Chelsea and Westminster Hospital
NHS Foundation Trust

Switch from stable cART containing ABC/3TC or TAF/FTC plus dolutegravir or bictegravir to TDF/3TC/doravirine in people living with HIV: Impact on lipids, body composition, insulin sensitivity, neuroendocrine function and inflammation markers

Meta-D

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Protocol Approval:

Damon Foster Date 19JAN2024

CONFIDENTIAL

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsors, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

GCP Compliance Statement:

This trial will be conducted in compliance with the protocol, the principles that have their origin in the Declaration of Helsinki and all applicable regulatory requirements

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial in accordance with ICH-GCP and the applicable regulatory requirements and with the approved protocol.

I agree to comply with the procedures for data recording/reporting.

I agree to permit monitoring, auditing and inspection at this site and to retain all trial related essential documentation for the duration of the study as required according to ICH-GCP.

Site Name:		**Site ID:**	
Name: (please print)			
Signature:			
Date:			

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	
3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
cART	Combination antiretroviral therapy
(e)CRF	(Electronic) Case Report Form
DAA	Direct-acting antiviral
DTG	Dolutegravir
EuroQoL	European Quality of Life
FTC	Emtricitabine
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH-GCP	International conference of harmonization good clinical practice
INSTI	Integrase Strand Transfer Inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PI	Principal Investigator
SmPC	Summary of Product Characteristics
PIS	Participant Information Sheet
PSQI	Pittsburgh Sleep Quality Index
PLWH	Person/People living with HIV
SOC	Standard Of Care
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil
WOCBP	Women of Childbearing Potential

1. BACKGROUND & RATIONALE

Continuous antiretroviral therapy dramatically reduces HIV-associated morbidity and mortality [1] but may be complicated by adverse effects including metabolic adverse events such as dyslipidemia, and clinical adverse events including cardiovascular events [2]. Comparative clinical data indicate that Abacavir/Lamivudine (ABC/3TC) and Tenofovir alafenamide/Emtricitabine (TAF/FTC) is associated with greater increases in total cholesterol and other lipid fractions relative to Tenofovir disoproxil/ Emtricitabine (TDF/FTC)-based regimens [3, 4, 5, 6].
Healthy volunteer data indicate TDF has a small lipid lowering effect, reducing total cholesterol by 8% over 2 weeks and does not trigger insulin resistance [8].
HIV infection per se appears to be a risk factor for cardiovascular disease [9], and viral suppression may reduce risk of cardiovascular events [9]. Lipid elevation is a key modifiable risk factor for cardiovascular disease. Some cohort data have reported an association between current or recent ABC use and coronary heart disease (CHD) but not stroke risk [2, 10].
In a retrospective analysis in the NA-ACCORD, 22% of those with normal BMI at the start of anti-retroviral therapy (ART) became overweight after 3 years of ART with ABC and 18% of those overweight at baseline becoming obese [11].
More recently, Taramasso et al [12] have reported weight gain associated with all ART, with low baseline BMI and older age as risk factors.
A recent retrospective analysis by Menard et al [13] on patients stopping Dolutegravir (DTG) due to adverse effects in the clinical setting, found that 7% had done so due to weight gain. Norwood and colleagues [14], recently reported significantly increased weight gain in those switching to an INSTI-based regimen from an efavirenz-based regimen.
Further analysis of the NA-ACCORD and other cohorts have suggested that DTG and some other INSTI are associated with significantly greater weight gain than NNRTI regimens and that TDF based therapy be partially protective against weight gain [15, 16].

Hypothesis
The hypothesis of the study is that a switch to Delstrigo, which is a combination of tenofovir disoproxil, lamivudine and doravirine (TDF/3TC/DOR) has a favourable impact on lipid metabolism, glucose, weight, body composition and hepatic steatosis.

1.1 Assessment and management of risk

Potential risk to trial participants would include switching to a new regimen; there is potential for new adverse events, as well as possible risk of loss of virological control.

Such risks will be managed through regular assessment of participants' general health and HIV viral load as well as CD4:CD8 ratio. Adverse events will be closely monitored and followed up (see Section 6).

2. TRIAL OBJECTIVES

2.1 Primary Objective

To quantify the effect on lipid profile (change from baseline in total fasting cholesterol to Week 24) of switching from suppressive, stable cART containing ABC/3TC or TAF/FTC plus dolutegravir or bictegravir to Delstrigo (TDF/3TC/DOR) in HIV positive patients.

2.2 Secondary Objectives

To investigate:

1. The safety and tolerability of switch from stable cART to Delstrigo (TDF/3TC/DOR)
2. Glucose and lipid changes including insulin sensitivity and cholesterol levels
3. Changes in body composition including body fat content and waist to hip ratio
4. Comparison of cardiovascular risk changes
5. Patient reported outcomes including dietary preferences, quality of life and sleep quality
6. Changes in hepatic steatosis and fibrosis
7. Changes in renal parameters

2.3 Exploratory Objective

Metabolomics: To investigate the metabolic changes associated with study treatment.

2.4 Study Endpoints

2.4.1 Primary Endpoint

Lipid biochemistry (Total cholesterol, Cholesterol fractions and Triglycerides) in the blood of participants will be analysed at the baseline and compared to Week 24 after switching to Delstrigo.

2.4.2 Secondary Endpoints

Safety and Tolerability:

1. Percentage of patients with treatment-related adverse events by week 48 (including the severity of adverse events and occurrence of treatment discontinuations due to tolerability)
2. Changes in CD4 count and CD4:CD8 ratio at screening, weeks 24 and 48
3. Occurrences and details of viral resistance in study participants

Impact on lipids and glucose:

4. Change in insulin sensitivity from baseline to week 24 and 48 by HOMA-IR (glucose & insulin levels)
5. Change in PBMC cholesterol and cholesteryl levels (for applicable sites)
6. Change at week 24 and 48 in adipocytokines by assessing adiponectin and leptin
7. Change in Pituitary hormones (TSH, LH, FSH, IGF-1, Testosterone)

Impact on body composition:

8. Median change in body fat content (g) measured by total body and regional (hip and spine) DXA at week 24 and 48
9. Waist to hip ratio changes at week 24 and 48

Impact on cardiovascular risk:

10. Change in estimated cardiovascular risk (QRISK3 equation)
11. Change in estimated cardiovascular risk (D:A:D (f) equation)

Impact on patient recorded outcome measures:

12. Change in Dietary preferences (Food preference questionnaire for adolescents and adults)
13. Change in Quality of Life (EuroQoL questionnaire)
14. Change in Sleep quality (Pittsburgh Sleep Quality Index questionnaire)
15. Change in Treatment satisfaction (HIV Treatment Satisfaction Questionnaire)

Hepatic impact:

16. Change in hepatic steatosis and fibrosis by transient elastography-CAP score (measured by FibroScan® with the CAP probe)

Renal impact:

17. Change in renal parameter assessed by uPCR
18. Change in renal parameter assessed by eGFR

2.4.3 Exploratory Endpoints (applicable sites only)

Investigation of the metabolic changes associated with study treatments at week 0 and 48.

