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Investigating if switching HIV patients from stable combined antiretroviral therapy to Delstrigo has fewer unwanted side effects e.g. weight gain, while being just as effective at maintaining an undetectable HIV viral load

Submission date
09/06/2022

Recruitment status
No longer recruiting

Registration date
21/09/2022

Overall study status
Completed

Last Edited
13/10/2023

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Combination antiretroviral therapy (cART) HIV treatments are associated with increased quality of life and normalisation of life expectancy in people living with HIV. However, long-term use of certain cARTs can lead to side effects such as weight gain through exposure to drug-related toxicity. This study investigates if a switch to Delstrigo (a combination of tenofovir disoproxil, lamivudine and doravirine) might result in improvement or stabilisation of metabolic parameters (lipids and weight), while providing the same effectiveness and quality of care as existing treatments for HIV.

Who can participate?
People aged 18 years and over living with HIV on stable and suppressive cART.

What does the study involve?
The trial will last 48 weeks plus a screening visit and a follow-up visit. This includes seven visits to the clinic and one telephone visit. Blood and urine samples will be taken, as well as a DEXA scan and CAP Fibroscan to measure body fat and liver function.

What are the possible benefits and risks of participating?
The potential risks to participants include switching to a new regimen; there is the potential for new adverse events, as well as a possible risk of loss of virological control. Such risks will be managed through regular assessment of HIV viral load as well as the CD4:CD8 ratio. Adverse events will be closely monitored and followed up. Delstrigo is a combination of tenofovir disoproxil, lamivudine and doravirine, and each carries its own risks. Lamivudine has been linked to increased early embryonic deaths in rabbits and not much data is available on the effects during human development and in pregnant and breastfeeding women for all three drugs. Therefore, participants or participants with partners who are pre-menopausal and sexually

active will be asked to use contraception. Pregnant or breastfeeding women will not be able to join the trial. Female participants of childbearing potential are required to take a pregnancy test as part of screening to join the trial and as part of the 30-day follow-up at the end of their participation in the trial. Delstrigo has been found to exacerbate hepatitis B, and the researchers therefore exclude participants with hepatitis B and C. Delstrigo provides some risk of kidney damage so kidney markers and performance are monitored by measuring creatinine clearance and excluding potential participants with <50 ml/min. Finally, the researchers perform regular scans to monitor bone density and mineralisation in participants to reduce the risk of participants developing any bone defects. Participants will have to adhere to other restrictions (such as fasting for 8 hours before certain visits) as detailed in the participant information sheet. These restrictions will be explained in full to all participants.

Where is the study run from?
Chelsea and Westminster Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
June 2022 to October 2024

Who is funding the study?
Merck Sharp and Dohme (UK)

Who is the main contact?
Dr Tess Cheetham, tess.cheetham@nhs.net

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2021-006507-15

IRAS number
1004705

ClinicalTrials.gov number
NCT05289986

Secondary identifying numbers
CRF006, IRAS 1004705

Study information

Scientific Title
Switch from stable combined antiretroviral therapy containing abacavir/lamivudine or emtricitabine/tenofovir alafenamide plus dolutegravir or bictegravir to tenofovir disoproxil fumarate/lamivudine/doravirine in people living with HIV: Impact on lipids, body composition, insulin sensitivity, neuroendocrine function and inflammation markers

Acronym
Meta-D

Study objectives
Primary objectives:
To quantify the effect on lipid profile (change from baseline in total fasting cholesterol to Week 24) of switching from suppressive, stable combined antiretroviral therapy (cART) containing abacavir (ABA)/lamivudine (3TC) or emtricitabine/tenofovir alafenamide (FTC/TAF) plus dolutegravir or bictegravir to Delstrigo (tenofovir disoproxil fumarate [TDF]/3TC/doravirine [DOR]) in HIV-positive patients.

Secondary objectives:
To investigate:
1. The safety and tolerability of switch from stable cART to Delstrigo
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

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, ref: 22/LO/0468

Study design
Open randomized controlled parallel-group cross over trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Human immunodeficiency virus-1 (HIV-1)

Interventions
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 maintain 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.

Drug: Delstrigo 100 mg - 300 mg - 300 mg tablet (300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil, 300 mg of lamivudine and 100 mg of doravirine - TDF/3TC/DOR)

Experimental: immediate switch arm
Experimental arm (baseline visit switch group, n = 30): one DOR/TDF/3TC tablet taken orally once daily for 48 weeks.

Active comparator: delayed switch arm
Control arm (deferred switch group, n = 30): Participants will continue their current triple cART regimen for 24 weeks, and then switched to taking one TDF/3TC/DOR tablet orally once daily (24 -48 weeks).

