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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

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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

HEPMARC Study

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Abstract

Introduction

At least 30% of people living with HIV-1 (PLWH) infection have non-alcoholic fatty liver disease (NAFLD), which has now become the leading cause of hepatic fibrosis and cirrhosis. Management is based largely on lifestyle modifications, which are difficult to achieve ,and urgently therapeutic options are needed. Maraviroc, through antagonism of CCR5 receptors, may reduce hepatic fibrosis progression and could be an effective treatment for NAFLD. However, dosing is recommended as a twice daily, unlike most currently recommended antiretroviral therapies. This study will investigate the feasibility and acceptability of addition of maraviroc to combination antiretroviral therapy in PLWH and NAFLD as a treatment for NAFLD.

Methods and analysis

This is a phase IV, randomised, open-label, non-invasive pilot study. Sixty individuals with well controlled HIV-1 and NAFLD will be recruited from UK HIV clinics and randomised 1:1 to receiving either optimised background therapy (OBT) plus maraviroc or OBT alone. Follow up will be every 24 weeks for 96 weeks. The primary outcome measures will include recruitment and retention rates, adverse events and adherence. Secondary outcomes will include changes in markers of hepatic fibrosis including the Enhanced Liver Fibrosis (ELF) score, median stiffness and controlled attenuation parameter scores on Fibroscan, and quality of life assessments. Analyses will be performed according to intention to treat principles. For secondary outcomes, estimated differences and 95% confidence intervals between the groups using a t-method will be presented for continuous variables and as exact 95% binomial confidence intervals for categorical variables.

Ethics and dissemination

Ethical approval was through the London Dulwich UK Research Ethics Committee (Reference 17/LO/2093). Results will be disseminated both through community groups and peer-reviewed scientific literature.

Strengths and limitations

Strengths

- Investigating a novel treatment for NAFLD in PLWH
- Simple study design ensuring ease of understanding for potential recruits
- Non-invasive approach likely to increase acceptability to participants
- Minimal difference in frequency of follow up from standard of care for PLWH

Limitations

- The gold standard for assessment of liver disease is biopsy; hence non-invasive markers may under or over quantify the degree of steatosis or fibrosis. However, a requirement for histology is likely to deter many potential recruits, particularly those unlikely to have advanced disease.

Keywords: non-alcoholic fatty liver disease (NAFLD), HIV-1, maraviroc, non-invasive markers, hepatic fibrosis, Enhanced Liver Fibrosis (ELF), Fibroscan

1 INTRODUCTION

Recent systematic reviews have identified a prevalence of non-alcoholic fatty liver disease (NAFLD) in people living with HIV (PLWH) of between 30-50% (1, 2). Risk factors include those associated with the metabolic syndrome, in particular high BMI, type II diabetes mellitus and dyslipidaemia, as well as genetic polymorphisms. Additional HIV-related risk factors include immunoactivation, gut microbiome dysregulation and antiretroviral therapy toxicity (3, 4). Of those with NAFLD, 20-40% will develop steatohepatitis, which may progress to fibrosis and cirrhosis. Thus, NAFLD has now become the leading cause of liver disease in PLWH.

Several management approaches are recommended for NAFLD. These include addressing underlying lifestyle factors including reduction in weight by 5-10%, increasing exercise, and optimising glycaemic control (5). Pharmacological interventions include vitamin E and pioglitazone (5). However, there are few data to inform optimal interventions, particularly in PLWH, which has led to increasing interest in novel approaches.

The chemokine CCL5/RANTES, the ligand for CCR5, plays a key role in hepatic inflammation and fibrosis. CCR5 mediates intrahepatic immune cell interactions which promote activation and migration of Kupffer cells and hepatic stellate cells; these in turn promote inflammation and hepatic fibrosis (6, 7). Antagonism of this pathway could therefore reduce fibrosis progression (7-9)

Maraviroc (MVC) is licensed for the treatment of HIV-1 infection in both treatment-naïve and –experienced individuals, where the infecting strain is R5 tropic, as part of combination therapy (10, 11). MVC inhibits the binding of HIV-1 gp120 to the CCR5 co-receptor, thereby preventing virus entry into the cell. The property of MVC antagonising CCL5-CCR5 mediated interactions has led to interest in its potential anti-inflammatory benefits additional to its anti-HIV activity, including in the liver and brain (12-14). Furthermore, there are almost 10 years of data relating to the safety of MVC in humans and the drug is well tolerated, including in individuals with chronic liver disease caused by HIV/HCV or HIV/HBV coinfection (15).

In vitro, maraviroc reduces the release of pro-inflammatory cytokines implicated in fibrosis from immortalised human hepatic stellate cells, with reduced expression of extracellular matrix proteins (16). Maraviroc also reduces rates of hepatic fibrosis progression in mice (17).

Furthermore, in an analysis of HIV/HCV-coinfected individuals receiving MVC-containing combination antiretroviral therapy (cART), MVC reduced hepatic fibrosis progression over 18 months, indicated through the AST:platelet ratio index, with 1/3 individuals showing fibrosis regression (13). Transient elastography studies also demonstrated a benefit of MVC on liver stiffness measurements in HIV/HCV-coinfected individuals receiving MVC (18).

Finally, in a phase 2 study, cART-naïve individuals were randomised to receiving efavirenz or the novel antiretroviral, cenicriviroc (CVC), an antagonist of both CCR2 and CCR5, both in combination with Truvada. Those in the CVC arm experienced a decrease in the Enhanced Liver Fibrosis (ELF) biomarker score (19). Similarly, in a phase 2b study of CVC in HIV-uninfected individuals with NASH, twice as many individuals receiving CVC vs placebo achieved an improvement in biopsy-assigned fibrosis stage (20) .

Following these observations, it is plausible that CCR5-receptor antagonism by MVC may reduce hepatic fibrosis in HIV-monoinfected individuals with NAFLD. However, no study has yet investigated this.

2 STUDY RATIONALE

In vitro data for MVC and clinical trials outcomes for CVC suggest CCR5 antagonism may reduce hepatic fibrosis. MVC is licensed for HIV-1 treatment as part of combination therapy and may be an effective treatment for NAFLD in PLWH. However, recommended dosing is twice daily, which could be associated with reduced acceptability to PLWH and NAFLD. There is therefore a need to investigate the feasibility and acceptability of the addition of MVC to antiretroviral therapy in PLWH and NAFLD as a possible therapeutic option for NAFLD.

3 OUTCOME MEASURES

Primary and secondary outcome measures are shown in Boxes 1 and 2.

Rationale for primary outcome measure

Primary outcome measures will assess the feasibility and acceptability of addition of maraviroc to effective cART in a cohort of PLWH as a possible therapy for NAFLD. Should feasibility and acceptability be confirmed, this would support the establishment of larger, randomised, double-blind, placebo-controlled study to assess the efficacy of the intervention.

Rationale for secondary outcome measure

Measures of the efficacy of maraviroc on a combination of non-invasive markers of hepatic inflammation and fibrosis will be identified, including the ELF score and median stiffness and controlled attenuation parameter (CAP) scores on Fibroscan. Invasive procedures have been avoided, as liver biopsy would deter potential participants, particularly those without advanced liver disease.

Box 1

Primary outcome measures

Proportion of eligible individuals approached who are successfully recruited

Monthly participant recruitment rate

Participant retention in the study at 48 and 96 weeks

Proportion of participants for whom there is missing data at 48 and 96 weeks

Proportion of participants reporting adverse events at 48 and 96 weeks

Level of self-reported adherence to the study drug at 48 and 96 weeks in those allocated to the maraviroc group

Box 2

Secondary outcome measures

Mean change in the ELF score by 48 and 96 weeks

Mean change in Fibroscan median stiffness by 48 and 96 weeks

Mean change in the Fibroscan Controlled Attenuation Parameter (CAP) score by 48 and 96 weeks

Change in the % with a CT liver:spleen attenuation ratio <1.0 by 96 weeks

Mean change in blood-derived biochemistry by 48 and 96 weeks: fasting HDL:cholesterol ratio, LDL, HDL, TG, glucose, Hb1AC and ALT

Mean change in clinical signs of the metabolic syndrome by 48 and 96 weeks: BMI, waist circumference and weight

Mean change in HIV parameters: CD4 cell count and % with undetectable HIV VL.

Differences in the quality of life of participants by 48 and 96 weeks as assessed by responses to the chronic liver disease questionnaire for NAFLD (CLDQ:NAFLD), and the SF-36 and WPAI:SHP questionnaires.

4 TRIAL DESIGN

This is a phase IV, open-label, randomised, dual arm pilot study. Randomisation 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 and

(2) BMI ≥ 25 versus < 25 and

(3) current exposure to a lipid-lowering agent* and

(4) diabetes mellitus status (DM 1 or 2 versus no DM)

*HMG CoA reductase inhibitors eg statins; cholesterol absorption inhibitors eg ezetimibe; bile acid binding drugs eg cholestyramine; fibrates; omega 3 fatty acids

Stratification will be undertaken to balance the treatment groups on important prognostic factors (ie to prevent confounding) given that high BMI, diabetes mellitus (2) and concurrent administration of PIs (1) have been associated with faster hepatic fibrosis progression. Statin use has conversely been associated with relative protection from fibrosis (21).

