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Feasibility trial: temporary reduction in the number of antiviral medicines people with both HIV and HBV infection need to take

Submission date
24/05/2022

Recruitment status
No longer recruiting

Registration date
08/08/2022

Overall study status
Ongoing

Last Edited
14/04/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Most people with HIV take three antiviral drugs to control the virus. Increasingly, with modern antivirals, many people with HIV now only need to take two drugs. This can have benefits – for example, the commonly used drug tenofovir disoproxil fumarate (TDF) sometimes affects the kidneys or bones in the long term, so using a two drug combination without TDF might avoid these side effects. However, people who have both HIV and hepatitis B virus (HBV) together are usually recommended to take three drugs including tenofovir. This is because tenofovir is an effective treatment for both HIV and HBV. As part of an antiviral combination, tenofovir suppresses growth of both viruses, as shown by undetectable HIV and HBV viral loads in the blood. People who have dual infection with HIV and HBV and who don't take tenofovir are at risk of rising HBV viral loads causing liver inflammation (hepatitis). This can lead to tummy pain and vomiting and, if not treated, result in serious problems such as liver failure.

Recently, new HBV markers in blood, called pgRNA and HBcrAg, have been discovered. We can use these new markers to more accurately group people who have undetectable HBV viral loads on treatment into two groups: those with very low levels of HBV viral growth, where the pgRNA and HBcrAg are not detected, and those with low but ongoing levels of viral growth, where pgRNA or HBcrAg are detected. People with very low levels of viral growth can more likely stop tenofovir safely without the HBV viral load rising. In contrast, those with low levels of HBV viral growth should continue tenofovir. This has been shown in people with HBV who do not have HIV.

Who can participate?
Patients who are HIV-1 antibody and HBsAg positive and receiving tenofovir or entecavir.

What does the study involve?
We will recruit 12 people who have both HBV and HIV with undetectable viral loads of both viruses. In those with very low levels of HBV viral growth, as shown by the new HBV markers, we will stop tenofovir for 6 months and continue the other antiviral drugs. We will confirm whether

this treatment approach is safe by closely monitoring for any new medical problems and taking regular blood tests, including liver tests and HBV viral loads. After 6 months, tenofovir will be restarted.

What are the possible benefits and risks of participating?
Benefits:
There are unlikely to be direct benefits of stopping tenofovir for 6 months to people taking part in this study. However, if we find that temporarily stopping tenofovir is safe and acceptable, these results will help us set up a larger trial to provide more information as to whether this strategy of reducing treatment is effective. This in turn could improve the treatment options for people with HIV and HBV in future.
Risks:
1. The main risk relates to temporary discontinuation of the antiviral drug tenofovir leading to an increase in the level of HBV DNA and in turn elevated liver function tests and liver flare. However this risk will be minimised through multiple steps:
(a) selection of participants with well compensated liver disease who have undetectable levels of HBV DNA, HBV pgRNA and HBcrAg , indicating a very high level of HBV control with minimal risk of ALT flare off tenofovir or entecavir
(b) continuation of lamivudine or emtricitabine, which provides some anti-HBV activity
(c) close monitoring after tenofovir/entecavir withdrawal through liver tests and HBV DNA levels to pick up any liver flare early and reintroduce tenofovir/entecavir rapidly if needed to prevent any significant harm
(d) reintroduction of tenofovir/entecavir after 24 weeks in all patients.
(e) all participants will be given emergency phone numbers to contact should they have any significant symptoms out of working hours and can attend A&E if required.
2. Extra visits for blood tests additional to those of routine care will be undertaken with 10 visits over 7 months instead of the usual 2-3 visits in standard of care. Participants will have travel expenses reimbursed plus £200 in view of the inconvenience. In addition, telephone follow up will be held at weeks 6, 10, 14, 18 and 22 to identify any adverse events early.
3. There is some pain and discomfort associated with a blood test and patients will have multiple tests (10x) over 7 months. However, symptoms are likely to be minimal and the number of tests will be made clear to participants in the consent process.
4. Only those who are willing to use condoms or abstain during the trial will be eligible. This will ensure any detectable HBV or HIV during the withdrawal phase of the study, even though unlikely, will not be transmitted to sexual partners.

Where is the study run from?
King's College Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
May 2022 to October 2025

Who is funding the study?
British HIV Association (UK)
King's College Hospital Charity (UK)

Who is the main contact?
Dr Daniel Bradshaw, daniel.bradshaw2@nhs.net

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2021-005910-32

IRAS number
1004892

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
3633, IRAS 1004892

Study information

Scientific Title
REgimen optimisation: Feasibility of sImplifying NucleotidE therapy in HIV/HBV coinfection (REFINE-B study)

Acronym
REFINE-B

Study objectives
Primary objectives:
1. What proportion of people with HIV and HBV infection, who may be eligible to take part in the study and are asked if they would participate, agree to be assessed for eligibility?
2. What proportion of those who are screened to see if they are eligible to take part in the study have undetectable levels of the blood marker HBV pgRNA?
3. What proportion of those who are screened to see if they are eligible to take part in the study have undetectable levels of the blood marker HBcrAg?
4. What proportion of people who meet eligibility criteria after screening proceed to consent to the study?
5. What proportion of people who attend for the first (baseline) study visit are still in the study at 24 weeks?
6. What proportion of people report new or worsening of existing medical problems during the study?

Secondary objectives:
1. What proportion of individuals have a liver enzyme ALT or AST increase > 3x the level at the baseline visit, or >120U/L, at any point over 24 weeks?
2. What proportion of individuals have an HBV DNA level > 20 IU/ml at any point over 24 weeks?
3. What proportion of individuals have an HBV DNA level >200 IU/ml at any point over 24 weeks?
4. What proportion of individuals have an HIV-1 RNA level >50 c/ml at any point over 24 weeks?
5. What proportion of individuals have an HIV-1 RNA level >200 c/ml at any point over 24 weeks?
6. What proportion of individuals remain on simplified therapy at 24 weeks?
7. What is the change in HBsAg levels over 24 weeks?
8. What is the change in HBV pgRNA levels over 24 weeks?