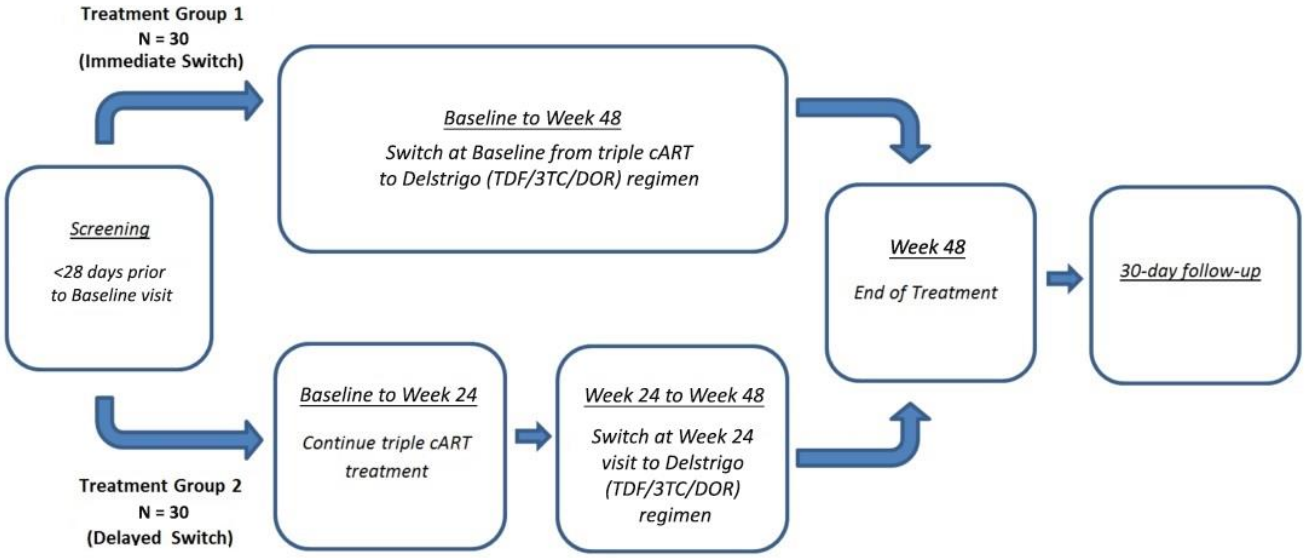
Metabolomics can be used to profile the maximum number of metabolites found within an organism tissue, cell or biofluids, enabling detailed mapping of perturbed pathways involved in cART drug response. This approach has the potential to unravel on- and off-target effects of cART and further our understanding of mechanisms of action, metabolism and toxicities. With new safer antiretrovirals becoming available, it is important to understand what the drug effect could be on certain metabolic pathways, especially in view of people living with HIV ageing and needing access to such safer drugs. We therefore aim to carry out metabolomic analysis on plasma samples from the patients enrolled in the study before drug switch and after to investigate the metabolic changes associated with the study treatments.

These studies will not be powered for drug/metabolomics changes associations but will enable us to build a data base on drug/metabolomics changes. Prospective studies would need to be planned based on these preliminary data.

3. TRIAL DESIGN

3.1 Study Schema

Image 3.1: Meta-D Study Schema



60 HIV-1 positive individuals on triple cART will be enrolled if they are willing to participate, have provided written, informed consent and meet the inclusion criteria. This is an open label, randomised, two-arm switch study over 48 weeks in which virally suppressed participants on a stable combined ART regimen will be randomised (1:1) to an immediate switch to 3TC/TDF/DOR (immediate switch arm, N=30) for the duration of the 48-week study, or to maintaining their current cART followed by a switch to 3TC/TDF/DOR from week 24-48 (delayed switch arm, N=30). Participants will be monitored for the length of the study (48 weeks) plus a 30-day follow-up period.

If patients withdraw or are withdrawn from the study treatment prematurely, an early termination visit (ETV) should occur within 30 days post withdrawal.

Based on this the following stopping rules will apply:

- Virological failure, defined as two consecutive HIV-RNA plasma viral loads > 50 copies/mL within an interval of two to four weeks.

3.2 Study Setting

Patients will be identified through HIV clinic visits by their direct study medical care team and visits will be captured on a participant-screening log. A Trial Management Team will facilitate the project and liaise with participating sites in study set-up and progress.

3.3 Inclusion and Exclusion Criteria

Inclusion Criteria

1. HIV-1 infected, 18 years or older
2. On stable & suppressive cART containing ABC/3TC or TAF/FTC plus dolutegravir or bictegravir for at least 6 months
3. No evidence of resistance to DOR, 3TC or TDF
4. No laboratory abnormalities, medical/psychiatric conditions or alcohol/drug use considered a barrier to participation by investigators
5. Women of childbearing potential (WOCBP) need to use the hormonal contraceptive methods, associated with inhibition of ovulation, listed below*.
    - Implant
    - Progesterone injection
    - Intra-uterine device or system
    - Oral hormonal contraception

    *The list does not apply to a) WOCBP with same sex partners, when this is their preferred and usual lifestyle, b) WOCBP who are abstinent from penile-vaginal intercourse, when true abstinence is their preferred and usual lifestyle, or, c) WOCBP whose male partner has undergone sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

6. Men who are sexually active and have partners who are women of childbearing potential must be using an adequate method of contraception to avoid pregnancy (male condom or sterilisation confirmed prior to the participant’s entry into the study).