Blinding will not be used for this pilot study although results may inform the design of a subsequent larger, blinded placebo-controlled randomised controlled trial. However, it is unlikely that there will be behavioural differences in the maraviroc versus non-maraviroc group which would change risk of fibrosis progression (such as dietary modifications, increase in exercise or reduction in alcohol consumption). Therefore, the use of placebo is not considered essential.

5 ELIGIBILITY CRITERIA

Inclusion and exclusion criteria are shown in Boxes 3 and 4.

Box 3

Inclusion criteria

Aged 18 years and older
HIV-1 infected with durably suppressed HIV VL (<50 copies/ml for ≥ 6 months) NB. One HIV VL blip (VL 50-200 copies/ml) is allowed in the 6 months prior to screen.
Has evidence of NAFLD on hepatic imaging (USS, CT or MRI) or on biopsy either at screen or in the 6 months prior to screen
Provides written, informed consent to participate
Is willing to comply with the protocol requirements
If female and of child bearing potential, is using effective birth control methods (as agreed by the investigator) and willing to continue practicing 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
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

Box 4

Exclusion criteria

Severe cardiovascular disease including known angina or history of myocardial infarction

History of postural hypotension, defined as a reduction in the systolic blood pressure of ≥ 20mmHg after standing for at least one minute

Individuals previously exposed to MVC

HIV viral load detectable (>50 copies/ml)

NB One blip (VL >50 copies/ml) within 6 months prior to screen is allowed)

Current HCV or HBV (HBcAb-positive, HBsAg-negative is permitted; anti-HCV Ab positive with HCV RNA or HCV antigen negative for ≥ 6 months following treatment or spontaneous clearance is permitted)

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

Note: alcohol-related liver disease includes liver disease in the presence of excess alcohol intake as defined according to EASL guidelines 2016 (ie >20g/day or >17 units/week for women and >30g/day or >26 units/week for men).

ALT or AST > 205 IU/L

Severe renal insufficiency (creatinine clearance < 30 mL/min)

HIV-2 infection

Known allergy or intolerance to MVC or its constituents including hypersensitivity to peanuts or soya

If female, pregnancy or breastfeeding

Individuals currently taking medications or herbal agents that are contraindicated with MVC including St John's Wort.

6 TRIAL PROCEDURES

The schedule of assessments is summarised in Table 1.

Table 1. Summary of trial procedures

	Screening visit (-42d)	Baseline	Wk 4[1] +/- 2d	Wk 24 +/- 7d	Wk 48 +/- 7d	Wk 72 +/- 7d	Wk 96 +/- 7d	Early Termination Visit
Informed consent	X							
Demographic data and medical history including full ART history and alcohol assessment	X							
Randomisation		X						
Vital signs	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Physical examination including height, weight and waist circumference	X[3]	X[3,4]		X[3,4]	X[3,4]	X[3,4]	X[3,4]	X[3,4]
ECG	X							
Urine dip[5] and pregnancy test (for WOCBP)	X	X		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
HIV associated conditions	X	X		X	X	X	X	X
Symptom & AE review	X	X	X	X	X	X	X	X
Diet and exercise history[6]		x			x		X	X
CLDQ:NAFLD, SF36, WPAI:SHP questionnaires		X			X		X	X
ELF Score		X			X		X	X
CD4/CD8 T cell count	X				X		X	X
HIV-1 RNA level	X		X	X	X	X	X	X
Proviral DNA Tropism[7]		X						
Haematology[8]	X	X	X	X	X	X	X	X
Routine chemistry[9]	X	X	X	X	X	X	X	X
Fasting chemistry[10]		X			X		X	X
Additional chemistry[11]	X				X		X	X
HIV, HBV & HCV serology[12]	X							
Full liver screen[13]	X							
Ultrasound Liver[14]	X							
Fibroscan[15]	X				X		X	X
CT liver:spleen attenuation ratio[16]		X					X	
Drug dispensation[17]		X	X	X	X	X		

1 Week 4 visit only for individuals receiving maraviroc. Bloods are unfasted.

2 HR, RR, Temp, BP, Lying and standing BP (postural BP at screening only and to be repeated if history indicates)

3 Height only at screening; weight and waist circumference at every visit except week 4

4 Symptom directed physical examination only

5 Point of care urine dip for haematuria, proteinuria, glycosuria, leucocytes and nitrites

6 Dietary history will be daily intake of olive oil, fruit, vegetables or salad, legumes, fish, wine, meat, white bread, rice and whole-grain bread)(22). Exercise history will be number of times per week exercise is undertaken, number of minutes of exercise per episode and type of exercise.

7 If no result within the preceding 24 weeks

8 Haemoglobin, white cell count and differential, eosinophils, platelets

9 Sodium, potassium, chloride, creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), albumin, phosphate, CK, glucose (screening, weeks 4, 24 and 72); lipids (total cholesterol, HDL, LDL, triglycerides) (weeks 24 and 72 only)

10 Fasting glucose and fasting lipids (total cholesterol, HDL, LDL, triglycerides)

11 HbA1c

12 anti-HCV Ab, HCV RNA or HCV antigen, HBsAg; if no prior record of result: anti-HBcAb. HIV Ab/Ag only if no previous documented result

13 If no previous record of result: INR, ferritin, caeruloplasmin, copper, thyroid function, alpha-1 antitrypsin, anti-mitochondrial antibodies, anti-nuclear antibodies, anti-smooth muscle antibody, anti-liver/kidney/microsomal antibodies-1, coeliac serology

14 If no previous imaging (US, CT, MRI) result confirming fatty liver in the preceding 24 weeks

15 Includes both median stiffness and controlled attenuation parameter scores. To be performed within 7 days of the study visit..

16 Optional. To be performed within 7 days of the study visit. Preference is for the 7 days prior to baseline.

17 Only for individuals assigned to the maraviroc group

7 RECRUITMENT

Participants will be recruited in UK HIV clinics. Potentially eligible individuals with evidence of hepatic steatosis on imaging or biopsy performed as part of routine clinical care will be identified by clinical staff, either from the direct care team or by research clinicians working in the same HIV team. The following approach will be used: *(i) review of a database of patients in the HIV department with NAFLD, (ii) pre- identification of patients due to attend a routine pre-arranged follow up appointments and (iii) review of medical notes during routine clinical follow up.* Anonymised information on individuals who are contacted but are not randomised will include: age, gender, ethnicity, the reason for lack of eligibility for participation, or if they are eligible but declined.

8 STUDY VISITS

Study visits and assessments will take place according to the schedule in Table 1.

Screening Visit

Potentially eligible participants will be invited to attend for an appointment, having been provided with a participant information sheet. Adequate time (at least 24 hours) will be allowed for questions and to consider the study before agreeing to participate. Written, informed consent will be received by the investigator. Results of screening evaluations must be available within 42 days of randomisation and eligibility established.

The randomisation scheme

Subjects will be randomised 1:1 into the maraviroc and non-maraviroc groups at the baseline visit. In addition, there will be stratification according to the factors outlined above. The web-based Sealed Envelope™ system will be used to allocate individuals randomly to the maraviroc or non-maraviroc groups. The statistician will provide the randomisation list and the HEPMARC Randomisation Guide will be followed by the study team.

Withdrawal

A participant is free to withdraw from the study at any time. In addition, the Investigator may decide, for reasons of medical prudence, to withdraw a subject. If a subject discontinues study medication dosing, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures and follow-up procedures. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

Study medication may also be discontinued in the following instances:

1. If the subject withdraws his/her consent.

2. If the investigator considers in the interest of the subject (i.e. intercurrent illness, unacceptable toxicity) that it is best for them to withdraw their consent.

3. The subject fails to comply with the protocol requirements or fails to cooperate with the investigator.

4. Pregnancy during the course of the study.

9 TRIAL MEDICATION

Name and description of investigational medicinal product(s) Maraviroc (Celsentri)

Maraviroc is a licensed drug indicated with other antiretroviral medications for treatment-experienced adults infected with only CCR5-tropic HIV-1. It is supplied as a film-coated tablet. The recommended dose is 150mg, 300mg or 600mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products, according to the Summary of Product Characteristics (SPC) (23).

Dosage schedules

For those randomised to receiving maraviroc, dosing will according to SPC recommendations. The total dose will be determined according to interactions with other medications in line with SPC recommendations. Modification of the dose of maraviroc will not be undertaken except where indicated due to potential drug-drug interactions with concomitant medications. Where a participant initiates a new medication or discontinues an existing medication, the investigator will confirm whether or not a drug drug interaction could occur and hence the need for any dose modification of MVC.

For women of child bearing potential, contraception needs to be used for the duration of the study and for 30 days after the end of the trial. This includes the following, according to the woman's preference and DDIs with concomitant medications:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection, implant, IUS etc.)
- Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence

Assessment of compliance

Compliance will be assessed through:

a) Self reporting of doses of MVC taken via a diary card
b) Pill counting at each visit by a pharmacist and recording of the number of pills returned

Participants will bring in all pill bottles at each study visit. The total number of IMP pills remaining at each visit will be counted and, then returned to the participant to take until the bottle is finished.

The percentage of IMP compliance for each participant will be calculated. Where this figure is <80%, this will lead to likely withdrawal from the study although this will be at the discretion of the PI. Where a

discrepancy exists between self reported compliance and compliance identified via pill counting, any decision to withdraw the participant will rest with the study PI.