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Doravirine, lamivudine, tenofovir disoproxil fumarate

Primary outcome measure
Lipid biochemistry (total cholesterol, cholesterol fractions and triglycerides) in the blood of participants will be analysed at baseline and compared to Week 24 after switching to Delstrigo without a change in detectable HIV RNA levels. Should a change in HIV RNA levels be detected and confirmed, then the trial will stop for that participant.

Secondary outcome measures
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 measured by dividing the CD4 cell count by the CD8 cell count at screening, weeks 24 and 48
3. Occurrences and details of viral resistance measured using genotypic assay when needed: HIV viral load (VL)>200 copies/ml

Lipids and glucose:
4. Insulin sensitivity assessed by HOMA-IR (glucose and insulin levels) from baseline to weeks 24 and 48
5. PBMC cholesterol and cholesteryl levels measured using blood test at 48 weeks
6. Adipocytokines by assessing adiponectin and leptin measured using blood test at 48 weeks
7. Pituitary hormones (TSH, LH, FSH, IGF-1, testosterone) measured using blood test at 48 weeks

Body composition:
8. Median change in body fat content (g) measured by total body dual-energy x-ray absorptiometry (DXA) at weeks 24 and 48
9. Waist-to-hip ratio measured using a tape measure at weeks 24 and 48

Cardiovascular risk:
10. Estimated cardiovascular risk assessed using the QRISK3 equation at 48 weeks
11. Estimated cardiovascular risk assessed using the D:A:D equation at 48 weeks

Patient-recorded outcome measures:
12. Dietary preferences measured using a food preference questionnaire for adolescents and adults at 48 weeks
13. Quality of life measured using the EuroQoL questionnaire at 48 weeks
14. Sleep quality measured using the Pittsburgh Sleep Quality Index questionnaire at 48 weeks
15. Treatment satisfaction measured using HIV Treatment Satisfaction Questionnaire at 48 weeks

Hepatic impact:
16. Hepatic steatosis and fibrosis measured using transient elastography - CAP score (measured by FibroScan® with the CAP probe) at 48 weeks

Renal impact:
17. Renal parameters assessed by urine protein/creatinine ratio (uPCR) at 48 weeks
18. Renal parameters assessed by estimated glomerular filtration rate (eGFR) at 48 weeks

Exploratory endpoint:
Platelet aggregation, endothelial markers and metabolism measured using metabolomics. This will include investigation of the metabolic changes associated with study treatments at weeks 0 and 48

Overall study start date
07/06/2022

Completion date
31/10/2024

Eligibility

Key inclusion criteria
1. HIV-1 infected, 18 years or older
2. On stable & suppressive triple cART 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 who are of childbearing potential and sexually active need to use the hormonal contraceptive methods, associated with inhibition of ovulation, listed in the protocol and detailed in Appendix IV of the protocol:
5.1. Implant
5.2. Depot injection
5.3. Intra-uterine device or system
5.4. Oral hormonal contraception
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.
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) as described in Appendix IV of the protocol

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60

Key exclusion criteria
1. History of virological failure on a non-nucleoside reverse transcriptase inhibitors (NNRTI) in the absence of a post-failure genotypic resistance test proving the absence of resistance to DOR
2. History of virological failure on an 3TC and TDF in absence of a post-failure genotypic resistance test proving the absence of resistance to DOR (INSTI mutations that will lead to the need of administering DOR twice daily are considered as resistance to DOR – and the participant will be considered NOT eligible)
3. Concomitant medication contra-indicated with DOR, 3TC or TDF
4. Haemoglobin <9 g/dl
5. Platelets <80,000/mm^3

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
11. Individuals testing positive for HBcAb, but negative HBsAg/HBeAg, may be included in the trial
12. Individuals with positive anti-HCV results, but with HCV RNA not detected may be included in the trial
13. Pregnant or breastfeeding women, or individuals actively trying to conceive
14. History of osteoporosis or bone fractures/loss
15. Hypersensitivity to the active substance or to any of the excipients in tenofovir disoproxil fumarate, lamivudine and/or doravirine formulations

Date of first enrolment
31/10/2022

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
Spain

United Kingdom

Study participating centre
Not provided at time of registration
United Kingdom
-

Sponsor information

Organisation
Chelsea and Westminster Hospital NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
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ROR
https://ror.org/02gd18467

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Submission to regulatory authorities

The anonymised study results will be presented at international medical conferences and published in research journals. Personal data will not be identifiable in the study database, clinical study report, or in any publication arising from the study. The anonymised primary research data set will be available to share with future researchers. Participants will be informed

of this possibility within the informed consent form and participant information sheet. Any data sharing will comply with the General Data Protection Regulation (GDPR)/Data Processing Agreement and the scope of participant consent.

Intention to publish date
31/10/2025

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No