Exclusion Criteria

1. History of virological failure on an NNRTI in absence of a post-failure genotypic resistance test proving absence of resistance to DOR
2. History of virological failure on an NRTIs in absence of a post-failure genotypic resistance test proving absence of resistance to 3TC and TDF
3. Concomitant medication contra-indicated with DOR, 3TC or TDF
4. Haemoglobin <9 g/dL
5. Platelets <80,000/mm3
6. Creatinine clearance <50 mL/min
7. AST or ALT ≥5N
8. Acute Hepatitis A infection
9. Concomitant DAA for anti-HCV therapy
10. Known acute or chronic viral hepatitis B or C
    - Individuals testing positive for HBcAb, but negative HBsAg/HBeAg, may be included on the trial

- Individuals with positive anti-HCV results, but with HCV RNA not detected may be included on the trial

11. Severe hepatic impairment (Child-Pugh Class C - total Child-Turcotte-Pugh score of 10 to 15 points)
12. Pregnant or breastfeeding women, or individuals actively trying to conceive
13. History of osteoporosis or bone fractures/loss
14. Hypersensitivity to the active substance or to any of the excipients in tenofovir disoproxil fumarate, lamivudine and/or doravirine formulations

3.4 Number of participants

This trial aims to enroll 60 participants (30 in the immediate switch arm and 30 in the delayed switch arm).

3.5 Time period of trial

After screening (≤28 days prior to Baseline Visit), trial participants will spend 48 weeks from baseline to final visit. There is a 30-day follow-up assessment scheduled.

4. TRIAL PROCEDURES

The schedule of assessments is summarised in the study flow chart below. From the Baseline visit through to follow up, visits may take place +/- 7 days from that specified at the discretion of the Investigator.

Should there be a pandemic surge that restricts local capacity; the assessments may be modified to limit in-person visits. This may include virtual appointments and/or viral load and other safety bloods and urine done via home-testing. The sponsor will communicate when such measures are implemented.

See Appendix I for schedule of trial assessments.

Please note that if additional tests or procedures are required in accordance with local practice then these should still be performed (no usual procedures should be withheld from the participants during the study).

4.1 Participant Identification and Recruitment

Patients will be identified through clinic visits by their direct study medical care team and visits will be captured on a participant screening log. There will be an effort to recruit participants from a diverse ethnic background to reflect the local population of the site. The demographics (ethnicity, gender identity and age) of participants will be recorded for Equality, Diversity and Inclusion anonymised reporting.

Participants will be provided with written information about the study in the form of a participant information sheet and will be allowed adequate time for questions and to consider the study before agreeing to participate.

4.2 Participant Consent

It will be the responsibility of the investigator or co-investigator to obtain written informed consent prior to undertaking any procedures detailed in the protocol. This responsibility may be delegated to other suitably trained personnel if indicated on the delegation log.

The investigator or designee must provide adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the participant that they are free to refuse or withdraw from the study for any reason without detriment to their future care or treatment.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

4.3 Screening

Following full written informed consent, sites must keep a record of all screening and enrolled participants using screening and enrolment logs. Diagnostic tests procedures may be used in determining eligibility however, written informed consent must be obtained prior to any study specific procedures. All information collected for eligible participants will be completely anonymised and recorded in the Investigator Site File (ISF).

Once consent has been provided, participants will be assessed for eligibility and assigned a unique Study ID number through an electronic study database. Written informed consent must be obtained from the participant prior to performing any study related evaluations or procedures.

Information collected at screening:

- Age
- Gender / Gender Identity
- Ethnicity
- If applicable, reason not eligible for trial participation, or if they are eligible but declined

The following evaluations must be performed within 28 days prior to any baseline procedures, including study randomisation:

- Assessment of participant eligibility according to the inclusion and exclusion criteria
- Medical and social history (past and current), including HIV-associated conditions [social history includes smoking, recreational drugs, alcohol and caffeine consumption]
- Full antiretroviral history (including resistance history i.e. record all resistance history by major mutations in NRTI, NNRTI, PI and II regions).
- Concomitant medication check
- Review of any reported Adverse Events (AEs)
- Physical examination
- Height, weight, hip/waist circumference
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- HBV & HCV testing

- Hep A Ab IgM
- HIV RNA viral load
- Whole blood cells count
- CD4 & CD8 count / % and ratio
- Non-fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.4 Randomisation

Eligible individuals will be randomly assigned in a 1:1 ratio to start 3TC/TDF/DOR immediately, or to delay the switch to week 24. Randomisation will be performed in blocks of patients, allowing interim analysis of results in appropriate steps during the study. A participant identification number will be provided by the system to the person entering the data.

4.5 Baseline/Day 1 Visit

The following evaluations and procedures are to be completed at the baseline visit:

- Concomitant medication check
- Review of any reported Adverse Events (AEs)
- Symptom directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- DXA Scan (Total body and regional (hip and spine))
- PBMCs (for applicable sites)
- Adipocytokines (adiponectin and leptin levels)
- Pituitary hormones (TSH, LH, FSH, IGF-1 and Testosterone)
- Estimation of cardiovascular risk (CVR)
- CAP Fibroscan of liver
- Urine or serum pregnancy test for WOCBP

Questionnaires - Participant is to complete the following:

- Food preference questionnaire for adolescents and adults
- EuroQoL Questionnaire
- HIV Treatment Satisfaction Questionnaire (Baseline only)
- Pittsburgh Sleep Questionnaire

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.6 Study Visit Assessments

All visits are to be scheduled relative to the Baseline visit date, and with +/- 7 days visit window.

4.6.1 Week 4 study assessments (Health check) – IMMEDIATE SWITCH ARM ONLY

The following evaluations and procedures are to be performed at the additional health check visit 4 weeks after participants in the immediate switch arm commence the study drug. This study visit can be conducted by qualified healthcare staff on the delegation log, unless a physical exam by clinician or appropriately trained personnel (e.g. nurse practitioner) is medically indicated.

- Concomitant medication check
- Symptom-directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- Adherence to study drug and dosage assessment
- Review of any reported Adverse Events (AEs)
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.6.2 Week 12 study assessments

This study visit can be conducted by qualified healthcare staff on the delegation log, unless a physical exam by clinician or appropriately trained personnel (e.g. nurse practitioner) is medically indicated.

