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Comparing a two-drug fixed dose combination containing dolutegravir and lamivudine to the usual three-drug combination for maintenance treatment in children aged 2-14 years with HIV infection living in Europe, Thailand and Africa

Submission date
07/04/2020

Recruitment status
No longer recruiting

Registration date
30/04/2020

Overall study status
Ongoing

Last Edited
01/09/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims

Human immunodeficiency virus (HIV) is a virus that attacks the cells that help the body fight infection. This means that a person living with HIV may be more likely to become ill as they are not able to fight off other infections and cope with other illnesses such as certain cancers. If untreated, it can damage a person's immune system leading to acquired immune deficiency syndrome (AIDS). There are now many medicines available to treat HIV infection, although the virus cannot currently be completely cleared from the body. Treatment usually involves a combination of three or four different medicines that target different points in the virus's lifecycle.

This study aims to find out whether treating children and young people living with HIV with a new tablet made up of two anti-HIV medicines, dolutegravir (DTG) and lamivudine (3TC), is safe and as effective as the anti-HIV treatments currently used in routine practice. When medicines need to be taken for life, as for HIV infection, it is important that they not only work well, but also that they continue to be safe, with a low chance of long-term side effects, and that they are easy to take every day. Dolutegravir (DTG) is one kind of anti-HIV medicine that works very well and has few unwanted side effects. In many countries, it is now one of the recommended medicines for adults and young people who need to start anti-HIV medicines for the first time. Lamivudine is another anti-HIV medicine that is used in many HIV treatment combinations and has been shown to be safe with not many side effects. Both of these medicines are taken once a day. Anti-HIV treatment using a two-drug regimen including DTG and 3TC may offer treatment which is as safe and effective as currently used three-drug regimens.

Who can participate?

Children aged 2-14 years with HIV infection

What does the study involve?
This study will include 370 children and young people aged 2 to less than 15 years who are living with HIV and are being treated with anti-HIV medicines for the first time. They will be split into two groups, by chance, by a process called 'randomisation'. One group will continue to receive the anti-HIV medicines that they are already taking according to routine practice in their country (standard of care, or SOC). The second group will change to the new combination of medicine, dolutegravir and lamivudine (with the combination written usually as “DTG/3TC”). Depending on their weight, those in the second group will be able to take the new medicine either as one tablet a day or as a small number of dispersible tablets that are also taken once a day. All children and young people in the study will have regular clinic assessments that are at a similar frequency to the clinic visits that they would have outside of the study. Blood tests will be performed to check that the medicine is safe and, at some visits, participants and their carers will also be asked to answer some questions on how they feel about taking their medicine. The research team will follow all children and young people until the last participant who joins the study has been in the study for 96 weeks.

What are the possible benefits and risks of participating?
Possible benefits:
It is hoped that children and young people will be helped by taking part in this study, but this cannot be guaranteed. The knowledge learned will definitely help other children with HIV in the future, as the information gained from this study will help to improve treatment for children and young people across the world who are living with HIV and, in future, it may mean that children have the chance to change to medicines that are easier to take.
Children allocated DTG/3TC might get fewer side effects long term as they are only taking two medicines, not three or four. Children in the DTG/3TC group who are able to take the adult tablet will only have to take one small tablet a day. Other children in the DTG/3TC group will take 3 to 6 dispersible tablets that should be mixed with a small amount of water.
The number of study visits is similar to the number of visits that most children living with HIV would have if they were not taking part in the study. All children, whether they are in the DTG /3TC or SOC group, will be watched very carefully for any side effects and responses to the treatment.

Possible risks:
All treatments can have unwanted side effects. The most common side effects are non-severe and for DTG and 3TC these are headache, feeling and being sick, diarrhoea, abdominal pain, rash, joint pains and feeling weak.
There is very little information about the effect of DTG in unborn babies. In a recent study from Botswana, approximately 3 in 1000 women who were taking DTG when they became pregnant had babies with neural tube defect (a serious brain and/or spine problem). In the same study, approximately 1 in 1000 women who were taking other antiretrovirals had babies with neural tube defects, which is similar to what is seen in women without HIV. These problems happen very early in pregnancy, before many women even know that they are pregnant. Researchers do not know for sure if this occurs because of DTG. The study in Botswana and other similar studies are ongoing.