Toxicity Management

In the event of toxicity or intolerance to MVC in this study, subjects will be managed as in standard clinical practice. This may involve discontinuing MVC in some cases.

10 ADVERSE EVENTS

Adverse events (AEs) observed by the Investigator, or reported by the subject, and any remedial action taken, will be recorded in the subject's CRF and should be verifiable in the subject'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 subjects 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. Clinically significant changes in physical examination and blood safety profiles should also be recorded as adverse events.

Assessment of Intensity

Severity should be recorded and graded according to the AIDS Clinical Trial Group (ACTG) Grading Scale.

AEs, Serious AEs (SAEs), Adverse Reactions (ARs), Serious ARs (SARs) and Suspected Unexpected SARs (SUSARs) may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. These will be followed up until they are resolved or the subject's participation in the study ends (i.e. until the final CRF is completed for that subject). In addition, all serious adverse events assessed by the Investigator as possibly related to the investigational medication should continue to be followed even after the subject's participation in the study is over.

Such events should be followed until resolution, or until no further change can reasonably be expected.

Data Safety and Monitoring Board (DSMB)

A group of independent clinicians and a statistician comprise the DMSB. The DSMB will periodically review overall safety data according to its Charter (available from Brighton Clinical Trials Unit), in addition to all other study parameters. It will determine patterns and trends of events, or identify safety issues, which would not be apparent on an individual case basis.

11 POST TRIAL CARE

Post trial, all individuals will be provided with standard of care interventions indicated for the treatment of NAFLD in line with current UK NICE guidelines.

All participating individuals will be advised, as part of the informed consent process, that maraviroc would be discontinued post-trial. Where individual patients and/or their treating clinicians request the continuation of maraviroc post trial, this request will be considered on a case by case basis by the HIV multidisciplinary team at each NHS site. Although the primary endpoint of the current study does not include efficacy of the drug, a substantial improvement in hepatic fibrosis markers in individual patients is likely to strengthen the case for continuation of drug, which will be made based on its need within the overall HIV treatment regimen.

In addition, any beneficial effect identified in the trial may inform a change in relevant guidelines as well as the establishment of a larger study on the effect of maraviroc in NAFLD in PLWH. This in turn may lead to a change to national recommendations with the possibility that maraviroc could be prescribed to them through existing NHS funding schemes.

12 STATISTICS AND DATA ANALYSIS

Sample size calculation

As this is a pilot study, no formal sample size calculation has been conducted. Results may be used to estimate the variability of the treatment effect of MVC on the ELF score which may inform the sample size calculation for a larger, placebo-controlled RCT.

In a previous biopsy study, a unit increase of 1 in the ELF score was associated with a 2.5-fold increased risk of a liver-related event (adjusted for age and stage of fibrosis) and therefore a unit increase of 1 is deemed to represent a clinically important entity (24). Assuming the SD of the ELF score is 1.12, with 20 patients in each group for the analysis, a difference in ELF of 1 point can be estimated with a 95% confidence interval from 0.6 to 1.4. Assuming an attrition rate of 33%, a target of 30 individuals will be recruited per group [23].

A t-method will be used to estimate the difference in ELF scores, together with 95% confidence intervals, between the two groups. P-values will not be presented.

Planned recruitment rate

An estimated 3-4 individuals will be recruited per month over an 18 month period. This takes into account the following factors:

- The estimated prevalence of NAFLD amongst HIV-infected cohorts at is predicted to be 30%.. Although many individuals are undiagnosed, recruitment at seven sites with > 5000 HIV-infected patients overall is expected to yield at least 200 who have been diagnosed with NAFLD on previous imaging as part of routine clinical care
- All HIV-infected patients are expected to attend a minimum of two medical appointments per year. For a minimum of 5000 HIV-infected individuals, a monthly target of 4-5 is predicted to be feasible, allowing for 1-2 screen failures per month, leaving 3-4 to be recruited.

Statistical analysis plan

Summary of baseline data and flow of patients

Baseline comparability between the two randomised groups will be described by considering the variables below.

For categorical data, % will be presented. For continuous data, the mean or median will be presented for variables following a normal and non-normal distribution, respectively, in addition to the interquartile range (IQR).

Age

% male

% each ethnicity

Duration of HIV infection

Nadir CD4 count

Baseline CD4 count

% with undetectable HIV VL

% receiving PI-based cART vs non-PI based cART

% receiving concomitant lipid lowering therapy

BMI

Waist circumference

Weight

BP

Fasting glucose

HbA1c

Bilirubin

ALT

Fasting TG

Fasting LDL

Fasting HDL

Fasting total cholesterol

Fasting HDL:cholesterol ratio

Baseline ELF score

Baseline Fibroscan stiffness result

Baseline Fibroscan CAP score

% with a CT liver:spleen attenuation ratio <1.0

Baseline diet score

See Figure 1 for the CONSORT flow diagram for this study.

Feasibility Outcome analyses

All analyses will be performed on available cases according to intention to treat (ITT) principles. Therefore all individuals randomised within the study (including those subsequently withdrawn) will be included in outcome analyses.

The following analyses will be presented:

a) Proportion of eligible individuals approached who are successfully recruited
It is envisaged that a recruitment rate of at least 50% will achieved. This takes into account the likelihood that a proportion of potential recruits will decline particularly owing to the requirement for twice daily pill taking.

b) Monthly participant recruitment rate. This is expected to be at least 2 participants consistently per month, with an average of 3-4.

c) Participant retention in the study at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups. This is expected to be at least 65% (cf 35% discontinuation in the MOTIVATE study (10)).

d) Proportion of participants for whom there is missing data at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups. This is expected to be less than 20% for all participants.

e) Proportion of participants reporting adverse events at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups. This is expected to be less than 10% based on the SPC for maraviroc (19).

f) Level of self-reported adherence to the study drug at 48 and 96 weeks in those allocated to the maraviroc group. This is expected to be greater than 90%.

Secondary outcome analysis

The analysis of the secondary outcomes, shown in Box 2, will be presented as the estimated difference and 95% confidence interval between groups using a t-method for continuous variables and as exact 95% binomial confidence intervals for categorical variables, from baseline to 48 and 96 weeks.

In the event of missing data, only available data will be included in the analyses.

13 DATA HANDLING, CONFIDENTIALITY and MONITORING

An Electronic Data management system MACRO™ will be used in this study. All information will be recorded in source data and documentation that will be filed in patients' notes. Direct access to data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities when appropriate to permit trial-related monitoring, audits and inspections. A specific Trial Monitoring Plan has been developed for the study (available from Brighton Clinical Trials Unit).

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998.

Personal information will be collected, kept secure, and maintained. This will involve the creation of coded, depersonalised data, secure maintenance of the data and the linking code in separate locations using encrypted digital files and limiting access to the minimum number of individuals necessary for quality control, audit, and analysis. The confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators by using only pseudynomised codes rather than personal identifiable information. Data will be stored for 25 years

14 ETHICS and DISSEMINATION

This study has been approved by the Research Ethics Committee – London Dulwich, UK (REC reference 17/LO/2093). Protocol amendments will be communicated to all relevant parties. Results of the study will be written up and submitted for publication in both HIV and hepatology journals, as well as disseminated through HIV community groups. Study data will be made available upon reasonable request to the Brighton Clinical Trials Unit.

15 SUMMARY

This pilot study will investigate the feasibility and acceptability of addition of maraviroc to OBT in PLWH and NAFLD *vs* continuing OBT alone, through identification of recruitment and retention rates, adherence to study drug and adverse events rates over 96 weeks. Secondary outcome measures will include changes in the ELF score and median liver stiffness and CAP scores recorded through Fibroscan, comparing the maraviroc and non-maraviroc groups.

16 REFERENCES

1. Vuille-Lessard E, Lebouche B, Lennox L, Routy JP, Costiniuk CT, Pexos C, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients. Aids. 2016;30(17):2635-43.
2. Maurice JB, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of non-alcoholic fatty liver disease in HIV-monoinfection: a systematic review and meta-analysis. Aids. 2017.
3. Tafesh Z, Verna, EC. Managing nonalcoholic fatty liver disease in patients living with HIV. Current opinion in infectious diseases. 2017;30:12-20.
4. Seth A, Sherman KE. Fatty liver disease in persons with HIV infection. Top Antivir Med. 2019;27(2):75-82.
5. NICE. https://www.nice.org.uk/guidance/NG49/chapter/Recommendations#lifestyle-modifications-for-nafld 2016 [