- Concomitant medication check
- Symptom-directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- Adherence to study drug and dosage assessment
- Review of any reported Adverse Events (AEs)
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.6.3 Week 24 study assessments – Mid-point visit

- Concomitant medication check
- Symptom-directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- Adherence to study drug and dosage assessment
- Review of any reported Adverse Events (AEs)
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP
- CAP Fibroscan of liver
- Immune Function Test: CD4 & CD8 (count / % and ratio)
- DXA Scan (Total body and regional (hip and spine))
- PBMCs (for applicable sites)
- Adipocytokines (adiponectin and leptin levels)
- Pituitary hormones (TSH, LH, FSH, IGF-1 and Testosterone)
- Estimation of cardiovascular risk (CVR)

Questionnaires - Participant is to complete the following:

- Food preference questionnaire for adolescents and adults
- EuroQoL Questionnaire
- HIV Treatment Satisfaction Questionnaire
- Pittsburgh Sleep Questionnaire

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.6.4 Week 28 study assessments (Health check) – DELAYED SWITCH ARM ONLY

The following evaluations and procedures are to be performed at the additional health check visit 4 weeks after participants in the delayed switch arm commence the study drug. This study visit can be conducted by qualified healthcare staff on the delegation log, unless a physical exam by clinician or appropriately trained personnel (e.g. nurse practitioner) is medically indicated.

- Concomitant medication check
- Symptom-directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- Adherence to study drug and dosage assessment
- Review of any reported Adverse Events (AEs)
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.6.5 Week 36 study assessments

This study visit can be conducted by qualified healthcare staff on the delegation log, unless a physical exam by clinician or appropriately trained personnel (e.g. nurse practitioner) is medically indicated.

- Concomitant medication check
- Symptom-directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- Adherence to study drug and dosage assessment
- Review of any reported Adverse Events (AEs)
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.6.6 Week 48 study assessments – End of Study visit / Early Termination Visit (ETV)

- Concomitant medication check
- Symptom-directed physical examination (if clinically required)
- Vital signs (Temperature, Blood Pressure, Heart Rate and Respiratory Rate)
- Weight and waist/hip circumference measurements
- Adherence to study drug and dosage assessment
- Review of any reported Adverse Events (AEs)
- HIV RNA viral load
- Urinalysis including urine dipstick and protein creatinine ratio (uPCR)
- Whole blood cells count
- 8 hour fasted blood sample for biochemistry analysis
- Urine or serum pregnancy test for WOCBP
- CAP Fibroscan of liver
- Immune Function Test: CD4 & CD8 (count / % and ratio)
- DXA Scan (Total body and regional (hip and spine))
- PBMCs (for applicable sites)
- Adipocytokines (adiponectin and leptin levels)
- Pituitary hormones (TSH, LH, FSH, IGF-1 and Testosterone)
- Estimation of cardiovascular risk (CVR)

Questionnaires - Participant is to complete the following:

- Food preference questionnaire for adolescents and adults
- EuroQoL Questionnaire
- HIV Treatment Satisfaction Questionnaire

- Pittsburgh Sleep Questionnaire

Please see the laboratory manual for details on blood, serum and urine sample collection and processing.

4.7 Post-treatment Assessments

4.7.1 Follow-up Assessments

This visit will be conducted by phone 30 days post the week 48 visit (+/- 7-day window). The following evaluations are to be performed:

- Symptoms review and adverse events
- Home pregnancy test for WOCBP

A follow-up assessment is not required if a patient withdraws from IMP prior to week 48. In this case, an early termination visit should be conducted instead. See section 4.8.1.

4.8 Withdrawals

A participant is free to withdraw from the study at any time. In addition, the Investigator may decide, for reasons of medical prudence, to stop study medication.

All patients who discontinue study medication will be followed up and requested to attend for study visits up until week 48.

If this is not possible or acceptable to the participant or Investigator, the participant may be withdrawn from the study and the reason for withdrawal recorded in the CRF.

If any participants experience virological failure (two consecutive HIV-RNA VLs >50 copies/ml), the study medication must be stopped and participants should be managed in accordance with local processes, participants will be followed up and asked to attend all study visits (see Section 4.9 for further details).

Study medication may be discontinued in the following instances:

1. If the participant withdraws their consent.
2. If the investigator considers in the interest of the participant (i.e. inter-current illness, unacceptable toxicity) that it is best for them to stop study medication.
3. The participant fails to comply with the protocol requirements or fails to cooperate with investigator.

The date and reasons for stopping medication will be clearly stated on the participant's CRF and source document. Every attempt should be made to arrange follow up visits for participants who are withdrawn from study medication. This visit should involve assessments as outlined within section 4.6.6.

Participants withdrawing from the trial may be replaced if considered necessary by the Chief Investigator.

4.8.1 Early Termination Visit (ETV)

In the case of early termination, every attempt will be made to ensure the subject has a termination visit within 30 days post-withdrawal. At this visit, the following evaluations and procedures are to be performed as described in 4.6.6.

4.9 Virological failure

A virological failure is defined as two consecutive HIV-RNA plasma viral loads > 50 copies/mL within an interval of two to four weeks. During the course of the trial, if a participant experiences a HIV-RNA plasma VL > 50 copies/mL, the site must perform an unscheduled blood collection visit within an interval of two to four weeks to confirm the rebound of the HIV-RNA plasma VL. If the virological failure is confirmed, an HIV resistance genotype and a dosage of ARV drugs concentration in plasma will be performed on the second HIV-RNA plasma VL test. A plasma bank should also be done.

- If the HIV-RNA plasma VL rebound is not confirmed by the second test, the trial treatment will be maintained without any specific adaptation.

- If the HIV-RNA plasma VL rebound is confirmed by the second test the baseline ARV drug will be changed by the physician according to national guidelines. If needed, treatment will be subsequently adapted according to resistance genotype.

4.10 Follow-up of abnormal laboratory test values

In the event of unexplained abnormal laboratory test values, the tests should be repeated and followed up as per medical need, until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.

4.11 Storage and Analysis of Samples

Please see the laboratory manual for full details on sample collection, storage, analysis and shipment.

All samples for biochemistry, haematology and virology should be collected in accordance with routine clinical practice. Where possible, samples will be analysed at each site's local laboratory and destroyed after analysis. For samples unable to be processed at local sites, samples will be shipped to appropriate laboratories. Please see the laboratory manual for full details.

At the end of the trial and once all sample analysis is complete, all samples will be destroyed.

4.11.1 Evaluation of glucose and lipid metabolism

Glucose and lipid metabolism will be evaluated by measuring the fasting glucose, triglycerides, total-cholesterol, LDL-cholesterol and HDL-cholesterol in blood samples collected for biochemistry. At visits where these parameters will be measured, detailed above, the median values and the proportion of patients above the upper normal will be reported and analysed.

