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Children with HIV in Africa – pharmacokinetics and acceptability of simple second-line antiretroviral regimens

Submission date
11/08/2017

Recruitment status
No longer recruiting

Registration date
20/10/2017

Overall study status
Completed

Last Edited
01/10/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Human immunodeficiency virus (HIV) is a virus that damages the cells in the immune system and weakens the body's ability to fight everyday infections and disease. HIV is treated with antiretroviral medications which stop the virus replicating in the body. In 2014, an estimated 823,000 HIV-infected children and adolescents aged up to 15 years were receiving anti-retroviral therapy (ART) in low- and middle-income countries. From 2015, World Health Organisation (WHO) guidelines recommended all HIV-infected adults and children take ART, regardless of the strength of their immune system (CD4 count) or their clinical status. The numbers of HIV-infected children on first-line ART in low-income countries is therefore likely to continue to increase, despite reductions in many countries of new infections through mother-to child transmission. The growing number of children on ART, coupled with increased detection of ART treatment failure, will increase the number of children needing to switch from their first ART drug treatment (first line) to second-line treatment. This raises the question of whether current second-line ART is optimal in terms of maximising children's health gains and minimising toxicity (side effects) from the treatment long-term, given the need for children to receive life-long ART. The current WHO-recommended second-line ART for children failing standard first-line treatment is not ideal, as it is based on a fixed dose combination drug which needs to be taken as whole (non-crushed) pills, mini-pill pellets or unpalatable liquid, and also interacts with anti-tuberculosis drugs. The aim of this study is to optimise second-line treatment in HIV-infected children by testing new antiretroviral drugs/formulations, in order to maximise long-term health gains.

Who can participate?
HIV-infected children aged 3-15 years weighing 14 kg or higher and failing first-line antiretroviral treatment

What does the study involve?
A screening visit involving blood tests is carried out to confirm that the child is eligible. Participants are then randomly allocated to one 'third-drug' and one 'NRTI based regimen'. The four 'third-drug' options are:

1. The current standard of care, called lopinavir/ritonavir (LPV/r)
2. A different drug which belongs to the same family as LPV/r, called atazanavir/ritonavir (ATV /r). This drug is used a lot in adults but has not previously been available as a single pill for children
3. A different drug that also belongs to the same drug family as LPV/r, called darunavir/ritonavir (DRV/r)
4. A drug which belongs to a different family, called dolutegravir (DTG)

The two 'NRTI based regimens' are:
1. The current standard of care, which is lamivudine (3TC) combined with whichever of abacavir (ABC) or zidovudine (ZDV) is not taken as first-line ART
2. A new drug called'TAF (tenofovir alafenamide) combined with a drug very similar to lamivudine called emtricitabine (FTC). TAF is a new type of an existing ART drug called tenofovir which is much kinder on people's bones and kidneys and so can be tested in children

Enough ART is prescribed for the participant to take daily until they are seen at their next clinic visit. Participants are followed up for a minimum of 2 years with clinic visits every 3 months. At the visits side effects and responses to treatment are carefully checked by a nurse and a doctor. A small amount of blood is collected and stored at each visit. The first children enrolled into the study, plus children who receive anti-tuberculosis treatment during the study have additional blood tests to look at levels of the antiretroviral drugs in their blood.

What are the possible benefits and risks of participating?
There may be no direct benefit to the children participating in the study. However, the information from this study will help to improve treatment for children with HIV in the future. These children need to be treated with second-line ART regardless of whether or not they participate in the study, and all treatment has risks and side effects. The common side effects of ART are stomach upsets, changes in the liver, problems with kidney and bones, difficulty sleeping, hypersensitivity reactions and tiredness. Participating children need to attend the clinic more frequently than if they were receiving treatment outside of the study. In addition there are some extra blood tests.

Where will the study be run?
1. University of Zimbabwe Clinical Research Centre (UZCRC), Harare (Zimbabwe)
2. University Teaching Hospital, Lusaka (Zambia)
3. Joint Clinical Research Centre (JCRC), Kampala (Uganda)
4. Mbarara Regional Referral Hospital (Uganda)
5. Arthur Davison Children's Hospital (Zambia)
6. Mpilo Central Hospital (Zimbabwe)
7. It is coordinated by the Medical Research Council Clinical Trials Unit at UCL, London (UK)

When is the study starting and how long is it expected to run for?
April 2017 to February 2023

Who is funding the study?
European and Developing Countries Clinical Trials Partnership (EU) with additional funding from Janssen Pharmaceutica (Belgium) and Gilead Sciences (USA)

Who is the main contact?
CHAPAS-4 Trial Management Team
mrcctu.chapas4@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Diana Gibb

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Contact details
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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Children with HIV in Africa – pharmacokinetics and acceptability of simple second-line antiretroviral regimens (CHAPAS-4 trial): a randomised controlled trial

Acronym
CHAPAS-4

Study objectives
The CHAPAS-4 trial will evaluate four new drugs/formulations (dolutegravir (DTG), tenofovir alafenamide (TAF), darunavir/ritonavir (DRV/r) and atazanavir/ritonavir (ATV/r)) to optimise treatment for children, and better harmonise with adult anti-retroviral therapy (ART). CHAPAS-4 will also evaluate options for second-line treatment given concomitantly with anti-tuberculosis drugs.

There are four main hypotheses:
1. DTG will provide superior virological suppression 96 weeks after starting second-line ART compared to second-line ART based on the bPIs LPV/r or ATV/r
2. DRV/r will provide superior virological suppression 96 weeks after starting second-line ART compared to second-line ART based on the bPIs LPV/r or ATV/r
3. ATV/r will provide non-inferior virological efficacy compared to lopinavir/ritonavir (LPV/r) in second-line ART
4. TAF will provide non-inferior virological efficacy compared to standard of care NRTIs in second-line ART

Ethics approval required

Old ethics approval format

Ethics approval(s)
1. UCL Research Ethics Committee, 21/07/2017, ref: 11205/001
2. Ethics approval sought from the appropriate national ethics committees in Uganda, Zambia and Zimbabwe

Study design
4x2 open-label factorial multi-centre randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Current interventions as of 12/05/2021:
A screening visit involving blood tests will be carried out to confirm that the child is eligible. Consented participants will then be randomly assigned to one 'third-drug' and one 'NRTI based regimen'. Randomisation lists will be prepared by the trial statistician using permuted blocks and sites will randomise using the trial database.

Specifically, one third drug from (randomised in a 1:1:1 ratio):
1. Research: dolutegravir (DTG) once-daily (OD) (an integrase inhibitor, INI)
2. Research: atazanavir/ritonavir (ATV/r) OD (boosted protease inhibitor, bPI)
3. Research: darunavir/ritonavir (DRV/r) OD (boosted protease inhibitor, bPI)
4. Standard of care: lopinavir/ritonavir (LPV/r) twice-daily (BD) (bPI)

Together with one nucleoside reverse transcriptase inhibitor (NRTI) backbone from (randomised in a 1:1 ratio):
1. Research: tenofovir-alafenamide (TAF) plus emtricitabine (FTC) OD
2. Standard of care: whichever of abacavir (ABC) (OD) or zidovudine (ZDV) (BD) has not been used first-line, plus lamivudine (3TC)

The route of administration will be oral and each drug will be dosed according to weight bands.

Enough ART will be prescribed for the participant to take daily until they are seen at their next clinic visit. Participants will be followed up for a minimum of 2 years with clinic visits every 3 months. At the visits side effects and responses to treatment will be carefully checked by a nurse and a doctor. A small amount of blood will be collected and stored at each visit. The first children enrolled into the study, plus children who receive anti-TB treatment during the study will have additional blood tests to look at levels of the antiretroviral drugs in their blood.

Children will be enrolled over 18 months and followed for 96 weeks, where they will be invited to enrol in extended follow-up for up to a further 2 years. Treatment will continue throughout the trial.

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Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dolutegravir, atazanavir, darunavir, ritonavir, lopinavir, tenofovir, alafenamide, emtricitabine, abacavir, lamivudine, zidovudine

Primary outcome(s)
Percentage of children alive with viral load <400 copies/ml, measured with lab test at baseline and weeks 6, 24, 48, 72, 96

Key secondary outcome(s))
Secondary outcome measures through 96 weeks are:
1. Percentage of children alive with viral load <50 and <1000 copies/ml, measured with lab test at baseline and weeks 6, 24, 48, 72, 96
2. Change in Stanford drug resistance, accumulation of new NRTI, PI and INI resistance-associated mutations in those with viral load > 400 copies/ml, measured with lab test at weeks 48, 96

3. Percentage modifying ART due to adverse events (AEs), incidence/type of grade 3/4 AEs and serious AEs, measured throughout the study as they occur (investigator reported, reviewed by blinded Endpoint Review Committee)
4. Changes in total, LDL, HDL cholesterol and triglycerides, measured using lab test at baseline, weeks 48, 96
5. Changes in renal function (creatinine clearance estimated using bedside-Schwartz) and bilirubin, measured using lab test at baseline, weeks 6, 24, 48, 96
6. Changes in absolute and percentage CD4, measured using lab test at baseline, weeks 24, 48, 72, 96
7. New or recurrent WHO 3 or 4 events or death, reported on an event form by the site clinician and initially clinically reviewed at MRC CTU by the trial physician and finally reviewed and adjudicated by an independent endpoint committee
8. Self-reported adherence and acceptability, measured using nurse-led questionnaires and pill counts at all visits (baseline, weeks 2, 6, 12, 24, 36, 48, 60, 72, 84, 96)

Other outcome measures are:
1. Hospital inpatient episodes and total days admitted through 96 weeks, measured throughout the study as they occur (investigator reported)
2. Changes in bone mineral density Z-scores assessed by calcaneal ultrasound at baseline, weeks 6, 24, 48, 72, 96 and in a sub-set of patients measured by DEXA scan at baseline, weeks 48, 96
3. Changes in weight-for-age, height-for-age and body mass index-for-age Z scores, measured at all visits (baseline, weeks 2, 6, 12, 24, 36, 48, 60, 72, 84, 96)
4. Body composition, measured by bioelectrical impedance analysis
5. Population pharmacokinetics, measured using lab test at weeks 6, 24, 48, 72, 96
6. Cost-effectiveness: at the end of the trial health economists will analyse data collected on medical resource utilisation (e.g. hospital stays, drug usage) with data on clinical, virological and quality of life outcomes

Completion date
01/02/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/07/2019:
1. HIV-infected currently receiving NNRTI containing regimen with abacavir-, zidovudine- or stavudine-containing NRTIbackbone and failing according to current WHO criteria:
1.1. Confirmed VL >1000 copies/ml after adherence counselling (confirmatory may be at screening) OR
1.2. CD4 criteria for failure OR
1.3. Clinical criteria for failure
2. Aged 3-15 years inclusive
3. Weight 14 kg or higher
4. Viral load >400 copies/ml at screening visit
5. Able to swallow trial drug tablets (all children will have been receiving tablets within first-line ART)
6. If female and reached menses, then negative pregnancy test at screening (and randomisation if randomisation >2 weeks from screening) and willing to adhere to highly effective methods of contraception if sexually active
7. Parents/carers give informed written consent; child provides informed written assent as appropriate based on age, knowledge of HIV status and local country guidelines

Previous inclusion criteria:
1. HIV-infected failing first-line treatment with abacavir-, zidovudine- or stavudine-containing NRTI+NNRTI regimens as per current WHO criteria
2. Aged 3-15 years inclusive
3. Weight 14 kg or higher
4. Viral load >400 copies/ml at screening visit
5. Able to swallow trial drug tablets (all children will have been receiving tablets within first-line ART)
6. Parents/carers give informed written consent; child provides informed written assent as appropriate based on age, knowledge of HIV status and local country guidelines

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
3 years

Upper age limit
15 years

Sex
All

Total final enrolment
919

Key exclusion criteria
Current exclusion criteria as of 17/07/2019:
1. History or presence of known allergy or other contraindication to the study drugs or their components
2. Treatment of co-morbidities, except TB, with significant drug interactions with the study drugs, requiring their dose adjustment
3. Breastfeeding
4. More than 3 months (>91 days) from the screening visit
5. Evidence of previous failure on LPV/r
6. Evidence of previous failure on both abacavir and zidovudine
7. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN), OR ALT ≥3xULN and bilirubin ≥2xULN
8. Patients with severe hepatic impairment or unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

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2. Treatment of co-morbidities, except TB, with significant drug interactions with the study drugs, requiring their dose adjustment
3. More than 3 months (>91 days) from the screening visit

Date of first enrolment
17/12/2018

Date of final enrolment
01/04/2021

Locations

Countries of recruitment
Uganda

Zambia

Zimbabwe

Study participating centre
University of Zimbabwe Clinical Research Centre (UZCRC)
Harare
Zimbabwe
1578 Avondale

Study participating centre
Joint Clinical Research Centre (JCRC)
Kampala
Uganda
PO Box 10005

Study participating centre
University Teaching Hospital
Lusaka
Zambia
PO Box 50110

Study participating centre

Joint Clinical Research Centre (JCRC) - Mbarara RCE
Mbarara Regional Referral Hospital
Mbarara
Uganda
-

Study participating centre
Arthur Davison Children's Hospital
Corner of Chiwanangala and Kalewa Road
Box 240227
Ndola
Zambia
-

Study participating centre
Mpilo Central Hospital
Vera Road
Mzilikazi
PO Box 2096
Bulawayo
Zimbabwe
-

Sponsor information

Organisation
University College London (UK)

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Research organisation

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)

Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Funder Name
Janssen Pharmaceutica NV

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Gibb (mrcctu.chapas4@ucl.ac.uk) after main publication following the Unit's Data Sharing SOP and after approval from the Trial Steering Committee, which has majority independent membership, for any approved analyses, all data is anonymised.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Second-line anchor drugs	14/05/2025	09/06/2025	Yes	No
Interim results article	Pharmacokinetic substudy secondary outcome results	06/06/2023	07/06/2023	Yes	No
Other publications	Substudy results	09/05/2023	15/06/2023	Yes	No
Other publications	Substudy results	20/07/2023	21/07/2023	Yes	No
Other publications	Pharmacokinetic sub-study	16/06/2025	17/06/2025	Yes	No
Other publications	Pharmacokinetic sub-study	26/08/2025	01/09/2025	Yes	No
Other publications	Population sub-study of the pharmacokinetics of ritonavir given to boost lopinavir, atazanavir, or darunavir	26/09/2025	01/10/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
	Second-line anchor drugs	15/04	09/01		

Preprint results		/2024	/2025	No	No
Preprint results	Second-line tenofovir alafenamide	21/04 /2024	09/01 /2025	No	No