ISRCTN83717528 https://doi.org/10.1186/ISRCTN83717528

RIVER - Research In Viral Eradication of HIV Reservoirs

Submission date
18/07/2014

Recruitment status
No longer recruiting

Registration date
03/09/2014

Overall study status
Completed

Last Edited
17/04/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Human Immunodeficiency Virus (HIV) affects the immune system, making you less able to fight infection and disease. Acquired Immunodeficiency Syndrome (AIDS) is the stage of HIV infection where the body is no longer able to fight life-threatening infection. Although treatment with antiretroviral therapy (ART) for HIV infection has markedly changed the life expectancy of people living with HIV, ART alone is unable to cure the infection. This is because the virus is able to remain dormant or latent for the life time of the infected person in certain cells of the body- called the viral reservoir. It is for this reason that if ART is stopped the virus will return. There have been some very rare cases where people appear to have been, to at least some extent, cured from HIV infection through either very complicated treatment or very early ART at the time of birth. Here, we will test whether if ART is started as soon as someone has become infected with the virus, given a vaccination to strengthen their immune responses to HIV and then another drug that forces virus out of the latently infected cells this may work in combination to reduce the number of latently infected cells. The fewer latently infected cells the fewer viruses there are to damage the immune system with a better chance of controlling the virus without needing lifelong ART. In the first place this study will test whether the combination of treatments (interventions) in very recent HIV infection has the ability to make the size of the viral reservoir much smaller; this is called a proof of concept study and, if it works, may lead on to further research.

Who can participate?
Adults aged 18 to 60 years who have been recently infected with HIV.

What does the study involve?
Participants are randomly allocated into one of two groups. Group 1 (intervention) are given the combination of three treatments. Group 2 (control) are given ART only. The number of cells infected with HIV for all participants are measured at 40 weeks and also at 42 weeks after the start of the treatment.

What are the possible benefits and risks of participating?
Taking the drugs used in this trial may result in a number of side effects. These include blood clots, dehydration, a drop in the number of red blood cells and platelets and high blood sugar.

Taking other medications with the drugs used in this study may result in other serious or potentially life-threatening side effects. Participants are asked to give blood samples a number of times during the trial. This can be uncomfortable but rarely results in major problems. Side effects, however, can include feeling faint, fainting, bruising or infection at the site where the blood has been taken.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
November 2015 to March 2023

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Sarah Fidler
s.fidler@imperial.ac.uk

Study website
https://www.mrcctu.ucl.ac.uk/studies/all-studies/r/river/

Contact information

Type(s)
Scientific

Contact name
Dr Sarah Fidler

Contact details
Winston Churchill Wing
St Mary's Hospital
Pread Street
London
United Kingdom
W2 1NY
-
s.fidler@imperial.ac.uk

Additional identifiers

EudraCT/CTIS number
2014-001425-32

IRAS number

ClinicalTrials.gov number
NCT02336074

Secondary identifying numbers
RIVER001

Study information

Scientific Title
Research In Viral Eradication of HIV Reservoirs - a two-arm (proof of concept) randomised phase II trial

Acronym
RIVER

Study objectives
We anticipate that following successful immunological priming there will be generation of vaccine induced HIV-specific CTLs that will then be capable of recognising HDACi-activated cells of the HIV reservoir, induced to express viral antigens ¨C a form of therapy never previously explored in vivo. Our strategy is entirely different from previous therapeutic vaccination approaches which have been largely unsuccessful. Immunological priming to conserved HIV proteins will drive CD8+ T lymphocyte recognition of latently-infected cells rendered immunogenic by HDACi. We anticipate that the viral antigens expressed by latently infected cells will be unable to adapt to, or escape from, the immune response as they will be expressed directly from chromosomal DNA, avoiding the steps of the viral life-cycle that facilitate immune-driven adaptation. We have chosen a prime-boost immunisation strategy with recombinant replication-defective chimpanzee adenovirus and modified vaccinia Ankara vectors, bearing conserved HIV antigens; these products have been shown to induce high titres of HIV-specific CD8+ T cells. In addition, these vaccines will drive immune responses against conserved regions of the virus that may be well preserved in individuals with PHI.

Primary HIV Infection (PHI) is a unique period when HIV proviral reservoir is smaller than in chronic disease, is likely to be more homogeneous than in later stage disease and hence more susceptible to immunological elimination, and provides an opportunity to use a vaccine to re-direct HIV-specific immune responses towards genetically fragile regions in the viral proteome. Immunisation in PHI should result in potent immune responses because ART initiated in PHI preserves CD4 function and early ART-mediated viral suppression limits viral diversification, reducing the chance of immune escape. The other key reason for conducting this trial in PHI is that, in some patients, an early sustained course of ART started very early in infection may induce a state of viral remission in which therapy can be stopped without any rebound viraemia. This has been most notably reported in the VISCONTI cohort in which post-treatment control was identified in 15.6% of selected individuals.

We hypothesise that the combination of HDACi with immunisation in ART-suppressed PHI will significantly impact the HIV reservoir .The primary end point of the combination study is 50% reduction of proviral HIV DNA between the intervention arm vs. standard therapy (ART alone). The secondary endpoints will examine the underlying mechanisms. Whilst each of the individual components of the proposed combination intervention has already been trialled in humans, there has never been a proof-of-concept study of this combination in recently infected individuals.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/12/2014, NRES Committee South Central - Oxford A (Temple Quay House, Health Research Authority, Bristol, BS1 6PN, United Kingdom; +44 (0)117 342 1380; oxforda.rec@hra.nhs.uk), ref: 14/SC/1372

Study design
Two-arm prospective 1:1 randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice, Hospital, Other

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
HIV

Interventions
Current interventions as of 04/02/2016:
This study will be a two-arm prospective 1:1 randomised controlled trial comparing the control arm (A) of ART alone, with the combination intervention arm (B) of ChAdV63. HIVconsv prime and MVA.HIVconsv boost; followed by a 28-day course of vorinostat (10 doses in total).

Previous interventions:
This study will be a two-arm prospective 1:1 randomised controlled trial comparing the control arm (A) of ART alone, with the combination intervention arm (B) of ChAdV63. HIVconsv prime and MVA.HIVconsv boost; followed by a 20-day course of vorinostat (10 doses in total).

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Current primary outcome measures as of 04/02/2016:
HIV total DNA from CD4 T cells average at post-randomisation week 16 and 18

Previous primary outcome measures:
HIV total DNA from CD4 T cells average at week 40 and 42

Secondary outcome measures
1. Clinical and laboratory adverse events
2. Further assessment of the HIV reservoir e.g. HIV integrated DNA
3. HIV cell associated RNA; plasma HIV RNA measured with an ultra-low copy assay i.e. with a threshold of <1 copy/ml
4. Studies of immune function including measuring the latently infected resting memory T-cells and cytotoxic immune responses
5. Changes in inflammatory biomarkers

Overall study start date
27/11/2015

Completion date
31/03/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 04/02/2016:
In total, 52 eligible individuals will be randomised across 6 UK collaborating centres according to the following criteria:
1. Aged 18 to 60 years old
2. Confirmed primary HIV-1 infection (PHI) by HIV antibody positive with a documented negative antibody test within the previous 3 months, antigen/antibody test positive or equivocal, or HIV-1 antibody positive with confirmed recent infection by PHE Recent Infection Testing Algorithm (RITA) avidity assay.
3. Willing to start immediate cART and be randomised to continue cART alone or cART plus intervention (HIV vaccines plus HDACi)
4. Hb 12 g/dL (Males), 11 g/dL (Females)
5. Weight ≥ 50 kg
6. Written informed consent; agree to long-term follow-up (at least 5 years)
7. Willing and able to comply with visit schedule and provide blood sampling

Previous inclusion criteria:
In total, 52 eligible individuals will be randomised across 6 UK collaborating centres according to the following criteria:
1. Aged 18 to 60 years old
2. Confirmed primary HIV-1 infection (PHI) by HIV antibody positive with a documented negative antibody test within the previous 3 months, antigen/antibody test positive or equivocal, or HIV-1 antibody positive with confirmed recent infection by PHE Recent Infection Testing Algorithm (RITA) avidity assay.
3. Willing to start immediate ART and be randomised to continue ART alone or ART plus intervention (HIV vaccines plus HDACi) at week 24
4. Hb 12 g/dL (Males), 11 g/dL (Females)
5. Weight ≥ 50 kg
6. Written informed consent; agree to long-term follow-up (at least 5 years)

Participant type(s)
Patient

Age group

Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
52

Total final enrolment
60

Key exclusion criteria
Current exclusion criteria as of 04/02/2016:
1. Women of child bearing potential (WCBP)
2. Planning to undertake egg donation to a surrogate in a woman who has intact ovaries and no uterus
3. Intention to donate sperm or father a child within 6 months of the intervention
4. Co-infection with hepatitis B (SAg +ve or detectable HBV DNA levels in blood) or C (HCV RNA +ve)
5. Any current or past history of malignancy including anal intraepitheilal neoplasia (AIN) or cervical intraepithelial neopalasia (CIN)
6. Concurrent opportunistic infection or other comorbidity e.g. ischaemic or other significant heart disease, malabsorption syndromes, autoimmune disease
7. Any contraindication to receipt of BHIVA recommended combination antiretrovirals
8. Any contraindication to receipt of the strand-transfer integrase inhibitor (INSTI), raltegravir
9. HIV-2 infection
10. Known HTLV-1 coinfection
11. Prior immunisation with any experimental immunogens
12. Current or planned immunosuppressive therapy (inhaled corticosteroids are allowed)
13. Any history of thromboembolism
14. Any inherited or acquired bleeding diathesis including gastric or duodenal ulcers, varices
15. Any bleeding diathesis including gastric or duodenal ulcers, varices
16. Concurrent or planned use of any drugs contraindicated with vorinostat i.e. antiarrhythmics; any other drugs that prolong QTc; warfarin, aspirin, sodium valproate
17. Prior intolerance of any of the investigational medicinal products in the protocol
18. Uncontrolled diabetes mellitus defined as an HBA1C>7%
19. Any congenital or acquired prolongation of the QTc interval, with normal defined as 0.40s (≤400 ms); bradycardia <55 bpm
20. Participation in any other clinical trial of an experimental agent or any non-interventional study where additional blood draws are required; participation in an observational study is permitted
21. Allergy to egg
22. History of anaphylaxis or severe adverse reaction to vaccines
23. Planned receipt of vaccines (including vaccines such as yellow fever; hepatitis B, influenza) within 2 weeks of the first vaccination in the study

24. Moderate to severe hepatic impairment as defined by Child-Pugh classification
25. ALT >5xULN
26. Platelets <150x109/L
27. eGFR <90 ml/min
28. uPCR >30 mg/mmol
29. Physical and Laboratory Test Findings: Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination and/or vital signs that the investigator believes is a preclusion from enrollment into the study
30. Active alcohol or substance use that, in the Investigators opinion, will prevent adequate adherence with study requirements
31. Insufficient venous access that will allow scheduled blood draws as per protocol

PARTICIPANT INCLUSION CRITERIA FOR RANDOMISATION

Additional criteria assessed at approximately week 22 to proceed to randomisation :
1. Participant is willing to continue on combination antiretroviral therapy
2. HCV PCR negative
3. Plasma HIV RNA <50 copies/mL (or <200 copies/mL for the Taqman Roche assay)
4. Laboratory parameters:
4.1. Platelet count ≥150x109/L
4.2. eGFR ≥90 ml/min
4.3. Hb ≥12 g/dL(Males), ≥11 g/dL(Females)
4.4. ALT <5 x ULN
4.5 uPCR ≤30 mg/mmol
4.6. In diabetics, HbA1C <7%
5. QTc interval normal, with normal defined as 0.40 s (400 ms)
6. Physical examination: No evidence of organ dysfunction or any clinically significant deviation from normal in physical examination and/or vital signs that in that in the opinion of the investigator would be a contraindication to randomisation.

ADDITIONAL INCLUSION CRITERIA FOR PARTICIPANTS IN ARM B POST-RANDOMISATION WEEK 08 DAY 1

Arm B participants must meet the following additional criteria at Post-Randomisation Week 8 Day 1 in order to commence vorinostat at Post-Randomisation Week 8 Day 3:
1. Participant is willing to continue on combination antiretroviral therapy.
2. Platelet count ≥150 x 109/L
3. eGFR >90 ml/min
4. Hb ≥12 g/dL(Males), ≥11 g/dL(Females)
5. ALT <5xULN
6. QTc interval normal, with normal defined as <0.40s (<400 ms)

Any out-of-range results from the above mean that the participant must not receive vorinostat. Participants in Arm B will then be followed for the rest of the study as per study visit schedule.

Previous exclusion criteria:
1. Women of child bearing potential (WCBP)
2. Planning to undertake egg donation to a surrogate in a woman who has intact ovaries and no uterus
3. Intention to donate sperm or father a child within 6 months of the intervention
4. Co-infection with hepatitis B (SAg +ve or detectable HBV DNA levels in blood) or C (HCV RNA +ve)
5. Any current or past history of malignancy including anal intraepitheilal neoplasia (AIN) or cervical intraepithelial neopalasia (CIN)
6. Concurrent opportunistic infection or other comorbidity e.g. ischaemic or other significant heart disease, malabsorption syndromes, autoimmune disease
7. Any contraindication to receipt of BHIVA recommended combination antiretrovirals

8. Any contraindication to receipt of the strand-transfer integrase inhibitor (INSTI), raltegravir
9. HIV-2 infection
10. Known HTLV-1 coinfection
11. Prior immunisation with any experimental immunogens
12. Current or planned immunosuppressive therapy (inhaled corticosteroids are allowed)
13. Any history of thromboembolism
14. Any inherited or acquired bleeding diathesis including gastric or duodenal ulcers, varices
15. Any bleeding diathesis including gastric or duodenal ulcers, varices
16. Concurrent or planned use of any drugs contraindicated with vorinostat i.e. antiarrhythmics; any other drugs that prolong QTc; warfarin, aspirin, sodium valproate
17. Prior intolerance of any of the investigational medicinal products in the protocol
18. Uncontrolled diabetes mellitus defined as an HBA1C>7%
19. Any congenital or acquired prolongation of the QTc interval, with normal defined as 0.40s (≤400 ms); bradycardia <55 bpm
20. Participation in any other clinical trial of an experimental agent or any non-interventional study where additional blood draws are required; participation in an observational study is permitted
21. Allergy to egg
22. History of anaphylaxis or severe adverse reaction to vaccines
23. Planned receipt of vaccines (including vaccines such as yellow fever; hepatitis B, influenza) within 2 weeks of the first vaccination at week 24 on study
24. Moderate to severe hepatic impairment as defined by Child-Pugh classification
25. ALT >5xULN
26. Platelets <150x109/L
27. eGFR <90 ml/min
28. uPCR >30 mg/mmol
29. Physical and Laboratory Test Findings: Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination and/or vital signs that the investigator believes is a preclusion from enrollment into the study
30. Active alcohol or substance use that, in the Investigators opinion, will prevent adequate adherence with study requirements
31. Insufficient venous access that will allow scheduled blood draws as per protocol

PARTICIPANT EXCLUSION CRITERIA FOR RANDOMISATION AT WEEK 24

Additional criteria at week 22 (or 23) to proceed to randomisation at week 24.

1. Participant is willing to continue on combination antiretroviral therapy
2. HCV PCR negative
3. Plasma HIV RNA <50 copies/mL (or <200 copies/mL for the Taqman Roche assay) at week 22
4. Laboratory parameters:
4.1. Platelet count ≥150x109/L
4.2. eGFR ≥90 ml/min
4.3. Hb ≥12 g/dL(Males), ≥11 g/dL(Females)
4.4. ALT <5 x ULN
4.5 uPCR ≤30 mg/mmol
4.6. In diabetics, HbA1C <7%
5. QTc interval normal, with normal defined as 0.40 s (400 ms)
6. Physical examination: No evidence of organ dysfunction or any clinically significant deviation from normal in physical examination and/or vital signs that in that in the opinion of the investigator would be a contraindication to randomisation.

ADDITIONAL INCLUSION CRITERIA FOR PARTICIPANTS IN ARM B AT WEEK 32 DAY 1

Arm B participants must meet the following additional criteria at Wk 32 Day 1 in order to commence vorinostat at Wk 32 Day 3:

1. Participant is willing to continue on combination antiretroviral therapy.

2. Platelet count ≥150 x 109/L
3. eGFR >90 ml/min
4. Hb ≥12 g/dL(Males), ≥11 g/dL(Females)
5. ALT <5xULN
6. QTc interval normal, with normal defined as <0.40s (<400 ms)
Any out-of-range results from the above mean that the participant must not receive vorinostat. Participants in Arm B will then be followed for the rest of the study as per study visit schedule.

Date of first enrolment
27/11/2015

Date of final enrolment
27/11/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Brighton and Sussex University Hospitals NHS Trust
Brighton
United Kingdom
BN1 6AG

Study participating centre
Central and North West London NHS Foundation Trust
London
United Kingdom
NW1 2PL

Study participating centre
Chelsea and Westminster NHS Foundation Trust
London
United Kingdom
SW10 9NH

Study participating centre

Guy's and St Thomas' NHS Foundation Trust
London
United Kingdom
SE1 9RS

Study participating centre
Imperial College Healthcare NHS Trust
London
United Kingdom
W2 1NY

Study participating centre
Royal Free Hospital NHS Foundation Trust
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
Imperial College London (UK)

Sponsor details
International Clinical Trials Research Management Office
Imperial College London
St Marys Campus
The Bays, 2nd Entrance
South Wharf Road
London
England
United Kingdom
W2 1NY

Sponsor type
University/education

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (UK)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date
31/03/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Dr Sarah Fidler (s.fidler@imperial.ac.uk or mrcctu.river@ucl.ac.uk). Written consent was required and obtained for all trial participants enrolled. Data was pseudo-anonymised using a randomised participant ID.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			16/10/2019	No	No
Results article	results	14/03/2020	23/09/2020	Yes	No
HRA research summary			28/06/2023	No	No
Other unpublished results	Final statistical report version 1.0	28/03/2019	17/04/2024	No	No
Other unpublished results	Long term follow up report version 1.0	27/03/2024	17/04/2024	No	No
Plain English results	version 1.0	20/07/2018	17/04/2024	No	Yes

Protocol file	version 7.0	14/06/2022	17/04/2024	No	No
Statistical Analysis Plan	version 1.0	04/12/2017	17/04/2024	No	No