4.12 End of Trial

The end of the trial is defined as the date of the last visit of the last participants undergoing the trial.

The sponsor must notify the Competent Authority and main REC of the end of a clinical trial within 90 days of its completion.

5 TRIAL MEDICATION

5.1 Name and description of investigational medicinal product

Participants in the immediate-switch arm will be dispensed an initial 4-week supply of Delstrigo film-coated tablets (containing 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil) at baseline, and then a 5-month supply at week 4 followed by a 6-month supply from week 24.

Participants in the delayed-switch arm will be dispensed standard care triple cART regimen (from Baseline to week 24), followed by an initial 4-week supply to week 28 and then a 5-month supply of Delstrigo tablets from week 28 to week 48.

All participants will discontinue their usual triple cART regimen when they start the Delstrigo regimen.

MSD will supply Delstrigo in the form of commercial stock. As part of supply chain verification, IMP from MSD will be shipped to Sponsor appointed Qualified Person (QP) holder of Manufacturing and Import Authorisation (MIA(IMP) namely Eramol Ltd for QP certification and/or verification (if required) before release to trial sites.

Dispensing weeks may be modified with sponsor's approval and in line with local regulations (if required).

5.2 Investigator Brochure/Safety Information

For safety information regarding the Delstrigo IMP, refer to relevant SmPC. The SmPC should be referenced for further information on contraindicated treatments, drug interactions and adverse events. Please refer to **Appendix II** for the Delstrigo Risk Assessment and mitigation strategies.

For pre-switch therapies, investigators are to refer to the applicable SmPC (per ATC code) for information on contraindicated treatments, drug interactions and adverse reactions. The pre-switch therapies are accepted as non-investigational products (NIMPs), therefore there are no regulatory requirements for expedited reporting in relation to those products.

5.3 Drug Storage and Supply

Investigators are to ensure that the investigational product will only be used in accordance with the protocol. Drug supplies will be kept in a secure, limited access storage area under the recommended storage conditions (see pharmacy manual), accessible only to those authorised by the investigator to dispense to eligible participants.

All study drugs will be stored per local practice procedures, and records kept according to local SOPs. Dispensing information will be recorded in the study CRF.

Partially used or empty containers may be destroyed by pharmacy/designee at local site after the study monitor has completed a final inventory to verify the quantity returned. The pharmacy/designee is required to document destruction for verification by the sponsor.

5.4 Preparation and labelling of Investigational Medicinal Product

In accordance with "EU Guideline to Good Manufacturing Practice − Annex 13 requirements" Delstrigo tablets (marketed products used within their marketing authorisation) can be labelled according to dispensed medicine requirements and labelled for clinical trial use.

Standard of care cART drug supply will be sourced from usual commercial supply by the local pharmacy department per local practice.

5.5 Dosage Schedules

Immediate switch arm: One-pill regimen Delstrigo tablet taken orally once daily (at the same time) for 48 weeks.

Delayed switch arm: Participants will continue their current triple cART regimen for 24 weeks, then one Delstrigo tablet taken orally daily (at the same time) for the remaining 24 weeks.

5.6 Concomitant medication and interaction with other therapies

All medications (prescriptions or over-the-counter medications, herbal and naturopathic products) continued at the start of the treatment or started during the treatment must be documented (dose, frequency, start and stop dates). Unnecessary changes or additions to any concomitant medication should be avoided.

Warnings and precautions regarding contraindicated concomitant medications, AE and drug interactions can be found in this section or within reference safety information.

Any medications excluded in the Exclusion criteria will not be permitted in this study. If there is a clinical need for the use of any of these medications then the participant may need to be discontinued from the study. If this is the case then the investigator should discuss with the CI or Sponsor trials team but the final decision remains that of the site investigator.

A risk assessment was performed to review the concomitant use of a COVID-19 vaccine and Delstrigo within the trial. The outcome is that a COVID-19 vaccine given to a trial participant enrolled in the trial is considered a simple concomitant medication with no interaction that requires advice on timing of the vaccine or other aspects.

All concomitant medication information will be captured in the participant's CRF.

Delstrigo is contraindicated in combination with the following:

- The anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- The androgen receptor inhibitor enzalutamide

- The antimycobacterials rifampin, rifapentine
- The cytotoxic agent mitotane
- St. John's wort (Hypericum perforatum)
- Cystic fibrosis drug: lumacaftor

Please see the current SmPC for Delstrigo for the latest information on contraindicated treatments.

5.7 Assessment of compliance

The investigator or designee is responsible for keeping accurate up-to-date accountability documentation for the study drugs such as: dispensing, returns, and supply. Adherence will be assessed at W4, W12, W24, W28, W36 and W48.

5.8 Provision of treatment after end of trial

No post trial medication will be provided to participants. Following study completion, patients are to receive treatment as per local standard of care.

5.9 Prior and Concomitant Therapy

Concomitant medications (prescription, over-the-counter or herbal) are to be administered during the study only if they are approved / prescribed by the Investigator for treatment of specific clinical events. Potential for drug interactions with the study treatment needs to be reviewed by the trial physicians. Any concomitant therapies must be recorded on the CRF.

6 TRIAL SAFETY

6.1 Definitions

6.1.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence (any new untoward medical occurrence or worsening of a pre-existing medical condition) in a clinical investigation participant administered a study drug and which does not necessarily have a causal relationship with the study treatments. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Adverse events observed by the Investigator, or reported by the participant, and any remedial action taken, will be recorded in the participant's CRF and should be verifiable in the participant's notes throughout the study. The nature of each event, time of onset after drug administration, duration and severity will be documented together with the Investigator's opinion of the causal relationship to the treatment (unrelated, unlikely, possible, probable, and definite).

All participants experiencing adverse events, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed.

Procedures such as surgery should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted on the CRF.

Planned procedures such as surgery (planned prior to the participant's enrolment into the study) need not be reported as adverse events if these are documented as planned at the screening visit.

Clinically significant changes in physical examination and blood safety profiles should also be recorded as adverse events.

6.1.2 Adverse Reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered or to the research (e.g. trial procedures, trial treatments).

