ISRCTN31461655 https://doi.org/10.1186/ISRCTN31461655

A phase IV, open-label pilot study investigating non-invasive markers of hepatic fibrosis in people living with HIV-1 and non-alcoholic fatty liver disease randomised to receiving optimised background therapy (OBT) plus maraviroc or OBT

Submission date
03/01/2018

Recruitment status
No longer recruiting

Registration date
23/02/2018

Overall study status
Completed

Last Edited
15/02/2023

Condition category
Digestive System

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Non-alcoholic fatty liver disease (NAFLD) is a common condition where too much liver fat is laid down. It is linked to other conditions like obesity and is more common in people with HIV. Sometimes it can lead to the liver becoming damaged by abnormal immune cells (inflammation or steato-hepatitis), which can progress to scarring (fibrosis). Irreversible scarring (cirrhosis) can cause serious liver-related conditions including cancer. We need to find ways of stopping NAFLD from turning into more serious liver disease. People with the condition are recommended to lose weight and exercise regularly but as these are difficult to achieve, medical therapies are needed. Unfortunately, there aren't any medicines that have yet been shown to improve NAFLD in people with HIV. The drug maraviroc is used to treat HIV and works by sticking onto a chemical (CCR5 receptor) on the surface of cells, blocking HIV virus from attaching and getting into the cell. CCR5 is also important in the pathway by which inflammation and scarring takes place in the liver. Blocking CCR5 may therefore reduce inflammation and scarring. This could benefit people with NALFD, but no one has yet looked at this. The aim of this study is to find out whether adding maraviroc to existing treatment has any effect for people with HIV and fatty liver disease.

Who can participate?
Patients aged 18 and over with well-controlled HIV (an undetectable viral load) and NAFLD

What does the study involve?
Participants are randomly allocated to start taking maraviroc and continue their existing antiviral medicines, or to just continue their antiviral medicines. Participants undergo regular blood tests every 6 months for a total of 2 years. There are also five or six liver scans over this period as well as three questionnaires about quality of life.

What are the possible benefits and risks of participating?
There may be an improvement in the patients' liver health by starting to take maraviroc, although there is no guaranteed benefit. Information gained from this study may help improve treatment options for people living with HIV and NAFLD. The additional monitoring in the study may also mean that patients can be referred earlier to specialised hepatology (liver) services if a problem is identified. This is a pilot study, meaning that it will recruit a small number of people (60 people overall) but the information gained may help to set up a larger study to find out more information about maraviroc over a longer period of time. This could lead to a change in national guidelines and make it available as an NHS treatment for NAFLD in the future. Blood taking may cause discomfort and may leave a temporary bruise. Every effort will be made to minimise this. As patients will already have an undetectable HIV viral load, there is no reason to believe that the viral load will change for the people who start taking maraviroc on top of their usual anti-HIV medicines. Taking part in the optional CT scan will involve exposure to ionising radiation. Two of these scans will be performed: one at baseline and one at 96 weeks. This is considered to be in addition to normal care. The total dose of radiation from these procedures could be up to 22 mSv. This represents a total lifetime cancer risk of approximately 1 in 610 for healthy males age 20 to 29 years (the risk reduces for older patients and is lower for female patients). This compares to a natural baseline lifetime risk of getting cancer in the UK of about 1 in 3. This dose of radiation is equivalent to about 10 years of natural background radiation to which we are all subjected. However, the CT scans are optional and patients are free to decline this part of the study.

Where is the study run from?
1. Brighton and Sussex University Hospitals NHS Trust (UK)
2. Chelsea and Westminster Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2018 to March 2022

Who is funding the study?
ViiV Healthcare (UK)

Who is the main contact?
Nicky Perry

Contact information

Type(s)
Scientific

Contact name
Ms Nicky Perry

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-004141-24

Integrated Research Application System (IRAS)
228763

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 36831, IRAS 228763

Study information

Scientific Title
A pilot study to investigate whether adding maraviroc to existing therapy has any effect for people with HIV and fatty liver disease

Acronym
HEPMARC

Study objectives
Non-alcoholic fatty liver disease (NAFLD) is a common condition, where too much liver fat is laid down. It is linked to other conditions like obesity and is commoner in people with HIV. Sometimes it can lead to the liver becoming damaged by abnormal immune cells (inflammation or steato-hepatitis), which can progress to scarring (fibrosis). Irreversible scarring (cirrhosis) can cause serious liver-related conditions including cancer.