6. Schwabe RF, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. American journal of physiology Gastrointestinal and liver physiology. 2003;285(5):G949-58.
7. Seki E, De Minicis S, Gwak GY, Kluwe J, Inokuchi S, Bursill CA, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. The Journal of clinical investigation. 2009;119(7):1858-70.
8. Berres ML, Koenen RR, Rueland A, Zaldivar MM, Heinrichs D, Sahin H, et al. Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice. The Journal of clinical investigation. 2010;120(11):4129-40.
9. Barashi N, Weiss ID, Wald O, Wald H, Beider K, Abraham M, et al. Inflammation-induced hepatocellular carcinoma is dependent on CCR5 in mice. Hepatology. 2013;58(3):1021-30.
10. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. The New England journal of medicine. 2008;359(14):1429-41.
11. Cooper DA, Heera J, Goodrich J, Tawadrous M, Saag M, Dejesus E, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. The Journal of infectious diseases. 2010;201(6):803-13.
12. Martin-Blondel G, Brassat D, Bauer J, Lassmann H, Liblau RS. CCR5 blockade for neuroinflammatory diseases--beyond control of HIV. Nature reviews Neurology. 2016;12(2):95-105.
13. Gonzalez EO, Boix V, Deltoro MG, Aldeguer JL, Portilla J, Montero M, et al. The effects of Maraviroc on liver fibrosis in HIV/HCV co-infected patients. J Int AIDS Soc. 2014;17(4 Suppl 3):19643.
14. Blanco JR, Ochoa-Callejero L. Off-label use of maraviroc in clinical practice. Expert review of anti-infective therapy. 2016;14(1):5-8.
15. Rockstroh JK, Soriano V, Plonski F, Bansal M, Fatkenheuer G, Small CB, et al. Hepatic safety in subjects with HIV-1 and hepatitis C and/or B virus: a randomized, double-blind study of maraviroc versus placebo in combination with antiretroviral agents. HIV clinical trials. 2015;16(2):72-80.
16. Martini S, Perna A, Lucariello A, Macera M, Carleo MA, Guerra G, et al., editors. Effects of treatment with maraviroc - a CCR5 inhibitor on human hepatic stellate cells. Conference on Retroviruses and Opportunistic Infections; 2017 13-16 February; Seattle.
17. Perez-Martinez L, Perez-Matute P, Aguilera-Lizarraga J, Rubio-Mediavilla S, Narro J, Recio E, et al. Maraviroc, a CCR5 antagonist, ameliorates the development of hepatic steatosis in a mouse model of non-alcoholic fatty liver disease (NAFLD). The Journal of antimicrobial chemotherapy. 2014;69(7):1903-10.
18. Nasta P, Gatti F, Borghi F, Chiari E, Paderni A, Carosi G. Liver stiffness (LS) change in HIV-hepatitis C (HCV) coinfected patients treated with CCR5 inhibitor based antiretroviral therapy. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; 17-20 September; Chicago2011.
19. Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay A, et al. A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus AIDS 2016;30:869-78.
20. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology. 2018;67(5):1754-67.
21. Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. Journal of hepatology. 2015;63(3):705-12.
22. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. European journal of clinical nutrition. 2004;58(11):1550-2.
23. Celsentri: summary of product characteristics Viiv Healthcare [updated 12/10/2018. Available from: https://www.medicines.org.uk/emc/product/6159/smpc.
24. Irvine KM, Wockner LF, Shanker M, Fagan KJ, Horsfall LU, Fletcher LM, et al. The Enhanced liver fibrosis score is associated with clinical outcomes and disease progression in patients with chronic liver disease. Liver international : official journal of the International Association for the Study of the Liver. 2016;36(3):370-7.

17. AUTHOR CONTRIBUTIONS, FUNDING and COMPETING INTERESTS

Authors contributions: Daniel Bradshaw led on the study concept, writing the protocol and carrying out the study. Nicky Perry and Iga Abramowicz assisted in writing and revising the protocol including

the safety assessments. Yvonne Gilleece and Sumita Verma assisted in writing the clinical sections of the protocol. Stephen Bremner wrote the statistical section and analysis plan.

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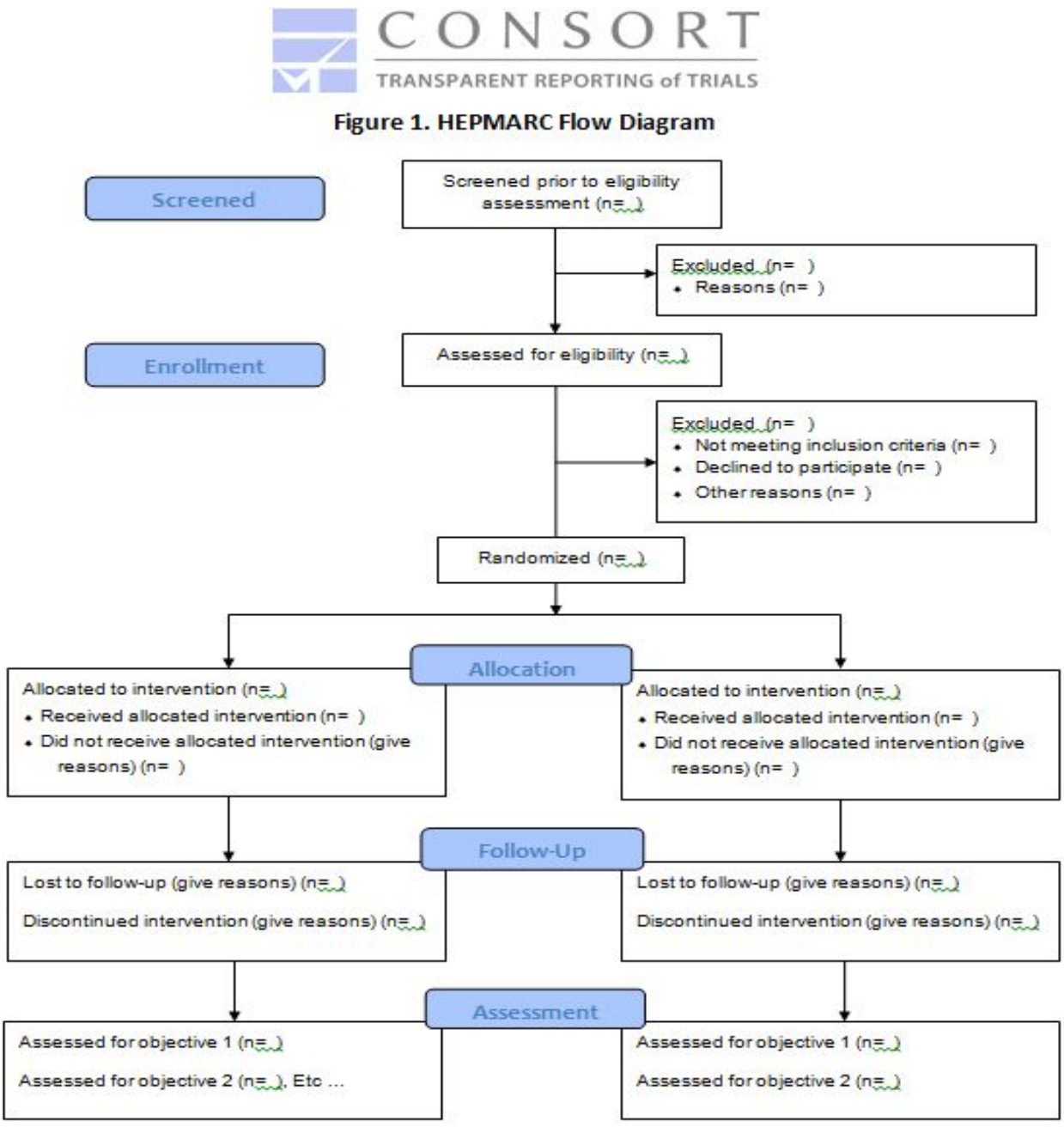
Competing interests statement: The authors have no competing interests to declare.

Trial steering committee: Overall trial supervision is delivered through the Trial Steering Committee, on behalf of the Sponsor and Funding to ensure it is delivered according to Good Clinical Practice guidelines.

Patient and public involvement: Patients were involved in the study design and a patient representative sits on the Trial Steering Committee.

Figure 1: CONSORT flow diagram for the HEPMARC study.



Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
HEPMARC Consort Flow Diagram v1.0

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A protocol for a phase IV, open-label, feasibility 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

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A protocol for a phase IV, open-label, feasibility 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

HEPMARC Study

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Abstract

Introduction

At least 30% of people living with HIV-1 (PLWH) infection have non-alcoholic fatty liver disease (NAFLD), which has now become a leading cause of hepatic fibrosis and cirrhosis. Management is based largely on lifestyle modifications, which are difficult to achieve ,and urgently therapeutic options are needed. Maraviroc, through antagonism of CCR5 receptors, may reduce hepatic fibrosis progression and could be an effective treatment for NAFLD. However, dosing is recommended as a twice daily, unlike most currently recommended antiretroviral therapies. This study will investigate the feasibility and acceptability of addition of maraviroc to combination antiretroviral therapy in PLWH and NAFLD as a treatment for NAFLD.

Methods and analysis

This is a phase IV, randomised, open-label, non-invasive feasibility study. Sixty individuals with well controlled HIV-1 and NAFLD will be recruited from UK HIV clinics and randomised 1:1 to receiving either optimised background therapy (OBT) plus maraviroc or OBT alone. Follow up will be every 24 weeks for 96 weeks. The primary outcome measures will include recruitment and retention rates, adverse events and adherence. Secondary outcomes will include changes in markers of hepatic fibrosis including the Enhanced Liver Fibrosis (ELF) score, median liver stiffness measurement and controlled attenuation parameter scores on Fibroscan, and quality of life assessments. Analyses will be performed according to intention to treat principles. For secondary outcomes, estimated differences and 95% confidence intervals between the groups using a t-method will be presented for continuous variables and as exact 95% binomial confidence intervals for categorical variables.

