ISRCTN04857074 https://doi.org/10.1186/ISRCTN04857074

A randomised controlled trial of a strategy of switching to boosted protease inhibitor monotherapy versus continuing combination antiretroviral therapy for the long-term management of HIV-1 infected patients who have achieved sustained virological suppression on highly-active antiretroviral therapy

Submission date
03/12/2007

Registration date
01/02/2008

Last Edited
16/02/2024

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

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

Plain English summary of protocol
http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=55

Study website
https://www.mrcctu.ucl.ac.uk/studies/all-studies/p/pivot/

Contact information

Type(s)
Scientific

Contact name
Dr Nicholas Paton

Contact details
Medical Research Council Clinical Trials Unit
222 Euston Road
London
United Kingdom
NW1 2DA
+44 (0)207 6704808
nick.paton@ctu.mrc.ac.uk

Additional identifiers

EudraCT/CTIS number
2007-006448-23

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
HTA 06/403/90; MRC ref: PIVOT

Study information

Scientific Title
A randomised controlled trial of a strategy of switching to boosted protease inhibitor monotherapy versus continuing combination antiretroviral therapy for the long-term management of HIV-1 infected patients who have achieved sustained virological suppression on highly-active antiretroviral therapy

Acronym
PIVOT

Study objectives
This trial aims to determine whether a strategy of switching to Protease Inhibitor (PI) monotherapy is non-inferior to continuing triple drug therapy, in terms of the proportion of patients who maintain all their available drug treatment options after at least 3 years of follow-up, and to compare clinical events, safety, toxicity and health economic parameters between the two strategies.

More details can be found at: http://www.nets.nihr.ac.uk/projects/hta/0640390
Protocol can be found at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0013/51403/PRO-06-403-90.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cambridgeshire 4 Research Ethics Committee, 28/04/2008, ref: 08/H0305/14

Study design
Open-label randomized controlled parallel-group strategic multi-centre trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)

Not specified

Study type(s)
Treatment, Efficacy

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 infection

Interventions
Patients randomised to the PI monotherapy group will stop other ART drugs and start/continue only on ritonavir-boosted PI monotherapy (selection of drug at discretion of physician or patient). Those who do not maintain complete virological suppression or who are unable to tolerate the PI (substitution for toxicity is allowed) will switch promptly back to their previous triple therapy. Patients randomised to the control group will continue their current regimen.

Duration of interventions: 5 years

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Protease Inhibitor (PI) monotherapy and standard ART

Primary outcome measure
Loss of future drug options, defined as the first occurrence of intermediate to high-level resistance to any one or more of the standard antiretroviral drugs (limited to licensed drugs in contemporary use) to which the patient's virus was considered to be sensitive at study entry (i.e. excluding drug resistance that was known to be present on previous resistance testing).

Duration of follow-up: 5 years (updated 12/09/2023: extended to 10 years, by amendment)

Secondary outcome measures
1. Serious drug or disease-related complication, defined as the first occurrence of one of the following in any individual patient:
1.1. Death from any cause
1.2. Serious AIDS-defining illness
1.3. Serious non-AIDS defining illness:
1.3.1. Acute myocardial infarction
1.3.2. Coronary artery disease requiring invasive procedures
1.3.3. Cirrhosis
1.3.4. Acute liver failure
1.3.5. End-stage renal disease
1.3.6. Stroke
1.3.7. Clinical acute pancreatitis

1.3.8. Severe lactic acidaemia
1.3.9. Severe facial lipoatrophy
1.3.10. Severe peripheral neuropathy
1.3.11. Non-AIDS malignancy
2. Adverse events, defined as the total number of Grade III and IV adverse events.
3. Virological rebound, defined in two ways using the "Time to Loss Of Virologic Response" (TLOVR) algorithm:
3.1. Two consecutive tests, taken at least 4 weeks apart, with a viral load more than 50 copies/ml (the first test must also be confirmed by re-testing the same blood sample). Patients who have virological rebound in the PI monotherapy arm, but re-suppress viral load to <50 copies/ml with re-introduction of NRTIs, will not count as failures; OR
3.2. As above, with at least one of the samples giving a viral load result more than 400 copies/ml.
4. CD4+ count change, defined as change from baseline in absolute CD4+ count.
5. Health-related Quality of Life change, defined as change from baseline in the mental and physical health summary scores.
6. Neurocognitive function change, defined as change from baseline in the neurocognitive function summary score.
7. Cardiovascular risk change, defined as change from baseline in the risk of cardiovascular disease calculated from the Framingham equation.
8. Health care costs, defined as the total cost of health care resources utilised per patient year.

Duration of follow-up: 5 years

Overall study start date
01/07/2008

Completion date
30/06/2014

Eligibility

Key inclusion criteria
1. Documented HIV infection on Enzyme-Linked Immuno-Sorbent Assay (ELISA) and confirmatory test.
2. Male or female patients, aged 18 years or more.
3. Receiving combination AntiRetroviral Therapy (ART) for at least 24 weeks with a regimen comprising 2 Nucleoside Reverse Transcriptase Inhibitor (NRTIs) and either an NonNucleoside Reverse Transcriptase Inhibitors (NNRTI) or a Protease Inhibitor (PI) (boosted or un-boosted).
4. No change in ART drugs in the 12 weeks prior to screening.
5. Plasma viral load <50 copies/ml for at least 24 weeks prior to screening (must have at least one documented result <50 copies/ml at more than 24 weeks prior to screening, and at least one documented result <50 copies/ml taken within 12 weeks prior to screening). A patient who has had one viral load "blip" to <200 copies/ml in the 24 weeks prior to screening may be included, provided that the two viral load tests that immediately preceded the blip and the two viral load tests that immediately followed the blip all gave results <50 copies/ml.
6. CD4+ count >100 cells/mm3 at screening.
7. Willing to continue unchanged or to modify antiretroviral therapy in accordance with the randomised assignment.
8. Likely to be resident in the UK for the full duration of the trial and willing to comply with trial visit schedule throughout the follow-up period.
9. Willing to provide written informed consent.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
400

Total final enrolment
587

Key exclusion criteria
1. Known major protease resistance mutation(s) documented on prior resistance testing if performed (prior resistance testing is not mandatory for trial participation).
2. Evidence of previous failure while taking a PI-containing regimen (defined as failure to achieve viral load <50 copies/ml within 24 weeks after starting a PI-containing regimen, or having two viral load results >50 copies/ml after having achieved a viral load <50 copies/ml on the PI-containing regimen).
3. Evidence of previous failure on an NNRTI-containing regimen (defined as in 2, above), unless a successful viral sequence (resistance test) was obtained following failure and within 60 days prior to the date of switching to a new fully suppressive regimen.
4. Previous allergic reaction to a PI.
5. Patient currently using or likely to require use of concomitant medication with known interaction with PIs including rifampicin, amiodarone, flecainide, bupropion, clozapine, ergotamine, mexilitine, midazolam, pethidine, pimozide, quinidine, sertindole, sildenafil, voriconazole, zolpidem, St John's Wort.
6. Patient requiring treatment with radiotherapy, cytotoxic chemotherapy, or is anticipated to need these during the trial period.
7. Treatment for acute opportunistic infection within 3 months prior to trial screening.
8. Pregnant or trying to become pregnant at the time of trial entry.
9. History of active substance abuse or psychiatric illness that, in the opinion of the investigator, would preclude compliance with the protocol, dosing schedule or assessments.
10. History of HIV encephalopathy with current deficit >1 in any domain of the Neuropsychiatric AIDS Rating Scale.
11. Past or current history of cardiovascular disease, or 10-year absolute coronary heart disease risk of >30% (calculated from the Framingham equation, and assessed using the Joint British Societies cardiovascular risk prediction charts).
12. History of insulin-dependent diabetes mellitus.
13. Patient currently receiving interferon therapy for Hepatitis C virus infection or considered likely to need such therapy during the course of the trial.
14. Co-infection with hepatitis B, defined as Hepatitis BsAg positive at screening or at any time since HIV diagnosis.
15. Any other active clinically significant condition, or findings during screening medical history

or examination that would, in the opinion of the investigator, compromise the patient's safety or outcome in the trial.
16. Anaemia (haemoglobin <9.5g/dl), neutropenia (absolute neutrophil count <1,000/mm3) or thrombocytopenia (platelet count <50,000mm3) at trial screening.
17. Alanine aminotransferase (ALT) or alkaline phosphatase greater than three times the upper limit of normal at trial screening.
18. Fasting plasma glucose >7.0mmol/L at trial screening.
19. Fasting plasma triglyceride level >3mmol/L at trial screening despite the use of lipid lowering drugs.
20. Fasting plasma total cholesterol >6.2mmol/L at trial screening despite the use of lipid lowering drugs.

Date of first enrolment
01/07/2008

Date of final enrolment
30/06/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Medical Research Council Clinical Trials Unit
London
United Kingdom
NW1 2DA

Sponsor information

Organisation
Medical Research Council (UK)

Sponsor details
MRC Clinical Trials Unit
222 Euston Road
London
United Kingdom
NW1 2DA
+44 (0)207 6704808
nick.paton@ctu.mrc.ac.uk

Sponsor type

Government

Website
http://www.ctu.mrc.ac.uk

ROR
https://ror.org/03x94j517

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from will be available for a period of 5 years commencing from the date of publication of the manuscript reporting the trial primary trial findings. Requests will be reviewed by the Trial Steering Committee for scientific validity prior to approval. Proposals should be submitted via the Chief Investigator (rmhznpa@ucl.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	31/07/2014		Yes	No
Results article	results	01/10/2015		Yes	No
Results article	results	01/03/2016		Yes	No
Results article	results	15/07/2016		Yes	No
Results article	sub-study results	01/07/2020	24/03/2020	Yes	No
Results article	8 year follow up	10/02/2024	16/02/2024	Yes	No