We need to find ways of stopping NAFLD from turning into more serious liver disease. People with the condition are recommended to lose weight and exercise regularly but as these are difficult to achieve, we need medical therapies. Unfortunately, there aren't any medicines that have yet been shown to improve NAFLD in people with HIV.

The drug maraviroc is used to treat HIV and works by sticking onto a chemical (CCR5 receptor) on the surface of cells, blocking HIV virus from attaching and getting into the cell. CCR5 is is also important in the pathway by which inflammation and scarring takes place in the liver. Blocking CCR5 may therefore reduce inflammation and scarring. This could benefit people with NAFLD, but no one has yet looked at this.

Hypothesis: In patients living with non-alcoholic fatty liver disease and HIV, taking maraviroc in addition to optimised background antiviral therapy will be acceptable and tolerable

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Dulwich Research Ethics Committee, 22/01/2018, REC ref: 17/LO/2093, IRAS Project ID: 228763

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Fatty liver disease in people with HIV infection

Interventions
The trialists plan to recruit people with well controlled HIV (that is, an undetectable viral load) and evidence of NAFLD on a scan, who attend care at Brighton and Sussex University Hospitals NHS Trust.

The web-based Sealed EnvelopeTM system will be used to allocate individuals randomly to the maraviroc or non-maraviroc groups. The statistician will provide the randomisation list. The HEPMARC Randomisation Guide should be followed by the study team.
Randomisation will take place at baseline and will be stratified according to:
1. Current exposure or past history of ≥ 6 months exposure to protease inhibitor (PI)-containing antiretroviral therapy versus no current exposure and < 6 months past exposure to PI-containing therapy
2. BMI ≥ 25 versus < 25
3. Current exposure to a lipid-lowering agent
4. Diabetes mellitus status (DM 1 or 2 versus no DM)

Following randomisation, one group will continue their current antiretrovirals. The other group will add in twice daily dosing of maraviroc to their current antiretrovirals. The dose of maraviroc cannot be specific as it will be contingent on the concomitant medications that patients are already taking as per UK prescribing guidelines.

Participants undergo regular blood tests every six months for a total of 2 years. There will also be five or six liver scans over this period (Fibroscans, optional CT scans and in some cases one ultrasound scan) as well as three questionnaires about quality of life.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Maraviroc

Primary outcome(s)

Current primary outcome measure as of 02/02/2022:
1. Proportion of eligible individuals approached who are successfully recruited using MACRO electronic case report form at week 96
2. Monthly participant recruitment rate collected by completed CRFS up to recruitment completion 07/01/2020
3. Participant retention collected through eCRF completion in the study at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups
4. Proportion of participants for whom there is missing data collected by eCRF at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups
5. Proportion of participants reporting adverse events collected by eCRF at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups
6. Level of self-reported adherence to the study drug as collected by patient questionnaire at 48 and 96 weeks in those allocated to the maraviroc group

Previous primary outcome measure:
1. Proportion of eligible individuals approached who are successfully recruited using MACRO electronic case report form at week 96
2. Monthly participant recruitment rate collected by completed CRFS up to recruitment completion 30/09/2019
3. Participant retention collected through eCRF completion in the study at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups
4. Proportion of participants for whom there is missing data collected by eCRF at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups
5. Proportion of participants reporting adverse events collected by eCRF at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups
6. Level of self-reported adherence to the study drug as collected by patient questionnaire at 48 and 96 weeks in those allocated to the maraviroc group

Key secondary outcome(s))
1. ELF score using ELF blood test at baseline, 48 and 96 weeks
2. Fibroscan stiffness fibroscan test at baseline, 48 and 96 weeks
3. Fibroscan Controlled Attenuation Parameter (CAP) using fibroscan test score at baseline, 48 and 96 weeks
4. % with a CT liver: spleen attenuation ratio <1.0 measured using patient notes and CT of liver at baseline and 96 weeks
5. Blood-derived biochemistry (fasting HDL:chol ratio, LDL, HDL, TG, glucose, plus Hb1AC and ALT) measured using blood test at baseline, 48 and 96 weeks
6. Clinical signs of the metabolic syndrome (BMI, waist circumference and weight) measured at baseline, 48 and 96 weeks
7. HIV parameters (CD4 cell count and % with undetectable HIV VL) measured using a blood test at baseline, 24, 48, 72, 96 weeks
8. Quality of life assessed using the chronic liver disease questionnaire for NAFLD (CLDQ: NAFLD), and the SF-36 and WPAI:SHP questionnaires at baseline, 48 and 96 weeks

Completion date
30/03/2022

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 02/02/2022:
1. Aged 18 years and older – male or female
2. HIV-1 infected with durably suppressed (≥6 months) HIV VL (<50 copies/ml) NB. One HIV VL blip (50-200 copies/ml) is allowed in the 6 months prior to screen
3. Has evidence of NAFLD on hepatic imaging (USS, CT or MRI) or liver biopsy either at screen or in the 6 months prior to screen
4. Provides written, informed consent to participate
5. Is willing to comply with the protocol requirements
6. If female and of child bearing potential, is using effective birth control methods (as agreed by the investigator) and willing to continue practising these birth control measures during the trial and for at least 30 days after the end of the trial. Note: Women who are postmenopausal for least 2 years, women with a total hysterectomy, and women who have a tubal ligation are considered of non-childbearing potential
7. If male, and sexually-active with female partners of child bearing potential, is using effective barrier contraception, and willing to continue using this during the trial and for at least 30 days after the end of the trial

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7. If male, and sexually-active with female partners of child bearing potential, is using effective barrier contraception, and willing to continue using this during the trial and for at least 30 days after the end of the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
53

Key exclusion criteria

Current participant exclusion criteria as of 02/02/2022:
1. Severe cardiovascular disease including known angina or history of myocardial infarction
2. History of postural hypotension, defined as a reduction in the systolic blood pressure of > = 20mmHg after standing for at least one minute
3. Individuals already receiving MVC at screening
4. HIV viral load detectable (one blip within 6 months prior to screen is allowed)
5. Current HCV or HBV (HBcAb-positive, HBsAg-negative is permitted; anti-HCV Ab positive with HCV RNA negative for > = 12 months following treatment or spontaneous clearance is permitted)
6. Other chronic liver disease including but not exclusively: cirrhosis, alcohol-related liver disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, non-cirrhotic portal hypertension, drug-induced as deemed by a hepatologist
7. ALT or AST >5x the ULN (where ULN is defined locally as 41 IU/L)
8. Severe renal insufficiency (creatinine clearance < 30 mL/min)
9. HIV-2 infection
10. Known allergy or intolerance to MVC or its constituents including hypersensitivity to peanuts or soya
11. If female, pregnancy or breastfeeding

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6. Other chronic liver disease including but not exclusively: cirrhosis, alcohol-related liver disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, non-cirrhotic portal hypertension, drug-induced as deemed by a hepatologist
7. ALT or AST > 3x the ULN (where ULN is defined locally as 41 IU/L)
8. Severe renal insufficiency (creatinine clearance < 30 mL/min)
9. HIV-2 infection
10. Known allergy or intolerance to MVC or its constituents including hypersensitivity to peanuts or soya
11. If female, pregnancy or breastfeeding

Date of first enrolment

31/03/2018

Date of final enrolment

07/01/2020

Locations

Countries of recruitment

United Kingdom

England

Study participating centre
Brighton and Sussex University Hospitals NHS Trust
Royal Sussex County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
Chelsea and Westminster Hospital
369 Fulham Road
London
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Study participating centre
Barts Health NHS Trust
Royal London Hospital
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Study participating centre
North Bristol NHS Trust
Clinical Research Centre
Southmead Hospital
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Royal Liverpool & Broadgreen University Hospitals Trust
Axess Sexual Health

Prescot Street
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United Kingdom
L7 8PX

Study participating centre
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The James Cook University Hospital
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Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Nottingham University Hospitals NHS Trust
City Hospital Campus
Hucknall Road
Nottingham
United Kingdom
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Sponsor information

Organisation
University Hospitals Sussex NHS Foundation Trust

ROR
https://ror.org/03wvsyq85

Funder(s)

Funder type
Industry

Funder Name
ViiV Healthcare

Alternative Name(s)
ViiV Healthcare Limited

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

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?
Protocol article		06/07/2020	24/08/2022	Yes	No
Basic results		20/12/2022	29/12/2022	No	No
HRA research summary			28/06/2023	No	No
Plain English results		13/09/2022	20/10/2022	No	Yes
Statistical Analysis Plan	version 1.0	24/03/2022	15/02/2023	No	No