noted with drawing blood include feeling light-headed or faint, fainting, pain and bruising at the needle stick site.

New information about genetic testing may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue with genetic testing.

5. Will I benefit from genetic testing?

You will not directly benefit from genetic testing. The results of the genetic tests completed on your samples will be used for research purposes only.

Neither you or your doctor will receive the results from these genetic tests.

The information gained from this study may be of benefit in the treatment of HIV in the future.

6. What will happen to my blood sample after it has been used?

After your sample has been used, any remaining blood or tissue will be destroyed.

Your stored sample will not be used by private or for-profit entities and will not be used for research leading to the development of commercial products.

7. What should I do if I want to discuss this study further before I decide?

When you have read this information, the researcher [insert name] will discuss it with you and answer any queries you may have. If you would like to know more at any stage, please do not hesitate to contact [insert name] on [insert number/email/other contact].

8. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by [insert EC name]. If you have any questions about your rights as a research participant, please contact [insert EC contact details] and quote [insert EC reference number].

Thank you for taking the time to learn about this study.
If you wish to join it, please sign the attached consent form.
This information is for you to keep or dispose of as you see fit.

[Insert institutional letterhead]
[Insert name of local institution/s where research is being conducted]

GENETIC TESTING CONSENT FORM

To be used in conjunction with Participant Information
D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

1. *I agree to have a blood sample collected that may be used for genetic testing as described in the Participant Information attached to this form.*

2. *I confirm that I have read and understood the Participant Information Statement above, which explains the nature and the possible risks involved, and that the information has been explained to me to my satisfaction.*

3. *Before signing this consent form, I have been given the chance to ask any questions relating to any possible harm I might suffer as a result of joining the study and I am satisfied with the answers.*

4. *I understand that I can withdraw from this study at any time and it will not affect my relationship with my doctor or to the [insert as applicable, e.g. University/Hospital/Research Institute].*

5. *I agree that research information gathered from the results of the study may be published, as long as I cannot be identified.*

6. *I understand that if I have any questions about joining in this research, I may contact [insert name] on telephone number [insert phone number], who will be happy to answer them.*

7. *I confirm that I have received a copy of this Consent Form and the Participant Information.*

Complaints may be directed to [insert local details].

Signature of participant [or person responsible (insert or delete as necessary)]	**Please PRINT name**	**Date**
Signature of witness* [if required]	**Please PRINT name**	**Date**
Signature of investigator	**Please PRINT name**	**Date**

*"By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative" (**ref: ICH GCP 4.8.9**)

[Insert institutional logo]
[name of local institution/s where research is being conducted]

D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

GENETIC TESTING

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to join in the genetic testing component of the **D²EFT** study described above and do not want my blood specimen used for future genetic testing. I understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the **[Insert Site Name]** or my medical attendants.

Signature of participant	**Please PRINT name**	**Date**

The section for Revocation of Consent should be forwarded to *[INSERT name and address of Principal Investigator]*

APPENDIX 3: INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

between the UNSW/Sponsor and the study investigator(s)

Site Name:

Principal Investigator:

Co-investigators (please list, if applicable):

Study Title: D²EFT: Dolutegravir and Darunavir Evaluation in adults Failing Therapy

A phase IIIB/IV randomised open-label trial to compare dolutegravir with pharmaco-enhanced darunavir versus dolutegravir with predetermined nucleosides versus recommended standard of care antiretroviral regimens in patients with HIV-1 infection who have failed recommended first line therapy.

Protocol Version Number: **3.0**

Protocol Version Date: **01 October 2020**

I/We agree to follow the procedures outlined in this protocol. I/We accept responsibility for the conduct of the research detailed in the proposal including all protocol-specific assessments, and I/We agree to abide by all decisions made by our Ethics Committee and Regulatory Agency. I/We agree to ensure the informed consent process is conducted with each participant in compliance with ICH GCP guidelines.

PRINCIPAL/RESPONSIBLE INVESTIGATOR
(signature and date)

_____

SPONSOR'S REPRESENTATIVE

(signature and date)

_____

SPONOR'S MONITOR(S)/COORDINATOR(S)

(signature(s) and date(s))

_____