Where is the study run from?
The Penta Foundation (Italy)

When is the study starting and how long is it expected to run for?
November 2019 to September 2026

Who is funding the study?
ViiV Healthcare (UK), which makes the dolutegravir + lamivudine combination drug

Who is the main contact?
1. Alessandra Nardone (public contact), alessandra.nardone@pentafoundation.org
2. Anna Turkova (scientific contact), a.turkova@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Mrs Anna Turkova

ORCID ID
https://orcid.org/0000-0002-7008-4145

Contact details
MRC Clinical Trials Unit at UCL
Infections Theme
90 High Holborn
London
United Kingdom
WC1V 6LJ
+44 (0) 207 670 4658
a.turkova@ucl.ac.uk

Type(s)
Public

Contact name
Miss Alessandra Nardone

Contact details
Fondazione Penta Onlus
Corso Stati Uniti 4
Padova
Italy
35127
+39 0498215447
Alessandra.Nardone@pentafoundation.org

Additional identifiers

Clinical Trials Information System (CTIS)
2020-001426-57

Integrated Research Application System (IRAS)
1005245

ClinicalTrials.gov (NCT)
NCT04337450

Protocol serial number
D3, IRAS 1005245

Study information

Scientific Title
A randomised non-inferiority trial with nested PK to assess DTG/3TC fixed-dose formulations for the maintenance of virological suppression in children with HIV infection aged 2 to <15 years

Acronym
D3 (Penta21)

Study objectives
DTG/3TC will provide non-inferior virological efficacy to a standard three-drug ART regimen.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 02/12/2021, Durban (-, -, -, South Africa; None provided; not@provided.com), ref: None provided

2. approved 03/04/2023, Hospital Sant Joan de Déu (-, -, -, Spain; None provided; not@provided.com), ref: None provided

3. approved 02/12/2021, Chiangrai Prachanukroh Hospital (-, -, -, Thailand; None provided; not@provided.com), ref: None provided

4. approved 03/12/2021, JCRC (-, -, -, Uganda; None provided; not@provided.com), ref: None provided

5. approved 24/06/2023, IRAS (-, -, -, United Kingdom; None provided; not@provided.com), ref: None provided

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions

Current interventions as of 01/09/2025:
This study will include 370 children and young people aged 2 to less than 15 years old who are living with HIV and are being treated with anti-HIV medicines for the first time. Participants will be split into two groups, by chance, by a process called "randomisation". One group will continue to receive the anti-HIV medicines already taken according to country-specific routine practice. The second group will change to the new combination of medicine, dolutegravir and lamivudine (with the combination written usually as "DTG/3TC"). Depending on their weight, participants in the second group will be able to take the new medicine either as one tablet a day or as a small number of dispersible tablets that are also taken once a day. All children and young people in the study will have regular clinic assessments that are at a similar frequency to the clinic visits that participants would have outside of the study. Blood tests will be performed to check that the medicine is safe and at some visits, participants and their carers will also be asked to answer some questions on how they feel about taking their medicine. All children and young people will be followed until the last participant to join the study has been in the study for 96 weeks.

After 96 weeks, children who were randomised to the DTG/3TC arm may decide to enter extended follow-up, continuing to receive ViiV-supplied DTG/3TC at the end of the randomised phase.

Active Comparator: Standard-of-care (SOC)
2 nucleo(s/t)ide reverse transcriptase inhibitor (NRTI) and a third (anchor) drug (either an integrase strand transfer inhibitor (INSTI), a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI)

Experimental: DTG/3TC
Dolutegravir (DTG) and lamivudine (3TC)
Once-daily DTG/3TC fixed-dose combination dispersible or film-coated tablets dosed using the WHO weight bands criteria.

Previous interventions:
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Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Dolutegravir (DTG) and lamivudine (3TC)

Primary outcome(s)
Proportion of children with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50 copies/ml) assessed all real-time and retrospective viral loads measured by PCR after randomisation and up to the week 96 assessment

Key secondary outcome(s))
1. Proportion of children with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50 copies/ml assessed using PCR using all real-time and retrospective viral loads) after randomisation and up to the week 48 assessment
2. Proportion of children with confirmed HIV-1 RNA ≥50 copies/ml assessed using PCR at weeks 48 and 96 (modified FDA snapshot) using cross-sectional viral load data within the respective visit window in addition to data on treatment changes prior to the visit window
3. Proportion of children with HIV-1 RNA ≥50 copies/ml assessed using PCR at weeks 24, 48 and 96 (including blips and confirmed measures ≥50 copies/ml) using cross-sectional viral load data closest to the respective scheduled visit date
4. New resistance-associated mutations identified using DNA sequencing in those with confirmed HIV-1 RNA ≥50 copies/ml through to the end of follow-up based on baseline resistance data and resistance data at or post-failure
5. Time to any new or recurrent WHO 3 or WHO 4 event or death assessed using clinical reports of these events completed by treating clinicians
6. CD4 count assessed using standard laboratory tests at baseline and weeks 24, 48 and 96
7. Incidence of serious adverse events, grade 3 and 4 clinical and laboratory adverse events assessed using clinical reports of these events completed by treating clinicians and laboratory data from the start to the end of participation
8. Incidence of adverse events leading to discontinuation or modification of the treatment regimen assessed using clinical reports of these events completed by treating clinicians and longitudinal data on antiretroviral treatment from the start to the end of participation
9. Proportion of children with a change in ART for toxicity or switch to second-line through to the end of follow-up assessed using longitudinal data on antiretroviral treatment and adverse event data/viral load data from the start to the end of participation
10. Blood lipids (total cholesterol, LDL, HDL, triglycerides) assessed using standard laboratory tests at baseline and weeks 48 and 96
11. Creatinine clearance estimated by measurement of eGFR (estimated glomerular filtration rate) using the bedside-Schwartz method to weeks 48 and 96
12. Adherence as assessed by participant/care-giver questionnaires, including the D3 Medicine Acceptability Questionnaire (adapted from the Medicine Acceptability Questionnaire) at weeks

0, 4, 24, 48, 72 and 96 then every 24 weeks until the end of study and D3 Adherence Questionnaire (adapted from an in-house questionnaire used in the ODYSSEY study) throughout the study
13. Sleep quality assessed using the D3 Sleep Questionnaire (adapted from Pittsburgh Sleep Quality Index) at weeks 0, 4, 24, 48, 72 and 96 then every 24 weeks until the end of study
14. Mood assessed using the D3 Mood Questionnaire (adapted from The Revised Child Anxiety and Depression Scale) at weeks 0, 4, 24, 48, 72 and 96 then every 24 weeks until the end of study
15. Suicidality assessed using the Columbia-Suicide Severity Rating Scale Screener (which is not validated but provided by the The Columbia Lighthouse Project like the C-SSRS) throughout the study

Completion date
30/09/2026

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 01/09/2025:
Inclusion criteria for the main trial:
1. HIV-1-infected children who are virologically suppressed for at least the last 6 months prior to enrolment
2. Aged 2 to <15 years
3. Weight 6 kg or higher
4. Children on the same triple-drug PI/r-, NNRTI- or INSTI-containing ART regimen for at least 3 months
5. Girls who have reached menarche must have a negative pregnancy test at screening and randomisation
6. Girls who are sexually active must be willing to adhere to highly effective methods of contraception
7. A parent or legal guardian is willing and able to give informed consent on behalf of the child as per national legislation and willing to adhere to the protocol
8. Participant is willing to give informed assent if the trial site clinician deems them old enough and able to understand the age-appropriate information about participation in the study

Inclusion Criteria for the extended follow-up:
1. Participants remain on DTG/3TC at the end of the randomised phase, and in the opinion of the treating physician, derive ongoing benefit from DTG/3TC
2. Participants have no access to weight-appropriate DTG/3TC formulation via their national programme

Previous key inclusion criteria:
1. HIV-1-infected children who are virologically suppressed for at least the last 6 months prior to enrolment
2. Aged 2 to <15 years
3. Weight 6 kg or higher
4. Children on the same triple-drug PI/r-, NNRTI- or INSTI-containing ART regimen for at least 3 months
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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 years

Upper age limit
15 years

Sex
All

Total final enrolment
386

Key exclusion criteria
Current key exclusion criteria as of 01/09/2025:
Exclusion criteria for the main trial:
1. Any previous switch in ART regimen for virological, immunological or clinical treatment failure
2. Any changes in ART in the last 6 months for reasons other than due to child's growth, drug stock-outs, changes in country guidelines and treatment simplification
3. Evidence of previous resistance to 3TC or INSTI
4. Any prior use of regimens consisting of single or dual NRTIs with the exception of a course of zidovudine for prevention of mother-to-child transmission (PMTCT)
5. Known allergy or contraindications to dolutegravir or lamivudine
6. Diagnosis of tuberculosis and on anti-tuberculosis treatment; children can be enrolled after successful tuberculosis treatment
7. Treatment of co-morbidities with drugs which have significant interactions with antiretroviral treatment, requiring dose adjustment of the study drugs (children can be enrolled after the illness resolves)
8. Randomisation visit more than 12 weeks after the most recent screening visit
9. Evidence of hepatitis B virus (HBV) infection with no protective immunity against hepatitis B: participants positive for HBsAg or HBcAb and negative for HBsAb
10. Anticipated need for hepatitis C virus (HCV) therapy with interferon-based regimen prior to the primary endpoint.
11. Screening ALT equal to 3 or more times the upper limit of normal AND bilirubin equal to 2 or more times the upper limit of normal (ALT ≥3xULN AND bilirubin ≥2xULN)
12. Screening ALT equal to 5 or more times the upper limit of normal ALT (≥5xULN)
13. 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), or known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
14. Screening creatinine clearance <50 ml/min/1.73 m2
15. Patients aged ≥6 years at moderate or high risk of suicide as determined by Columbia-Suicide Severity Rating Scale (C-SSRS)
16. Girls who are pregnant or breastfeeding
17. Children who are in the legal custody of the state and do not have a parent or guardian able to provide informed consent on their behalf

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1. Any previous switch in ART regimen for virological, immunological or clinical treatment failure
2. Any changes in ART in the last 6 months for reasons other than due to child's growth, drug stock-outs, changes in country guidelines and treatment simplification
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4. Any prior use of regimens consisting of single or dual NRTIs with the exception of a course of zidovudine for prevention of mother-to-child transmission (PMTCT)
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6. Diagnosis of tuberculosis and on anti-tuberculosis treatment; children can be enrolled after successful tuberculosis treatment
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12. Screening ALT equal to 5 or more times the upper limit of normal ALT (≥5xULN)
13. 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), or known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
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15. Patients aged ≥6 years at moderate or high risk of suicide as determined by Columbia-Suicide Severity Rating Scale (C-SSRS)
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Date of first enrolment
30/04/2021

Date of final enrolment
28/09/2023

Locations

Countries of recruitment
United Kingdom

England

South Africa

Spain

Thailand

Uganda

Study participating centre
Chris Hani Baragwanath Hospital
Perinatal HIV Research Unit
Soweto
South Africa
1864

Study participating centre
Klerksdorp/Tsepong Hospital Complex
Perinatal HIV Research Unit
Matlosana
South Africa
2575

Study participating centre
King Edward VIII Hospital
Durban International Clinical Research Site
Parkhome
Gate 1-King Edward VIII Hospital
Umbilo Road
Congella
Durban
South Africa
4013

Study participating centre
Hospital Universitario 12 de Octubre
Madrid
Spain
28041

Study participating centre
Hospital Sant Joan de Déu
Espluges
Spain
08950

Study participating centre
Prapokklao Hospital
Chantaburi
Thailand
22000

Study participating centre
Chiangrai Prachanukroh Hospital
Chiang Rai
Thailand
57000

Study participating centre
Nakornping Hospital
Chiang Mai
Thailand
50000

Study participating centre
Khon Kaen Hospital
Khon Kaen
Thailand
40000

Study participating centre
Kalasin Hospital
Kalasin
Thailand
46000

Study participating centre
Joint Clinical Research Centre (JCRC)
Kampala

Uganda
00256

Study participating centre
Makerere University
Makerere University – John Hopkins University Research Collaboration
Kampala
Uganda
23491

Study participating centre
Baylor College of Medicine Children's Foundation - Uganda
Kampala
Uganda
72052

Study participating centre
Great Ormond Street Hospital for Children
London
United Kingdom
WC1N 3JH

Study participating centre
Birmingham Heartlands Hospital
University Hospitals Birmingham NHS Foundation Trust
Birmingham
United Kingdom
B9 5SS

Study participating centre
St Mary's Hospital
Imperial College Healthcare Trust
London
United Kingdom
W2 1NY

Sponsor information

Organisation
PENTA Foundation

ROR
https://ror.org/00d7mpc92

Funder(s)

Funder type
Industry

Funder Name
ViiV Healthcare

Alternative Name(s)
ViiV Healthcare Limited

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The D3 trial data will be held at MRC CTU at UCL. The MRC CTU at UCL encourages optimal use of data by employing a controlled access approach to data sharing. All requests for data are considered and can be initiated by contacting mrcctu.ctuenquiries@ucl.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		16/04/2024	22/04/2024	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes