

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	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 30/04/2020	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 22/04/2024	Condition category Infections and Infestations	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

Plain English Summary

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 April 2025

Who is funding the study?

ViiV Healthcare (UK), which makes the dolutegravir + lamivudine combination drug

Who is the main contact?

1. Gabija Morkunaite (public contact), Gabija.Morkunaite@pentafoundation.org

2. Anna Turkova (scientific contact), a.turkova@ucl.ac.uk

Contact information

Type(s)

Scientific

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Additional identifiers

EudraCT/CTIS number

2020-001426-57

IRAS number

1005245

ClinicalTrials.gov number

NCT04337450

Secondary identifying numbers

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 hypothesis

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

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a participant information sheet.

Condition

HIV infection in children

Interventions

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.

Active Comparator: Standard-of-care (SOC)

2 nucleoside 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 WHO weight bands criteria.

Intervention Type

Drug

Pharmaceutical study type(s)

Pharmacokinetic, Pharmacogenomic, Pharmacoeconomic

Phase

Phase II/III

Drug/device/biological/vaccine name(s)

Dolutegravir (DTG) and lamivudine (3TC)

Primary outcome measure

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

Secondary outcome measures

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

Overall study start date

04/11/2019

Overall study end date

30/07/2025

Eligibility

Participant 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
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

Participant type(s)

Patient

Age group

Child

Lower age limit

2 Years

Upper age limit

15 Years

Sex

Both

Target number of participants

370

Total final enrolment

386

Participant exclusion criteria

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 $\geq 3 \times \text{ULN}$ AND bilirubin $\geq 2 \times \text{ULN}$)

12. Screening ALT equal to 5 or more times the upper limit of normal ALT ($\geq 5 \times \text{ULN}$)

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 $< 50 \text{ ml/min/1.73 m}^2$

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

Recruitment start date

30/04/2021

Recruitment end date

28/09/2023

Locations

Countries of recruitment

England

South Africa

Spain

Thailand

Uganda

United Kingdom

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
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Gate 1-King Edward VIII Hospital
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Congella
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Study participating centre
Hospital Universitario 12 de Octubre
Madrid
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28041

Study participating centre
Hospital Sant Joan de Déu
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08950

Study participating centre
Prapokklao Hospital
Chantaburi
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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
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Study participating centre
Kalasin Hospital
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Study participating centre
Makerere University
Makerere University – John Hopkins University Research Collaboration
Kampala
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Study participating centre
Baylor College of Medicine Children's Foundation - Uganda
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Study participating centre
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Sponsor information

Organisation
Fondazione Penta Onlus

Sponsor details
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Sponsor type
Charity

Website
<https://penta-id.org/>

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

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal.

Intention to publish date

31/12/2025

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 mrccctu.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