9. What is the change in HBcrAg levels over 24 weeks?
10. What is the change in the quality of life assessed through questionnaires at baseline and 24 weeks?

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 07/07/2022, South Central - Berkshire B REC (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +442071048276; berkshireb.rec@hra.nhs.uk), ref: 22/SC/0184

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
People with both Human immunodeficiency virus - the virus which causes HIV/AIDS - and Hepatitis B Virus infections

Interventions
A single arm trial. All eligible participants will temporarily discontinue tenofovir or entecavir whilst continuing their other antiviral medicines. Individuals will be closely followed up for 6 months, with HBV, HIV and liver blood tests, before restarting tenofovir or entecavir.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Tenofovir disoproxil fumarate, entecavir monohydrate, tenofovir alafenamide

Primary outcome measure
Feasibility of temporary simplification of antiviral therapy in HIV/HBV coinfection as determined at 24 weeks by:
1. % of those approached who agree to be assessed for eligibility
2. % of those screened with undetectable HBV pgRNA

3. % of those screened with undetectable HBcrAg
4. % of those eligible after screen who consent to the study
5. % of those participating at 24 weeks
6. % of those with Adverse Events by 24 weeks

Secondary outcome measures
1. Proportion of individuals with a liver enzyme ALT or AST increase > 3x the level at the baseline visit, or >120 U/L, at baseline and weeks 2, 4, 8, 12, 16, 20, 24
2. Proportion of individuals with an HBV DNA level >20 IU/ml at baseline and weeks 2, 4, 8, 12, 16, 20, 24
3. Proportion of individuals with an HBV DNA level >200 IU/ml at baseline and weeks 2, 4, 8, 12, 16, 20, 24
4. Proportion of individuals with an HIV-1 RNA level >50 c/ml at weeks 4, 12 and 24
5. Proportion of individuals with an HIV-1 RNA level >200 c/ml at weeks 4, 12 and 24
6. Proportion of individuals remaining on simplified therapy at 24 weeks
7. HBsAg levels at baseline and weeks 12 and 24
8. HBV pgRNA levels at baseline and weeks 12 and 24
9. HBcrAg levels at baseline and weeks 12 and 24
10. Quality of life assessed through questionnaires at baseline and 24 weeks

Overall study start date
20/05/2022

Completion date
30/10/2025

Eligibility

Key inclusion criteria
1. HIV-1 antibody and HBsAg positive
2. Receiving
2.1. Dolutegravir + tenofovir disoproxil fumarate/tenofovir alafenamide + lamivudine /emtricitabine, OR
2.2. Darunavir with cobicistat/ritonavir + tenofovir disoproxil fumarate/tenofovir alafenamide + lamivudine/emtricitabine, OR
2.3. Other antiretroviral combination including lamivudine/emtricitabine and tenofovir disoproxil fumarate/tenofovir alafenamide, where discontinuation of tenofovir would not be expected to lead to loss of HIV control*, OR
2.4. A tenofovir-free antiretroviral combination including lamivudine/emtricitabine, plus entecavir
3. Antiretroviral regimen stable for ≥6 months
4. HBV DNA <20 IU/ml and HIV-1 RNA <50 c/ml for at least 3 years. Note that blips are permitted.
5. HBV pgRNA <1.65 log10 IU/ml at screen
6. HBcrAg < 3 log 10 IU/ml at screen
7. HBeAg negative and anti-HBe positive
8. HBsAg <10,000 IU/mL
9. CD4 >350 c/mm³
10. No significant hepatic fibrosis (Fibroscan ≤6kPa or liver biopsy <F2)
11. Provides written, informed consent
12. Age 18 years or older
13. Is willing to comply with protocol requirements

14. Is willing to use condoms or abstain during the trial
* This will be determined at the investigator's discretion

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
12

Total final enrolment
7

Key exclusion criteria
1. Other viral hepatitis coinfection including HDV antibody positive or HCV antigen or HCV RNA positive. Note HCV antibody positive with RNA or antigen negative is permitted.
2. History of known or suspected HBV resistance
3. History of HIV resistance to nucleos(t)ide reverse transcriptase inhibitors or integrase strand transfer inhibitors or protease inhibitors, where the resistance could be expected to compromise the efficacy of the tenofovir-free regimen
4. HIV-2
5. Non-viral hepatitis liver comorbidity including alcohol-associated, metabolic or autoimmune
6. Fibroscan >6kPa or liver biopsy ≥F2
7. ALT > 40 IU/L
8. Less than 18 years old
9. Pregnancy or breastfeeding
10. History of hepatocellular carcinoma
11. Any malignancy within previous 2 years, other than skin basocellular carcinoma
12. Non-HIV immunodeficiency including organ transplantation or medication-induced immunosuppression within previous 6 months
13. Any medical condition, including neurological or psychiatric conditions, which in the judgement of the investigator may impair a volunteer's ability to give informed consent or attend study visits

Date of first enrolment
21/08/2022

Date of final enrolment
01/03/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
King's College Hospital NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
https://www.kch.nhs.uk/

ROR
https://ror.org/01n0k5m85

Funder(s)

Funder type
Research organisation

Funder Name
British HIV Association

Alternative Name(s)
BHIVA

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
King's College Hospital Charity

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Other researchers will be able to request access to anonymised study data after the trial has finished, by a written request to the CI.

Intention to publish date
01/04/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
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IPD sharing plan summary
Available on request

Study outputs

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