Ethics and dissemination

Ethical approval was through the London Dulwich UK Research Ethics Committee (Reference 17/LO/2093). Results will be disseminated both through community groups and peer-reviewed scientific literature.

Strengths and limitations

Strengths

- Investigating a novel treatment for NAFLD in PLWH
- Simple study design ensuring ease of understanding for potential recruits
- Non-invasive approach likely to increase acceptability to participants
- Minimal difference in frequency of follow up from standard of care for PLWH

Limitations

- The gold standard for assessment of liver disease is biopsy; hence non-invasive markers may under or over quantify the degree of steatosis or fibrosis. However, a requirement for histology is likely to deter many potential recruits, particularly those unlikely to have advanced disease.

Keywords: non-alcoholic fatty liver disease (NAFLD), HIV-1, maraviroc, non-invasive markers, hepatic fibrosis, Enhanced Liver Fibrosis (ELF), Fibroscan

1 INTRODUCTION

Recent systematic reviews have identified a prevalence of non-alcoholic fatty liver disease (NAFLD) in people living with HIV (PLWH) of between 30-50% (1, 2). Risk factors include those associated with the metabolic syndrome, in particular high BMI, type II diabetes mellitus and dyslipidaemia, as well as genetic polymorphisms. Additional HIV-related risk factors include immunoactivation, gut microbiome dysregulation and antiretroviral therapy toxicity (3, 4). Of those with NAFLD, 20-40% will develop steatohepatitis, which may progress to fibrosis and cirrhosis (2, 4). Thus, NAFLD has now become the leading cause of liver disease in PLWH.

Several management approaches are recommended for NAFLD. These include addressing underlying lifestyle factors including reduction in weight by ~10%, increasing exercise, and optimising glycaemic control (5). Pharmacological interventions include vitamin E and pioglitazone (5). However, there are few data to inform optimal interventions, particularly in PLWH, which has led to increasing interest in novel approaches.

The chemokine CCL5/RANTES, the ligand for CCR5, plays a key role in hepatic inflammation and fibrosis. CCR5 mediates intrahepatic immune cell interactions which promote activation and migration of Kupffer cells and hepatic stellate cells; these in turn promote inflammation and hepatic fibrosis (6, 7). Antagonism of this pathway could therefore reduce fibrosis progression (7-9)

Maraviroc (MVC) is licensed for the treatment of HIV-1 infection in both treatment-naïve and –experienced individuals, where the infecting strain is R5 tropic, as part of combination therapy (10, 11). MVC inhibits the binding of HIV-1 gp120 to the CCR5 co-receptor, thereby preventing virus entry into the cell. The property of MVC antagonising CCL5-CCR5 mediated interactions has led to interest in its potential anti-inflammatory benefits additional to its anti-HIV activity, including in the liver and brain (12-14). Furthermore, there are almost 10 years of data relating to the safety of MVC in humans and the drug is well tolerated, including in individuals with chronic liver disease caused by HIV/HCV or HIV/HBV coinfection (15).

In vitro, maraviroc reduces the release of pro-inflammatory cytokines implicated in fibrosis from immortalised human hepatic stellate cells, with reduced expression of extracellular matrix proteins (16). Maraviroc also reduces rates of hepatic fibrosis progression in mice (17).

Furthermore, in an analysis of HIV/HCV-coinfected individuals receiving MVC-containing combination antiretroviral therapy (cART), MVC reduced hepatic fibrosis progression over 18 months, indicated through the AST:platelet ratio index, with 1/3 individuals showing fibrosis regression (13). Transient elastography studies also demonstrated a benefit of MVC on liver stiffness measurements in HIV/HCV-coinfected individuals receiving MVC (18).

Finally, in a phase 2 study, cART-naïve individuals were randomised to receiving efavirenz or the novel antiretroviral, cenicriviroc (CVC), an antagonist of both CCR2 and CCR5, both in combination with Truvada. Those in the CVC arm experienced a decrease in the Enhanced Liver Fibrosis (ELF) biomarker score (19). Similarly, in a phase 2b study of CVC in HIV-uninfected individuals with NASH, twice as many individuals receiving CVC vs placebo achieved an improvement in biopsy-assigned fibrosis stage (20) .

Following these observations, it is plausible that CCR5-receptor antagonism by MVC may reduce hepatic fibrosis in HIV-monoinfected individuals with NAFLD. However, no study has yet investigated this.

2 STUDY RATIONALE

In vitro data for MVC and clinical trials outcomes for CVC suggest CCR5 antagonism may reduce hepatic fibrosis. MVC is licensed for HIV-1 treatment as part of combination therapy and may be an effective treatment for NAFLD in PLWH. However, recommended dosing is twice daily, which could be associated with reduced acceptability to PLWH and NAFLD. There is therefore a need to investigate the feasibility and acceptability of the addition of MVC to antiretroviral therapy in PLWH and NAFLD as a possible therapeutic option for NAFLD.

3 OUTCOME MEASURES

Primary and secondary outcome measures are shown in Boxes 1 and 2.

Rationale for primary outcome measure

Primary outcome measures will assess the feasibility and acceptability of addition of maraviroc to effective cART in a cohort of PLWH as a possible therapy for NAFLD. Acceptability will be considered through evaluation of participant recruitment rate, retention rate and adherence. Should feasibility and acceptability be confirmed, this would support the establishment of larger, randomised, double-blind, placebo-controlled study to assess the efficacy of the intervention.

Rationale for secondary outcome measure

Measures of the efficacy of maraviroc on a combination of non-invasive markers of hepatic inflammation and fibrosis will be identified, including the ELF score and median liver stiffness measurement and controlled attenuation parameter (CAP) scores on Fibroscan. Invasive procedures

have been avoided, as liver biopsy would deter potential participants, particularly those without advanced liver disease.

Box 1

Primary outcome measures

Proportion of eligible individuals approached who are successfully recruited

Monthly participant recruitment rate

Participant retention in the study at 48 and 96 weeks

Proportion of participants for whom there is missing data at 48 and 96 weeks

Proportion of participants reporting adverse events at 48 and 96 weeks

Level of self-reported adherence to the study drug at 48 and 96 weeks in those allocated to the maraviroc group

Box 2

Secondary outcome measures

Mean change in the ELF score by 48 and 96 weeks

Mean change in Fibroscan median liver stiffness measurement by 48 and 96 weeks

Mean change in the Fibroscan controlled attenuation parameter (CAP) score by 48 and 96 weeks

Change in the % with a CT liver:spleen attenuation ratio <1.0 by 96 weeks

Mean change in blood-derived biochemistry by 48 and 96 weeks: fasting HDL:cholesterol ratio, LDL, HDL, TG, glucose, Hb1AC and ALT

Mean change in clinical signs of the metabolic syndrome by 48 and 96 weeks: BMI, waist circumference and weight

Mean change in HIV parameters: CD4 cell count and % with undetectable HIV VL.

Differences in the quality of life of participants by 48 and 96 weeks as assessed by responses to the chronic liver disease questionnaire for NAFLD (CLDQ:NAFLD), and the SF-36 and WPAI:SHP questionnaires.

4 TRIAL DESIGN

This is a phase IV, open-label, randomised, dual arm feasibility study. Randomisation 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 and

(2) BMI ≥ 25 versus < 25 and

(3) current exposure to a lipid-lowering agent* and

(4) diabetes mellitus status (DM 1 or 2 versus no DM)

*HMG CoA reductase inhibitors eg statins; cholesterol absorption inhibitors eg ezetimibe; bile acid binding drugs eg cholestyramine; fibrates; omega 3 fatty acids

Stratification will be undertaken to balance the treatment groups on important prognostic factors (ie to prevent confounding) given that high BMI, diabetes mellitus (2) and concurrent administration of PIs (1) have been associated with faster hepatic fibrosis progression. Statin use has conversely been associated with relative protection from fibrosis (21).

Blinding will not be used for this feasibility study although results may inform the design of a subsequent larger, blinded placebo-controlled randomised controlled trial investigating efficacy of the intervention. However, it is unlikely that there will be behavioural differences in the maraviroc versus non-maraviroc group which would change risk of fibrosis progression (such as dietary modifications, increase in exercise or reduction in alcohol consumption). Therefore, the use of placebo is not considered essential.

5 ELIGIBILITY CRITERIA

Inclusion and exclusion criteria are shown in Boxes 3 and 4.

Box 3

Inclusion criteria

Aged 18 years and older
HIV-1 infected with durably suppressed HIV VL (<50 copies/ml for ≥ 6 months) NB. One HIV VL blip (VL 50-200 copies/ml) is allowed in the 6 months prior to screen.
Has evidence of NAFLD on hepatic imaging (USS, CT or MRI) or on biopsy either at screen or in the 6 months prior to screen
Provides written, informed consent to participate
Is willing to comply with the protocol requirements
If female and of child bearing potential, is using effective birth control methods (as agreed by the investigator) and willing to continue practicing 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
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

Box 4

Exclusion criteria

Severe cardiovascular disease including known angina or history of myocardial infarction
History of postural hypotension, defined as a reduction in the systolic blood pressure of ≥ 20mmHg after standing for at least one minute
Individuals previously exposed to MVC
HIV viral load detectable (>50 copies/ml) NB One blip (VL 50 -200copies/ml) within 6 months prior to screen is allowed)
Current HCV or HBV (HBcAb-positive, HBsAg-negative is permitted; anti-HCV Ab positive with HCV RNA or HCV antigen negative for ≥ 6 months following treatment or spontaneous clearance is permitted)
Other chronic liver disease including but not exclusively: cirrhosis[1], alcohol-related liver disease[2], 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
ALT or AST > 205 IU/L
Severe renal insufficiency (creatinine clearance < 30 mL/min)
HIV-2 infection
Known allergy or intolerance to MVC or its constituents including hypersensitivity to peanuts or soya
If female, pregnancy or breastfeeding
Individuals currently taking medications or herbal agents that are contraindicated with MVC including St John's Wort.

[1]. confirmed on biopsy, appearance on imaging (nodular liver with features of portal hypertension such as splenomegaly > 13cm and/or varices) or liver stiffness measurement score (> 13kPa)

[2.] includes liver disease in the presence of excess alcohol intake as defined according to EASL guidelines 2016 (ie >20g/day or >17 units/week for women and >30g/day or >26 units/week for men).

6 TRIAL PROCEDURES

The schedule of assessments is summarised in Table 1.

Table 1. Summary of trial procedures

	Screening visit (-42d)	Baseline	Wk 4[1] +/- 2d	Wk 24 +/- 7d	Wk 48 +/- 7d	Wk 72 +/- 7d	Wk 96 +/- 7d	Early Termination Visit
Informed consent	X							
Demographic data and medical history including full ART history and alcohol assessment	X							
Randomisation		X						
Vital signs	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Physical examination including height, weight and waist circumference	X[3]	X[3,4]		X[3,4]	X[3,4]	X[3,4]	X[3,4]	X[3,4]
ECG	X							
Urine dip[5] and pregnancy test (for WOCBP)	X	X		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
HIV associated conditions	X	X		X	X	X	X	X
Symptom & AE review	X	X	X	X	X	X	X	X
Diet and exercise history[6]		x			x		X	X
CLDQ:NAFLD, SF36, WPAI:SHP questionnaires		X			X		X	X
ELF Score		X			X		X	X
CD4/CD8 T cell count	X				X		X	X
HIV-1 RNA level	X		X	X	X	X	X	X
Proviral DNA Tropism[7]		X						
Haematology[8]	X	X	X	X	X	X	X	X
Routine chemistry[9]	X	X	X	X	X	X	X	X
Fasting chemistry[10]		X			X		X	X
Additional chemistry[11]	X				X		X	X
HIV, HBV & HCV serology[12]	X							
Full liver screen[13]	X							
Ultrasound Liver[14]	X							
Fibroscan[15]	X				X		X	X
CT liver:spleen attenuation ratio[16]		X					X	
Drug dispensation[17]		X	X	X	X	X		

1 Week 4 visit only for individuals receiving maraviroc. Bloods are unfasted.

2 HR, RR, Temp, BP, Lying and standing BP (postural BP at screening only and to be repeated if history indicates)

3 Height only at screening; weight and waist circumference at every visit except week 4

4 Symptom directed physical examination only

5 Point of care urine dip for haematuria, proteinuria, glycosuria, leucocytes and nitrites

6 Dietary history will be daily intake of olive oil, fruit, vegetables or salad, legumes, fish, wine, meat, white bread, rice and whole-grain bread)(22). Exercise history will be number of times per week exercise is undertaken, number of minutes of exercise per episode and type of exercise.

7 If no result within the preceding 24 weeks

8 Haemoglobin, white cell count and differential, eosinophils, platelets

9 Sodium, potassium, chloride, creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), albumin, phosphate, CK, glucose (screening, weeks 4, 24 and 72); lipids (total cholesterol, HDL, LDL, triglycerides) (weeks 24 and 72 only)

10 Fasting glucose and fasting lipids (total cholesterol, HDL, LDL, triglycerides)

11 HbA1c

12 anti-HCV Ab, HCV RNA or HCV antigen, HBsAg; if no prior record of result: anti-HBcAb. HIV Ab/Ag only if no previous documented result

13 If no previous record of result: INR, ferritin, caeruloplasmin, copper, thyroid function, alpha-1 antitrypsin, anti-mitochondrial antibodies, anti-nuclear antibodies, anti-smooth muscle antibody, anti-liver/kidney/microsomal antibodies-1, coeliac serology

14 If no previous imaging (US, CT, MRI) result confirming fatty liver in the preceding 24 weeks

15 Includes both median stiffness and controlled attenuation parameter scores. To be performed within 7 days of the study visit.

16 Optional. To be performed within 7 days of the study visit. Preference is for the 7 days prior to baseline.

17 Only for individuals assigned to the maraviroc group

7 RECRUITMENT

Sixty participants will be recruited in seven UK National Health Service (NHS) HIV clinics. Potentially eligible individuals with evidence of hepatic steatosis on imaging or biopsy performed as part of routine clinical care will be identified by clinical staff, either from the direct care team or by research clinicians working in the same HIV team. It is envisaged that ultrasound will be used to identify possible participants as this is the recommended first line diagnostic imaging procedure for NAFLD (23), although some cases, particularly individuals with mild hepatic steatosis, may be missed. It is also emphasised that this trial will recruit only PLWH and NAFLD who do not have cirrhosis. People with cirrhosis have been excluded in order that the study population is not too heterogeneous. However, people with cirrhosis would be included in a larger randomised controlled trial.

The following approach will be used for identification of participants: *(i) review of a database of patients in the HIV department with NAFLD, (ii) pre- identification of patients due to attend a routine pre-arranged follow up appointment in the HIV or hepatology service and (iii) review of medical notes during routine clinical follow up.* Individuals will be contacted either in person in clinic or by telephone. Anonymised information on individuals who are contacted but are not randomised will include: age, gender, ethnicity, the reason for lack of eligibility for participation, or if they are eligible but declined.

8 STUDY VISITS

Study visits and assessments will take place according to the schedule in Table 1.

Screening Visit

Potentially eligible participants will be invited to attend for an appointment, having been provided with a participant information sheet. Adequate time (at least 24 hours) will be allowed for questions and to consider the study before agreeing to participate. Written, informed consent will be received by the investigator. Results of screening evaluations must be available within 42 days of randomisation and eligibility established.

The randomisation scheme

Subjects will be randomised 1:1 into the maraviroc and non-maraviroc groups at the baseline visit. In addition, there will be stratification according to the factors outlined above. The web-based Sealed Envelope™ system will be used to allocate individuals randomly to the maraviroc or non-maraviroc groups. The statistician will provide the randomisation list and the HEPMARC Randomisation Guide will be followed by the study team.

Withdrawal

A participant is free to withdraw from the study at any time. In addition, the Investigator may decide, for reasons of medical prudence, to withdraw a subject. If a subject discontinues study medication dosing, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures and follow-up procedures. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study.

Study medication may also be discontinued in the following instances:

1. If the subject withdraws his/her consent.

2. If the investigator considers in the interest of the subject (i.e. intercurrent illness, unacceptable toxicity) that it is best for them to withdraw their consent.

3. The subject fails to comply with the protocol requirements or fails to cooperate with the investigator.

4. Pregnancy during the course of the study.

9 TRIAL MEDICATION

Name and description of investigational medicinal product(s) Maraviroc (Celsentri)

Maraviroc is a licensed drug indicated with other antiretroviral medications for treatment-experienced adults infected with only CCR5-tropic HIV-1. It is supplied as a film-coated tablet. The recommended dose is 150mg, 300mg or 600mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products, according to the Summary of Product Characteristics (SPC) (24).

Dosage schedules

For those randomised to receiving maraviroc, dosing will according to SPC recommendations. The total dose will be determined according to interactions with other medications in line with SPC recommendations. Modification of the dose of maraviroc will not be undertaken except where indicated due to potential drug-drug interactions with concomitant medications. Where a participant initiates a new medication or discontinues an existing medication, the investigator will confirm whether or not a drug drug interaction could occur and hence the need for any dose modification of MVC.

For women of child bearing potential, contraception needs to be used for the duration of the study and for 30 days after the end of the trial. This includes the following, according to the woman's preference and DDIs with concomitant medications:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection, implant, IUS etc.)
- Double Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)
- True abstinence

Assessment of compliance

Compliance will be assessed through:

a) Self reporting of doses of MVC taken via a diary card
b) Pill counting at each visit by a pharmacist and recording of the number of pills returned

Participants will bring in all pill bottles at each study visit. The total number of IMP pills remaining at each visit will be counted and, then returned to the participant to take until the bottle is finished.

The percentage of IMP compliance for each participant will be calculated. Where this figure is <80%, this will lead to a likely recommendation to discontinue IMP, although this will be at the discretion of the PI . In all circumstances, every effort will be made to continue to follow up the participant on the study. Of note, where a discrepancy exists between self reported compliance and compliance identified via pill counting, any decision to discontinue IMP will rest with the study PI.

Toxicity Management

In the event of toxicity or intolerance to MVC in this study, subjects will be managed as in standard clinical practice. This may involve discontinuing MVC in some cases.

10 ADVERSE EVENTS

Adverse events (AEs) observed by the Investigator, or reported by the subject, and any remedial action taken, will be recorded in the subject's CRF and should be verifiable in the subject'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 subjects 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. Clinically significant changes in physical examination and blood safety profiles should also be recorded as adverse events.

Assessment of Intensity

Severity should be recorded and graded according to the AIDS Clinical Trial Group (ACTG) Grading Scale.

AEs, Serious AEs (SAEs), Adverse Reactions (ARs), Serious ARs (SARs) and Suspected Unexpected SARs (SUSARs) may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. These will be followed up until they are resolved or the subject's participation in the study ends (i.e. until the final CRF is completed for that subject). In addition, all serious adverse events assessed by the Investigator as possibly related to the investigational medication should continue to be followed even after the subject's participation in the study is over.

Such events should be followed until resolution, or until no further change can reasonably be expected.

Data Safety and Monitoring Board (DSMB)

A group of independent clinicians and a statistician comprise the DMSB. The DSMB will periodically review overall safety data according to its Charter (available from Brighton Clinical Trials Unit), in addition to all other study parameters. It will determine patterns and trends of events, or identify safety issues, which would not be apparent on an individual case basis.

11 POST TRIAL CARE

Post trial, all individuals will be provided with standard of care interventions indicated for the treatment of NAFLD in line with current UK NICE guidelines.

All participating individuals will be advised, as part of the informed consent process, that maraviroc would be discontinued post-trial. Where individual patients and/or their treating clinicians request the continuation of maraviroc post trial, this request will be considered on a case by case basis by the HIV multidisciplinary team at each NHS site. Although the primary endpoint of the current study does not include efficacy of the drug, a substantial improvement in hepatic fibrosis markers in individual patients is likely to strengthen the case for continuation of drug, which will be made based on its need within the overall HIV treatment regimen.

In addition, any beneficial effect identified in the trial may inform a change in relevant guidelines as well as the establishment of a larger study on the effect of maraviroc in NAFLD in PLWH. This in turn may lead to a change to national recommendations with the possibility that maraviroc could be prescribed to them through existing NHS funding schemes.

12 STATISTICS AND DATA ANALYSIS

Sample size calculation

As this is a feasibility study, no formal sample size calculation has been conducted. Results may be used to estimate the variability of the treatment effect of MVC on the ELF score which may inform the sample size calculation for a larger, placebo-controlled RCT.

In a previous biopsy study, a unit increase of 1 in the ELF score was associated with a 2.5-fold increased risk of a liver-related event (adjusted for age and stage of fibrosis) and therefore a unit increase of 1 is deemed to represent a clinically important entity (25). Other studies have confirmed the accuracy of the ELF score in the assessment of hepatic fibrosis in PLWH and in those with NAFLD (26-29). Assuming the SD of the ELF score is 1.12, with 20 patients in each group for the analysis, a difference in ELF of 1 point can be estimated with a 95% confidence interval from 0.6 to 1.4. Assuming an attrition rate of 33%, a target of 30 individuals will be recruited per group [23].

A t-method will be used to estimate the difference in ELF scores, together with 95% confidence intervals, between the two groups. P-values will not be presented.

Planned recruitment rate

An estimated 3-4 individuals will be recruited per month over an 18 month period. This takes into account the following factors:

- The estimated prevalence of NAFLD amongst HIV-infected cohorts at is predicted to be 30%.. Although many individuals are undiagnosed, recruitment at seven sites with > 5000 HIV-infected patients overall is expected to yield at least 200 who have been diagnosed with NAFLD on previous imaging as part of routine clinical care
- All HIV-infected patients are expected to attend a minimum of two medical appointments per year. For a minimum of 5000 HIV-infected individuals, a monthly target of 4-5 is predicted to be feasible, allowing for 1-2 screen failures per month, leaving 3-4 to be recruited.

Statistical analysis plan

Summary of baseline data and flow of patients

Baseline comparability between the two randomised groups will be described by considering the variables below.

For categorical data, % will be presented. For continuous data, the mean or median will be presented for variables following a normal and non-normal distribution, respectively, in addition to the interquartile range (IQR).

Age

% male

% each ethnicity

Duration of HIV infection

Nadir CD4 count

Baseline CD4 count

% with undetectable HIV VL

% receiving PI-based cART vs non-PI based cART

% receiving concomitant lipid lowering therapy

BMI

Waist circumference

Weight

BP

Fasting glucose

HbA1c

Bilirubin

ALT

Fasting TG

Fasting LDL

Fasting HDL

Fasting total cholesterol

Fasting HDL:cholesterol ratio

Baseline ELF score

Baseline Fibroscan stiffness result

Baseline Fibroscan CAP score

% with a CT liver:spleen attenuation ratio <1.0

Baseline diet score

See Figure 1 for the CONSORT flow diagram for this study.

Feasibility Outcome analyses

All analyses will be performed on available cases according to intention to treat (ITT) principles. Therefore all individuals randomised within the study (including those subsequently withdrawn) will be included in outcome analyses.

The following analyses will be presented:

a) Proportion of eligible individuals approached who are successfully recruited
It is envisaged that a recruitment rate of at least 50% will achieved. This takes into account the likelihood that a proportion of potential recruits will decline particularly owing to the requirement for twice daily pill taking.

b) Monthly participant recruitment rate. This is expected to be at least 2 participants consistently per month, with an average of 3-4.

c) Participant retention in the study at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups. This is expected to be at least 65% (cf 35% discontinuation in the MOTIVATE study (10)).

d) Proportion of participants for whom there is missing data at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups. This is expected to be less than 20% for all participants.

e) Proportion of participants reporting adverse events at 48 and 96 weeks in the maraviroc and non-maraviroc assigned groups. This is expected to be less than 10% based on the SPC for maraviroc (19).

f) Level of self-reported adherence to the study drug at 48 and 96 weeks in those allocated to the maraviroc group. This is expected to be greater than 90%.

Secondary outcome analysis

The analysis of the secondary outcomes, shown in Box 2, will be presented as the estimated difference and 95% confidence interval between groups using a t-method for continuous variables and as exact 95% binomial confidence intervals for categorical variables, from baseline to 48 and 96 weeks.

In the event of missing data, only available data will be included in the analyses.

13 DATA HANDLING, CONFIDENTIALITY and MONITORING

An Electronic Data management system MACRO™ will be used in this study. All information will be recorded in source data and documentation that will be filed in patients' notes. Direct access to data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities when appropriate to permit trial-related monitoring, audits and inspections. A specific Trial Monitoring Plan has been developed for the study (available from Brighton Clinical Trials Unit).

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998.

Personal information will be collected, kept secure, and maintained. This will involve the creation of coded, depersonalised data, secure maintenance of the data and the linking code in separate locations using encrypted digital files and limiting access to the minimum number of individuals necessary for quality control, audit, and analysis. The confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators by using only pseudynomised codes rather than personal identifiable information. Data will be stored for 25 years

14 ETHICS and DISSEMINATION

This study has been approved by the Research Ethics Committee – London Dulwich, UK (REC reference 17/LO/2093). Protocol amendments will be communicated to all relevant parties. Results of the study will be written up and submitted for publication in both HIV and hepatology journals, as well as disseminated through HIV community groups. Study data will be made available upon reasonable request to the Brighton Clinical Trials Unit.

15 REFERENCES

1. Vuille-Lessard E, Lebouche B, Lennox L, Routy JP, Costiniuk CT, Pexos C, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients. Aids. 2016;30(17):2635-43.
2. Maurice JB, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of non-alcoholic fatty liver disease in HIV-monoinfection: a systematic review and meta-analysis. Aids. 2017.
3. Tafesh Z, Verna, EC. Managing nonalcoholic fatty liver disease in patients living with HIV. Current opinion in infectious diseases. 2017;30:12-20.
4. Seth A, Sherman KE. Fatty liver disease in persons with HIV infection. Top Antivir Med. 2019;27(2):75-82.

5. NICE. https://www.nice.org.uk/guidance/NG49/chapter/Recommendations#lifestyle-modifications-for-nafld 2016 [
6. Schwabe RF, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. American journal of physiology Gastrointestinal and liver physiology. 2003;285(5):G949-58.
7. Seki E, De Minicis S, Gwak GY, Kluwe J, Inokuchi S, Bursill CA, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. The Journal of clinical investigation. 2009;119(7):1858-70.
8. Berres ML, Koenen RR, Rueland A, Zaldivar MM, Heinrichs D, Sahin H, et al. Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice. The Journal of clinical investigation. 2010;120(11):4129-40.
9. Barashi N, Weiss ID, Wald O, Wald H, Beider K, Abraham M, et al. Inflammation-induced hepatocellular carcinoma is dependent on CCR5 in mice. Hepatology. 2013;58(3):1021-30.
10. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. N Engl J Med. 2008;359(14):1429-41.
11. Cooper DA, Heera J, Goodrich J, Tawadrous M, Saag M, Dejesus E, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. The Journal of infectious diseases. 2010;201(6):803-13.
12. Martin-Blondel G, Brassat D, Bauer J, Lassmann H, Liblau RS. CCR5 blockade for neuroinflammatory diseases--beyond control of HIV. Nature reviews Neurology. 2016;12(2):95-105.
13. Gonzalez EO, Boix V, Deltoro MG, Aldeguer JL, Portilla J, Montero M, et al. The effects of Maraviroc on liver fibrosis in HIV/HCV co-infected patients. J Int AIDS Soc. 2014;17(4 Suppl 3):19643.
14. Blanco JR, Ochoa-Callejero L. Off-label use of maraviroc in clinical practice. Expert review of anti-infective therapy. 2016;14(1):5-8.
15. Rockstroh JK, Soriano V, Plonski F, Bansal M, Fatkenheuer G, Small CB, et al. Hepatic safety in subjects with HIV-1 and hepatitis C and/or B virus: a randomized, double-blind study of maraviroc versus placebo in combination with antiretroviral agents. HIV clinical trials. 2015;16(2):72-80.
16. Martini S, Perna A, Lucariello A, Macera M, Carleo MA, Guerra G, et al., editors. Effects of treatment with maraviroc - a CCR5 inhibitor on human hepatic stellate cells. Conference on Retroviruses and Opportunistic Infections; 2017 13-16 February; Seattle.
17. Perez-Martinez L, Perez-Matute P, Aguilera-Lizarraga J, Rubio-Mediavilla S, Narro J, Recio E, et al. Maraviroc, a CCR5 antagonist, ameliorates the development of hepatic steatosis in a mouse model of non-alcoholic fatty liver disease (NAFLD). The Journal of antimicrobial chemotherapy. 2014;69(7):1903-10.
18. Nasta P, Gatti F, Borghi F, Chiari E, Paderni A, Carosi G. Liver stiffness (LS) change in HIV-hepatitis C (HCV) coinfected patients treated with CCR5 inhibitor based antiretroviral therapy. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; 17-20 September; Chicago2011.
19. Thompson M, Saag M, DeJesus E, Gathe J, Lalezari J, Landay A, et al. A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus AIDS 2016;30:869-78.
20. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology. 2018;67(5):1754-67.
21. Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. Journal of hepatology. 2015;63(3):705-12.
22. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. European journal of clinical nutrition. 2004;58(11):1550-2.
23. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-402.
24. Celsentri: summary of product characteristics Viiv Healthcare [updated 12/10/2018. Available from: https://www.medicines.org.uk/emc/product/6159/smpc.
25. Irvine KM, Wockner LF, Shanker M, Fagan KJ, Horsfall LU, Fletcher LM, et al. The Enhanced liver fibrosis score is associated with clinical outcomes and disease progression in patients with chronic liver disease. Liver international : official journal of the International Association for the Study of the Liver. 2016;36(3):370-7.
26. Sherman KE, Abdel-Hameed EA, Ehman RL, Rouster SD, Campa A, Martinez SS, et al. Validation and Refinement of Noninvasive Methods to Assess Hepatic Fibrosis: Magnetic Resonance Elastography Versus Enhanced Liver Fibrosis Index. Dig Dis Sci. 2020;65(4):1252-7.

27. Inadomi C, Takahashi H, Ogawa Y, Oeda S, Imajo K, Kubotsu Y, et al. Accuracy of the Enhanced Liver Fibrosis test, and combination of the Enhanced Liver Fibrosis and non-invasive tests for the diagnosis of advanced liver fibrosis in patients with non-alcoholic fatty liver disease. Hepatol Res. 2020.
28. Staufer K, Halilbasic E, Spindelboeck W, Eilenberg M, Prager G, Stadlbauer V, et al. Evaluation and comparison of six noninvasive tests for prediction of significant or advanced fibrosis in nonalcoholic fatty liver disease. United European Gastroenterol J. 2019;7(8):1113-23.
29. Guillaume M, Moal V, Delabaudiere C, Zuberbuhler F, Robic MA, Lannes A, et al. Direct comparison of the specialised blood fibrosis tests FibroMeter(V2G) and Enhanced Liver Fibrosis score in patients with non-alcoholic fatty liver disease from tertiary care centres. Aliment Pharmacol Ther. 2019;50(11-12):1214-22.

16. AUTHOR CONTRIBUTIONS, FUNDING and COMPETING INTERESTS

Authors contributions: Daniel Bradshaw led on the study concept, writing the protocol and carrying out the study. Nicky Perry and Iga Abramowicz assisted in writing and revising the protocol including the safety assessments. Yvonne Gilleece and Sumita Verma assisted in writing the clinical sections of the protocol. Stephen Bremner wrote the statistical section and analysis plan.

Funding statement: This work was supported by Viiv Healthcare, reference number 207967. Neither the funder nor the sponsor had no role in the writing of the protocol or the conduct of the study.

Competing interests statement: The authors have no competing interests to declare.

Trial steering committee: Overall trial supervision is delivered through the Trial Steering Committee, on behalf of the Sponsor and Funding to ensure it is delivered according to Good Clinical Practice guidelines.

Patient and public involvement: Patients were involved in the study design and a patient representative sits on the Trial Steering Committee.

Figure Legends

Figure 1: CONSORT flow diagram for the HEPMARC study.

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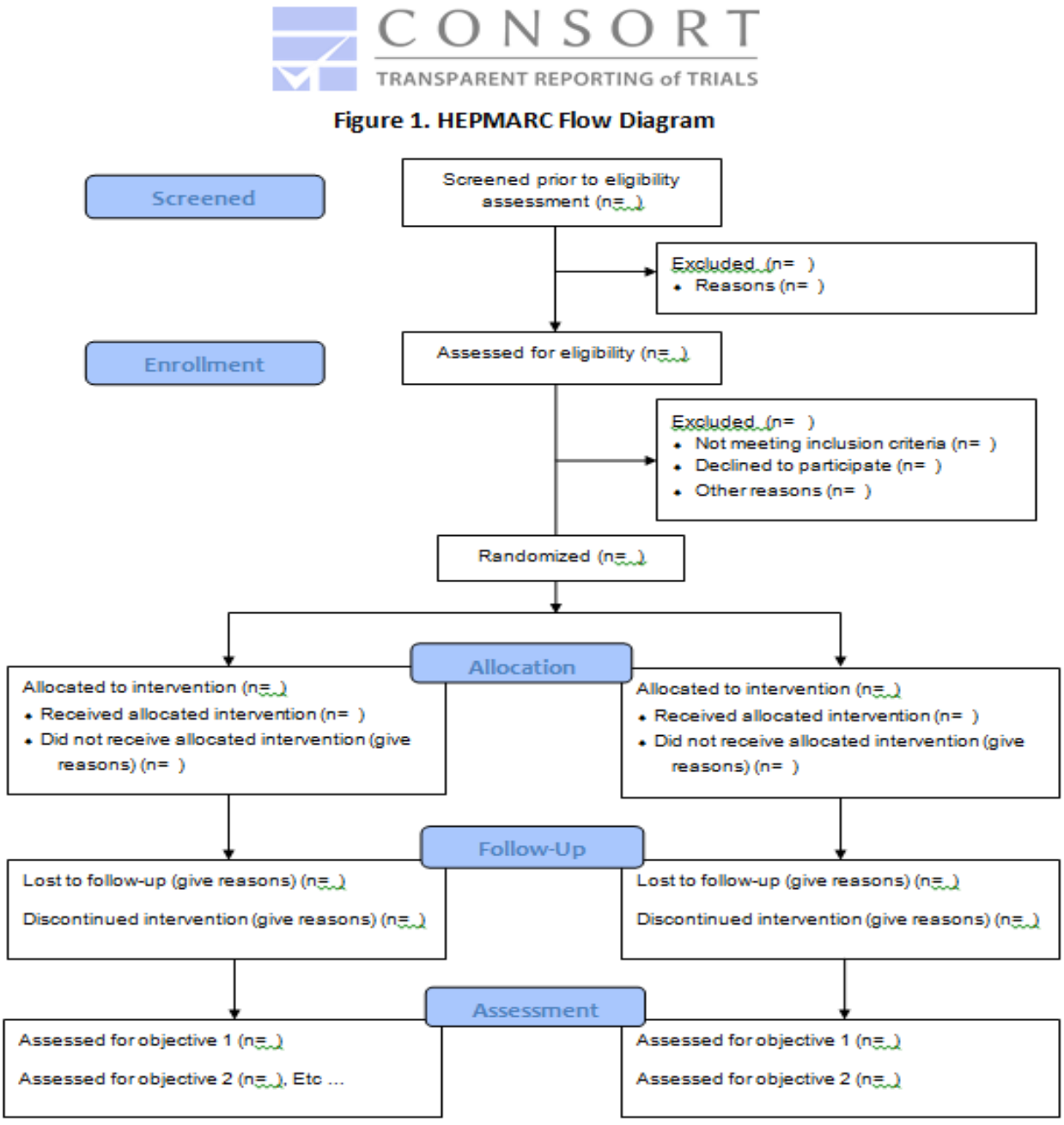

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	3
	2b	Specific objectives or research questions for pilot trial	4
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	12
	4c	How participants were identified and consented	12
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	15
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	17
Sample size	7a	Rationale for numbers in the pilot trial	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	12
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	12

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	NA
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	NA
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	NA
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	NA
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	NA
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	NA
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	1
Protocol	24	Where the pilot trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20
	26	Ethical approval or approval by research review committee, confirmed with reference number	2

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.