6.1.3 Serious Adverse Events (SAEs) or Serious Adverse Reaction (SAR)

A serious adverse event is any untoward medical occurrence that at any dose:

i) Results in death
ii) Is life-threatening
iii) Requires in-patient hospitalisation or prolongation of existing hospitalisation
iv) Results in persistent or significant disability/ incapacity
v) Is a congenital anomaly/ birth defect

OR

vi) Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Although pregnancy is not always serious by regulatory definition, for the purposes of this trial pregnancy must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE.

6.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction where the nature, outcome or severity of which is not consistent with the applicable product Reference Safety Information (SmPC, for the study drug) or the applicable trial procedures noted in the protocol.

6.2 Assessment of Adverse Events

6.2.1 Assessment of Intensity

Severity should be recorded and graded according to the DAIDS grading scale (see Appendix III).

Note: There is a distinction between the gravity and the intensity of an adverse event. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious adverse event. For example, a headache may be severe in intensity but would not be classified as serious unless it met one of the criteria for serious events.

6.2.2 Assessment of Causality

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following (Related means there is a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship):

DEFINITE: distinct temporal relationship with drug treatment. Known reaction to agent or chemical group, or predicted by known pharmacology. Event cannot be explained by participant's clinical state or other factors.

PROBABLE: reasonable temporal relationship with drug treatment. Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. Event cannot easily be explained by participant's clinical state or other factors.

POSSIBLE: reasonable temporal relationship with drug treatment. Event could be explained by participant's clinical state or other factors.

UNLIKELY: poor temporal relationship with drug treatment. Event easily explained by participant's clinical state or other factors.

UNRELATED: the event occurs prior to dosing. Event or intercurrent illness is due wholly to factors other than drug treatment. There is not a reasonable causal relationship between study drug administration and the AE.

6.3 Reporting of Adverse Events

6.3.1 Documentation and follow-up of Adverse Events

All adverse events, however minor, will be documented in the CRF whether or not the Investigator concludes the event to be related to drug treatment.

The adverse event-reporting period will be from participant consent until the participants final study visit. In addition, any untoward event that may occur subsequent to the reporting period that the Investigator assesses as possibly, probably or definitely related to the study drug medication should also be reported as an Adverse Event.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

All adverse events should be followed up until they are resolved or the participant's participation in the study ends (i.e. until the final CRF is completed for that participant). In addition, all serious and non-serious adverse events assessed by the Investigator as possibly related to the investigational medication should continue to be followed even after the volunteer's participation in the study is over. Such events should be followed until resolution, or until no further change can reasonably be expected. Deaths occurring more than 30 days after the final dose, which are considered to be unrelated to the study medication, should not be reported as a Serious Adverse Event.

6.3.2 Serious Adverse Event Reporting

SAEs requiring reporting and all relevant documentation related to these SAEs must be sent by the investigator to the sponsor immediately, and no later than 24 hours after being made aware of it. An SAE form should be completed, and an assessment of whether the SAE is a Suspected Unexpected Serious Adverse Reaction (SUSAR) conducted.

The Sponsor is responsible for determining whether the SAE is a SUSAR and for reporting this in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

An SAE form should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

The Summary of Product Characteristics (SmPC) represents the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and up to 28 days after discontinuation of the study drugs. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

SAEs after the end of the trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMP or experiment after the participant has ended the trial, the Investigator should report this SAE as per the process above, within the same timelines as for SAEs during the trial (however there will be not requirement to report the SAE in the CRF).

6.3.3 Pregnancy

Any pregnancy that occurs during study participation must be reported using the SAE form. To ensure participant safety, each pregnancy must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the sponsor, using the SAE form. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the sponsor where female study participants have been exposed to the IMP.

6.3.4 Other safety considerations

Any significant worsening noted during interim or final physical examinations, or any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

6.4 Reporting requirements to Ethics Committee's (EC's) and Competent Authorities (CA's)

The Investigator is responsible for ensuring that all safety events are recorded in the CRF and reported to the Sponsor in accordance with instructions provided.

The Sponsor will promptly evaluate all SAEs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, EC's and applicable CA's based on applicable legislation.

6.4.1 Sponsor's reporting of SUSARs

All Suspected Unexpected Adverse Reactions (SUSARs) have to be reported, within the legal timeframe, by the sponsor team or an approved delegate to the national competent authority of the Member State concerned.

The sponsor or their approved delegate must report the SUSAR either directly as an individual case safety report to the relevant Competent Authority (CA), or through the MHRA Portal (if UK) or EudraVigilance Clinical Trial Module (EVCTM) (if EU) to the national Competent Authority of the relevant Member State.

The sponsor or delegate should also report to the concerned Ethics Committee, all SUSAR occurred in the territory of that Member State.

The timelines for expedited initial reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

For fatal and life-threatening SUSAR, the sponsor should report at least the minimum information as soon as possible and no later than 7 calendar days after being made aware of the case.

Relevant complementary information should be collected and notified within 8 days of the initial CA report. SUSARs which are not fatal and not life-threatening are to be reported within 15 calendar days.

7 STATISTICS AND DATA ANALYSIS

7.1 Sample Size

It is anticipated that data from 60 participants are adequate to meet the trial objectives (30 in the immediate switch arm and 30 in the delayed switch arm). The study will be powered based on lipid fractions: TC, non-HDL cholesterol,

LDL cholesterol, HDL cholesterol, triglycerides, and TC/HDL cholesterol ratio at week 24, using total cholesterol as the primary endpoint. (14)

We expect total cholesterol decrease of approximately 12% we varied this between 70-95% based on other available estimates. Using the most conservative inputs, to detect total cholesterol decrease with 80% power and a 5% two-sided significance level, requires recruitment of 60 participants. This figure allows for a 20% non-response rate. (ROCKET study 14).

7.2 Statistical Analysis Plan

All deviations from the statistical analysis plan will be recorded during the conduct of the interim and final analysis. If there is a decision for major modifications to the statistical analysis while the clinical trial is in progress, this will be part of a protocol amendment.

Where quantitative data are hyper geometrically distributed median with inter-quartile ranges will be presented while Gaussian normal data will be summarized using the mean and standard deviation while qualitative data will be summarized using number of participants with percentages.

All data analyses will be performed using statistical software. All p-values presented will be two tailed.

7.2.1 Primary outcome analysis

The primary endpoint will be a comparison of the lipid profile of all participants at the baseline visit, week 24 and week 48. These values will be evaluated using repeated measures analysis of variance (ANOVA), including treatment, period, and sequence as fixed effects, and participant within sequence as a random effect in the model.

We will conclude Delstrigo has an impact on blood lipid profile of participants, if the 90% confidence interval for the difference between baseline and later time-points.

Least square mean difference between experimental Delstrigo and existing treatment period will be obtained from one-way ANOVA modelling and the associated 90% confidence interval will be constructed. It will be concluded that Delstrigo has an impact on blood lipid profile of participants, if the 90% confidence interval for the mean difference between the two treatments is significantly different.

7.2.2 Secondary outcomes analyses

All secondary outcome analysis will be performed using repeated ANOVA and one-way ANOVA as described for the primary outcome analyses.

For HIV-RNA viral load of participants, samples will be analysed using the snapshot approach at all time-points. The success will be defined as absence of virologic failure (HIV-RNA viral load remaining <50 copies/mL) and no discontinuation of study or treatment. The rate of success will be estimated by dividing the number of participants into success by the total number of participants in the study.

7.3 Interim Analysis and criteria for the premature termination of the trial

An interim analysis may be done at week 24. Additional issues could include treatment-emergent drug resistance, serious adverse events or high rates of discontinuation for adverse events.

The Trial Management Group (consisting of the Chief Investigator, the Principal Investigators at the different sites, trial co-investigators, and Sponsor members) will make any decisions on stopping the trial based on efficacy and safety results.

7.4 Participant Population

The primary population for analysis will be Intent to Treat exposed, including all randomised patients who have received at least one dose of study medication. The analyses of safety will also be conducted on the Intent to Treat exposed population.

The primary efficacy analysis will be repeated for the Per Protocol population, excluding patients with serious protocol violations which could interfere with the reliability of the efficacy outcome. Examples would include taking other antiretroviral treatment within the first 48 weeks of treatment, incorrect randomisation or early discontinuation from the study for reasons unconnected to efficacy or safety. This analysis will be conducted to check the reliability of the results from the primary efficacy analysis.

8 DATA HANDLING

8.1 Data collection tools and source document identification

8.1.1 Source Documents

Original documents, data and records (e.g. hospital records, laboratory notes, pharmacy dispensing records) will be maintained at site.

The participant's study number and date of entry into the study, along with a study identifier, should be recorded in the participant's study records. The following should also be recorded in the study records; confirmation of written and oral consent, the participant's clinical status, date of every study visit, date study medication was started and stopped, concomitant medications, copies of all relevant reports and laboratory tests, comments on results and reference to any adverse events.

Source documents include, but are not limited to participant medical records, SAEs & reportable event forms (see section 6), questionnaires, laboratory reports, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

8.1.2 Case Report Forms (CRFs)

For each participant consented data collected during the study will be recorded in the study specific electronic case report forms (eCRFs). In order to maintain confidentiality, the participant will be identified only by participant number. eCRFs will be completed by an authorised study staff member whose training for this function is documented according to study procedures. The eCRF should be completed within two weeks of the participant visit to enable the

sponsor to perform central monitoring of safety data. Paper CRFs will also be completed and kept in the ISFs to ensure an auditable data trail.

The data will be reviewed and approved by the Investigator following participant completion.

8.2 Data Handling and Record Keeping

The Study Monitor will review data on an on-going basis and raise any discrepancies with site staff as required.

At the end of the study, the Sponsor will be responsible for storing a copy of the eCRF prior to the eCRF being decommissioned.

Data extracted from the eCRF will be kept on a secure network drive with access to authorised personnel only.

Identified only by participant number, the data are pseudo-anonymised at all times and are transferred securely. All transfers will be fully documented.

8.3 Archiving and storage of data

Following completion of the trial, all trial records and documents, including signed informed consent forms, must be retained by the investigator site for a period no less than 15 years after trial completion unless regulations require a longer retention period.

Archiving will be authorised by the Sponsor following submission of the end of study report.

The sponsor will be responsible for archiving the TMF. The Investigators at sites will be responsible for retention/archiving of participant records, CRF, ISF and other study documentation (as applicable) in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

Destruction of essential documents will require authorisation from the Sponsor.

9 MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be followed for this study based on the trial risk assessment. The plan will detail monitoring frequency, requirements and processes.

The purpose of monitoring is to verify the rights and wellbeing of human participants are protected; that trial data is accurate, complete and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

A monitor will conduct regular site visits for the purpose of monitoring various aspects of the study. The Investigator must agree to allow the study monitor to inspect all CRF and corresponding source documents, e.g. original medical records, participant records and laboratory raw data, access to the clinical supplies, dispensing and storage areas and agree to assist with their activities if requested. The Investigator should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and Investigator's or designee's confirmation signature.

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for sponsor authorised Quality Assurance personnel and/or authorised personnel from an external regulatory agency to conduct an audit/inspection of an Investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with Good Clinical Practices, and Regulatory Agency guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator will be given sufficient notice to prepare for such visits, which are planned to take usually between one and two days and may be conducted at any stage during the study. The audit will involve the review of all study related documentation, which is required by GCP to be maintained by each site, review of drug storage, dispensing and return, review of all study related supplies and review of source documents against the CRF to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AEs which have occurred.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Trial Approvals

10.1.1 Initial Approval and Regulatory Compliance

Prior to the enrolment of participants, approval will be obtained from the NHS Research Ethics Committee (REC) and CAs for the conduct of the study at named sites, the protocol, the PIS and ICF, any other written information that will be provided to individuals before or when they are participants, and of any advertisements that will be used.

This study will be conducted in compliance with this protocol, GCP, and all applicable regulatory requirements.

10.1.2 Approval of Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial or substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the Clinical Trial Authorisation (CTA) or the documents that supported the original application, the sponsor will submit a valid notice of amendment to the appropriate REC and regulatory agencies.

Amendments requiring ethics approval will only be implemented after a copy of the REC's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

10.1.3 Annual Safety Reports and End of Trial Notification

The REC will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

10.2 Peer Review

The study sponsor is responsible for ensuring the trial protocol meets the following review criteria:

- **Independent**: At least two individual experts will review the study. Reviewers are external to the investigators' host institution and not involved in the study in any way.
- **Expert**: Reviewers have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.
- **Proportionate**: Peer review commensurate with the size and complexity of the study.

10.3 Data Protection

All investigators and trial site staff will comply with the requirements of current Data Protection Regulations with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

10.4 Declaration of financial and other competing interests

The sponsor will identify and collect the following disclosure information from the CI, PIs, and committee members of groups listed in Section 11:

- Ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- Commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

10.5 Post-trial Care

Post study medication will not be provided following completion of the trial. Investigators are to ensure patients have access to medication for their HIV treatment following study end.

10.6 Access to the final trial dataset

The investigators will be provided reasonable access to statistical tables, figures, and relevant reports. Sponsor will also provide the investigators with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policies.

11 OVERSIGHT AND TRIALS COMMITTEES

The Trial Management Group will be responsible for the set up and management of the clinical trial. There will be a Terms of Reference agreed and signed by members prior to the start of recruitment.

The TMG will comprise of the Chief Investigator, the principal investigators at the different sites, trial co-investigators, and sponsor members. The Trial Management Group should meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

The membership, frequency of meetings and the study aspects to be reviewed will be outlined in a separate document listing the Terms of Reference.

12 DISSEMINATION POLICY

A whole or part of this study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of participant's details will be maintained throughout. Participants wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

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14.1 Appendix I: Table of events

	Screen	Baseline	Health check (Immediate at W4 or Delayed at W28)	FU visit	Mid-point Visit	End of Study, or ETV	FU call
Time (day = D; week = W)	**-28D to 0**	**1D**	**W4 or W28 +/- 7 days**	**W12 & W36 +/- 7 days**	**W24 +/- 7 days**	**W 48 +/- 7 days**	**+30D after end**
Informed consent	X						
Eligibility assessment	X						
Demographics	X						
Medical, Social & ART history	X						
Height	X						
HIV testing (HIV-1/2)	X						
HBV & HCV testing[10]	X						
Hep A Ab IgM	X						
Randomisation		X					
Concomitant meds check	X	X	X	X	X	X	
Physical exam[1]	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	
Waist/Hip circumference	X	X	X	X	X	X	
HIV-1 plasma viral load	X	X	X	X	X	X	
Urine or serum pregnancy test	X	X	X	X	X	X	X
Urinalysis[2]	X	X	X	X	X	X	
Whole blood cell count	X	X	X	X	X	X	
Biochemistry[3]	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X
Immune Function test: CD4 & CD8 count, % & ratio	X				X	X	
Adherence assessment			X	X	X	X	
DXA Scan [4]		X			X	X	
PBMCs [5]		X			X	X	
Metabolomics sample		X			X	X	
Adipocytokines [6]		X			X	X	
Pituitary Hormones [7]		X			X	X	
Estimated CVR [8]		X			X	X	
Questionnaires [9]		X			X	X	
CAP Fibroscan		X			X	X	
Dispense Delstrigo		X[11]	X[12]		X[13]		

[1] Physical exam should only be performed by a clinician or appropriately trained personnel (e.g. nurse practitioner). It is compulsory at the screening visit only. For all other visits, a symptom-directed physical exam should occur only if clinically required.
[2] Urinalysis including urine dipstick and uPCR for renal safety
[3] Biochemistry (fasting for at least 8 hours on all visits except screening): creatinine, urea, potassium, sodium, bicarbonate, total cholesterol, triglycerides, calcium, phosphate, liver function tests (ALT, AST, GGT), ALP (Alkaline phosphatase), albumin, glucose, amylase, HDL-cholesterol, LDL-cholesterol (Friedewald equation), total cholesterol:HDL ratio, insulin, Hb1Ac, eGFR
[4] Total body and regional (hip and spine) DXA
[5] PBMC (for cholesterol markers and cholesteryl ester levels). Applicable sites only.
[6] Adipocytokines: (adiponectin, leptin)
[7] Pituitary hormones: (TSH, LH, FSH, IGF-1 and Testosterone)
[8] Estimated cardiovascular risk (QRISK3 and D:A:D (f) equations)
[9] Food preference questionnaire for adolescents and adults, European Quality of Life (EuroQoL), Pittsburgh Sleep Questionnaire and HIV Treatment Satisfaction Questionnaire
[10]HBV & HCV testing: Hepatitis B Core Total Ab, Hepatitis B Virus Surface Ab Screen, Hepatitis C Virus Ab, Screen, Hepatitis B Virus Surface Antigen, Hepatitis C Virus RNA Level
[11]4-week supply of Delstrigo dispensed to immediate switch arm only at baseline.
[12]5-month supply of Delstrigo dispensed to immediate switch arm at week 4 health check. 5-month supply of Delstrigo dispensed to delayed switch arm at week 28 health check.
[13]6-month supply of Delstrigo dispensed to immediate switch arm at week 24. 4-week supply of Delstrigo dispensed to delayed switch arm at week 24.

14.2 Appendix II: Risk Assessment of Delstrigo

One film-coated tablet of Delstrigo contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: Lamivudine (3TC) **Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information**		
Inhibition of cellular DNA replication	Early embryonic deaths in rabbits were observed.	Participants are asked to use contraception to prevent pregnancy for the duration of the study.
Lamivudine overexposure	Lamivudine is increased in plasma concentrations (AUC) in patients with renal dysfunction	Measuring creatinine clearance and excluding participants with <50mL /min. Safety measurements of uPCR and eGFR at visits
Severe acute exacerbation of hepatitis B	Reported in patients co-infected with HIV and HBV.	Participants are screened for HBV and excluded if positive.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: Tenofovir disoproxil Fumarate (TDF) **Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information**		
Excretion of tenofovir in human breast milk	No current data on the risks	Participants are asked to use contraception to prevent pregnancy for the duration of the study. Pregnant and breastfeeding women are excluded.
Severe acute exacerbation of hepatitis B	Reported in patients co-infected with HIV and HBV.	Participants are screened for HBV and excluded if positive.
Renal impairment	Acute renal failure and Fanconi syndrome reported with use of tenofovir disoproxil	Measuring creatinine clearance and excluding participants with <50mL /min. Safety measurements of uPCR and eGFR at visits
Bone loss and mineralisation defects	Slight decreases in bone mineral density associated in HIV-1 infected adults during trials	Exclusion of participants with a history of osteoporosis and pathologic bone loss/fractures. We will perform DXA scans at the start, mid-point and end of the study to highlight and treat any issues.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: Doravirine (DOR) **Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information**		
Doravirine overexposure	The single dose exposure of Doravirine was 31% higher in severe renal impairment.	Measuring creatinine clearance and excluding participants with <50mL /min. Safety measurements of uPCR and eGFR at visits

14.3 Appendix III: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Please reference latest version of grading scale available at below location.
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf