HEPMARC Study

Lay summary

Overview and Acknowledgements

The study team wishes to thank everyone who participated in the successful HEPMARC Study, without which its success could not have been achieved.

The HEPMARC Study was carried out between July 2018 and November 2021. The aim was to further understand the safety and acceptability of adding the drug maraviroc, that could have beneficial effects on liver disease, to the existing treatment combination for people living with both HIV and fatty liver. The study design was supported by a Patient and Public Involvement and Engagement (PPIE) panel. A PPIE representative was a member of the Trial Steering Committee. Overall, the study achieved its goals, showing that adding in maraviroc was safe and acceptable. This was down to the generosity and commitment of all those who agreed to take part.

Who had oversight and who conducted the study

The study was sponsored by University Hospitals Sussex NHS Foundation Trust and funded by ViiV Healthcare (UK). A Trial Management Group was organised by the Brighton & Sussex Clinical Trials Unit. In addition, they organised a Trial Steering Committee (TSC) and Independent Data Monitoring and Ethics Committee (DMEC) to monitor the conduct and safety of the research.

Participants were recruited across seven NHS hospitals at University Hospitals Sussex NHS Foundation Trust, Chelsea and Westminster Hospital NHS Foundation Trust, Barts Health NHS Trust, North Bristol NHS Trust, Liverpool University Hospitals NHS Foundation Trust, South Tees Hospitals NHS Foundation Trust and Nottingham University Hospitals NHS Trust. No competing interests were declared by the independent members of the TSC and the DMEC or any other study team member.

What is the medical condition we studied?

Non-alcoholic fatty liver disease (NAFLD, or fatty liver) is a common condition in the general public, whereby fat builds up within the liver. It is even more common in people living with HIV - around 1 in 3 people living with HIV are thought to have the condition.

In some people with fatty liver, it can progress to a more serious condition called non-alcoholic steatohepatitis (NASH) where inflammation takes place in the liver. This in turn can progress to scarring of the liver (fibrosis), which can in some cases become irreversible (cirrhosis). Irreversible scarring puts the person at risk of developing liver cancer or liver failure.

The total economic costs of diagnosed NASH in the UK, such as on people's health and productivity, are thought to be between £2 billion and £4 billion. NASH is also on course to become one of the commonest reasons for a liver transplant. The economic costs of diagnosed NASH for people with HIV in the UK are not known but likely to be more than £5 million.

The main treatments for people with fatty liver are improving the diet and increasing the amount of exercise, in order to lose weight. However, we know that achieving this is very difficult.

Unfortunately, as yet, there are not any approved medicines to treat fatty liver in people with HIV, and effective treatments are urgently needed.

The drug maraviroc, sometimes used as part of a combination of several antiretroviral drugs to treat HIV itself, has been shown to have beneficial properties for the liver. For example, it may reduce the level of liver inflammation and scarring.

We chose a study for people living with HIV and fatty liver, which involved adding in maraviroc to the existing antiretroviral drug combination. We decided to focus on people with HIV first, as we know maraviroc has already been used by people with HIV for over 10 years.

We wanted to see whether or not adding in maraviroc, usually taken twice a day, was acceptable, safe and well tolerated specifically in people with both HIV and fatty liver. Depending on the results of the study, we plan to do a further study in a larger number of people to see whether or not adding in maraviroc actually works in improving fatty liver in people with HIV.

How was the study carried out?

People with HIV and fatty liver, on antiretrovirals with an undetectable HIV viral load, were invited to take part at seven different hospitals in England.

People who were interested attended an eligibility appointment, where we checked that they were suitable to take part. For example, to make sure they did not have hepatitis B or hepatitis C, high alcohol use or severe liver scarring.

Eligible people were then invited to come back to their first study appointment. They were randomly divided into two groups using a computer program, which works as if by tossing a coin.

Group 1 continued their usual HIV antiretroviral medicines.

Group 2 added in maraviroc to their usual HIV antiretroviral medicines.

People then came back every 6 months for 2 years. At each visit, we checked on their symptoms, did blood tests and, on an annual basis, carried out scans of the liver and asked for questionnaires to be completed about people's quality of life. Effects of maraviroc on quality of life were measured by looking for any changes in particular activities of daily living and the number of days where fatty liver did not impact daily living. Effects on health were measured by changes in blood test results and liver scan readings.

What did the study results show?

Eighty people were initially interested in the study. Of these, 21 could not take part due to being thought not eligible, even before the formal eligibility appointment. This left 59 people who were formally assessed for eligibility.

Of these six were found not to be eligible. The remaining 53 all agreed to take part in the study. This exceeded our target of at least 50%.

Twenty-three people were allocated to the group where maraviroc was added to their usual treatment, and 30 people to the group taking usual treatment only. There were on average just

under three people enrolled into the study each month, over 18 months, which was greater than our target of at least two people consistently per month.

Around 90 per cent of people taking part were men, and 90% were white. This may not be representative of all people with HIV and fatty liver in the UK, although we do not yet have enough information to know this. In the UK general population, a greater proportion of people with fatty liver are likely to be women. The average age of people in the study was 54 years, ranging from 47 to 60 years. Metabolic syndrome, which is the term used to describe a combination of several conditions together - diabetes or high blood sugar, high blood pressure, high levels of fat in the blood, and obesity -, was seen in 48% of people in the maraviroc group and 53% of people in the non-maraviroc group.

Overall 83% of people managed to complete the study, greater than our target of at least 65%.

The data collected was very complete, with 96% of data collected at the 2 year visit. This was greater than our target of at least 80%.

There were no serious side effects from maraviroc, but five people (5/23, 22%) reported mild or moderate level side effects. Side effects were drowsiness with loss of appetite, worsening of restless leg syndrome, rash and vomiting, and two participants reported dizziness. Two people stopped maraviroc due to side effects (drowsiness with loss of appetite and worsening of restless leg syndrome) and one extra person stopped, finding the number of pills too much to take. In all five cases, the side effects went away. This took a few days for participants who continued with the treatment, and up to 3 weeks for participants who stopped the treatment.

Levels of fat and scarring in the liver were measured, using scans and blood tests over the 2 years. No evidence was found of a difference between the group taking maraviroc plus usual treatment and the group taking usual treatment alone. However, the trial was not designed to look for these differences, and the number of people on the study may have been too small to allow us to detect any differences.

Also, no difference was found between the two groups on: participants' weight, waist size, blood fat levels, blood sugar levels, and blood liver tests, nor on CD4 cell counts (used to check the health of the immune system in people infected with HIV) or on quality of life markers from questionnaires This could also have been due to the small number of participants on the study.

What happens next?

We were able to recruit enough people over time, despite the difficult circumstances created by the COVID pandemic and enough of those taking part were willing to complete the study.

People taking maraviroc managed almost all their doses, reporting no serious side effects.

Overall, maraviroc looked to be safe, acceptable and well tolerated for people with HIV and fatty liver. This provides a base and feasibility for setting up a larger study in future to assess whether adding maraviroc to usual antiretroviral treatment can improve fatty liver in people with HIV.

Study participants will be provided with a copy of the overall results of the study as described in this summary.