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Breather Plus: Short-cycle HIV therapy (5 days on/2 days off) in young people (12-19 years) with chronic HIV infection in sub-Saharan Africa

Submission date
03/02/2020

Recruitment status
No longer recruiting

Registration date
17/02/2020

Overall study status
Completed

Last Edited
22/05/2026

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
The goal of HIV treatment is to make sure the HIV virus in the blood remains very low. This is called having an undetectable viral load (virological suppression). If this goal is achieved and sustained life-long, then people living with HIV can live a healthy life, with a normal life expectancy. However, it is challenging to take medication every single day for life. This may be an even bigger challenge for teenagers living with HIV. In an earlier study, called BREATHER, having weekends off HIV medicines using a combination that including an HIV treatment called efavirenz, was found to be safe and effective in HIV-infected young people. The young people taking part in the study also liked having weekends off their treatment.

BREATHER Plus builds on what the researchers found in the BREATHER study. But, instead of looking at weekends off efavirenz-based HIV treatment, the researchers are looking at weekends off a different HIV treatment called dolutegravir.

In BREATHER Plus the researchers will compare two different ways of taking HIV medicines, that include the HIV medicine dolutegravir:
• Short cycle therapy: where people taking part will take all their HIV medicines during the week but stop taking them at weekends (either Friday and Saturday or Saturday and Sunday)
• Continuous Treatment: where people taking part will take all their HIV medicines every day without any interruptions.

Who can participate?
Patients aged 12 – 19 years who are HIV infected and have been on anti-retroviral therapy for over one year.

What does the study involve?
People joining BREATHER Plus will have an equal chance of being randomised to one of the two groups. The first 30 people who enter the trial, will be asked to come back every week for the first 4 weeks. There will be a blood test at these visits. The test will be to measure the amount of HIV virus (viral load) in the blood. In general, people taking part in the trial will be asked to visit

the clinic every 8 weeks until the last participant has been in the trial for 96 weeks. We will ask questions about health and wellbeing and your mood at each visit. at some of the visits. For girls who have started their periods, we will do a pregnancy test at each visit. At most visits, we will take a blood sample for routine tests. Some of the blood sample will be stored and looked at later to measure the amount of HIV virus in the blood. We will also take an additional blood and urine samples once a year, these stored samples will be used to look at the health of people's kidneys, heart and other organ systems. Everyone will get their viral load result once a year, like people not in the study. In a small group of people we will check how well their pills are being taken using a special pill bottle that triggers every time the bottle is opened and the pills are taken. These special bottles are called MEMSCAPS. The MEMSCAPS will be used in one small group of participants in the first year of the study for 6 months, and a different group in year 2 for 6 months. This is to closely monitor how well people manage to stick to taking their pills as they should in this trial. In addition to the main trial, there are several two sub-studies (smaller studies within the main trial), which people taking part will be invited to take part in. Participants in BREATHER Plus will be invited to take part in a social science substudy where there are interviews to find out how people feel about HIV and their medication, and a mood substudy, to find out if people are having problems with feeling down or worried about HIV, their medication and other things going on in their lives. These two substudies require additional consent, so people can decide if they do or don't want to take part in these, and it won't affect being in the BREATHER Plus trial.

What are the possible benefits and risks of participating?
Benefits: Making treatment better and easier to take for all young people living with HIV, a reduced dose of medicine and fewer side effects.
RIsks: The weekends off may not control the virus as well as taking medicines every day. This could mean viral load goes up, and participants have to change to different medicines to bring it down to undetectable.

Where is the study run from?
1. Baylor College of Medicine Children's Foundation (Uganda)
2. Joint Clinical Research Centre (JCRC) (Uganda)
3. University of Zimbabwe Clinical Research Centre (UZCRC)
4. Moi University, AMPATH Centre (Kenya)
5. Department of Paediatrics and Child Health, King Edward VIII Hospital (South Africa)

When is the study starting and how long is it expected to run for?
October 2020 to December 2025.

Who is funding the study?
1. European and Developing Countries Clinical Trials Partnership
2. Medical Research Council (UK)

Who is the main contact?
Prof. Sarah Pett, s.pett@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name

Prof Sarah Pett

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Additional identifiers

Protocol serial number
129629

Study information

Scientific Title
Breather Plus: A randomised open-label 2-arm, 96-week trial evaluating the efficacy, safety and acceptability of short cycle (five days on, two days off) dolutegravir/tenofovir-based triple antiretroviral therapy (ART) compared to daily dolutegravir/tenofovir-based triple ART in virologically suppressed HIV-infected adolescents aged 12 to 19 years of age in sub-Saharan Africa

Acronym
Breather Plus

Study objectives
Current study hypothesis as of 07/04/2020:
Dolutegravir-based SCT with a tenofovir and lamivudine/emtricitabine backbone will provide non-inferior sustained virological suppression compared to continuous dolutegravir-based ART with a tenofovir and lamivudine/emtricitabine backbone

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Previous study hypothesis:
Dolutegravir (DTG)-based SCT will provide non-inferior sustained virological suppression compared to continuous DTG-based ART.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 06/04/2020, UCL Research Ethics Committee (Office of the Vice Provost Research, 2 Taviton Street, University College London, London, UK; +44 (0)20 7679 8717; ethics@ucl.ac.uk), ref: 16929.001
2. Approved 06/12/2021, Institutional Research and Ethics Committee (IREC, Moi University,

College of Health Sciences, PO Box 4606, Eldoret, Kenya; +254 (0)787723677; irec@mtrh.go.ke), ref: 0004031
3. Approved 22/09/2021, Joint Research Ethics Committee For The University of Zimbabwe (JREC Office No.4, 5th Floor, Faculty of Medicine and Health Sciences Building, Zimbabwe; +263 (0)242 708140; jrec.office@gmail.com), ref: 147/2020
4. Approved 22/09/2021, Joint Clinical Research Centre Research Ethics Committee (Plot 101, Lubowa Estates, Off Entebbe Road, P.O Box 10005, Kampala, Uganda. Uganda; +256 (0)41 7723000; jcrc@jcrc.org.ug), ref: JCRC-2021-19
5. Approved 26/08/2021, Pharma-Ethics (PO Box 786, Irene, 0062, Gauteng, Republic of South Africa, 123 Amkor Road, Lyttelton Manor Ext 3, Centurion, 0157, South Africa; +27 (0) 126648690; marzelle@pharma-ethics.co.za), ref: 210624036

Primary study design
Interventional

Study design
Open-label randomized (1:1) multicentre non-inferiority trial

Study type(s)
Treatment

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

Interventions
Current interventions as of 07/04/2020:

Control group: Control group is continuous combination ART consisting of dolutegravir, with a tenofovir and lamivudine/emtricitabine backbone
Experimental group: Intervention group is short-cycle combination ART, consisting of dolutegravir, with a tenofovir and lamivudine/emtricitabine backbone. The SCT group will follow a cycle of 5 consecutive days on ART (Monday to Friday inclusive or Sunday to Thursday inclusive) and the same 2 consecutive days off every week (i.e. Saturday and Sunday, or Friday and Saturday)

Treatment will continue for the duration of the trial/follow-up. The total duration of treatment /follow up for all study arms is for a minimum of 96 weeks, until the last participant has reached 96 weeks visit (so for participants entering the trial early, this could mean 4 years on the trial). The randomisation will be 1:1, using permuted blocks with variable sizes, developed by the trial statistician. Randomisation will take place using an eDC platform.

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Previous interventions:

Control group: Continuous dolutegravir-based combination ART
Experimental group: Short-Cycle Therapy (SCT) dolutegravir-based combination ART. The SCT group will follow a cycle of 5 consecutive days on
ART (Monday to Friday inclusive or Sunday to Thursday inclusive) and the same 2 consecutive days off every week (i.e. Saturday and Sunday, or Friday and Saturday).

Treatment will continue for the duration of the trial/follow-up. The total duration of treatment /follow up for all study arms is for a minimum of 96 weeks, until the last participant has reached 96 weeks visit (so for participants entering the trial early, this could mean 4 years on the trial). The randomisation will be 1:1, using permuted blocks with variable sizes, developed by the trial statistician. Randomisation will take place using an eDC platform.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dolutegravir 50mg oral with tenofovir disproxil (245mg) fumarate co-formulated with emtricitabine (200mg) or lamivudine (300mg) (TRU) oral in a fixed dose combination or separately Dolutegravir 50mg oral with tenofovir alafenamide fumarate (25mg) co-formulated with emtricitabine (200mg) or lamivudine (300mg) (f/lTAF) oral in a fixed dose combination or separately

Primary outcome(s)
Current primary outcome measure as of 07/04/2020:

The proportion of participants with confirmed virological rebound, defined as the first of 2 consecutive plasma HIV-RNA ≥50 copies/mL at any time up to the 96-week assessment

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Previous primary outcome measure:

Incidence of confirmed virological rebound, defined as 2 consecutive plasma HIV-RNA ≥50 copies /mL at any time up to the 96-week assessment

Key secondary outcome(s)
Current secondary outcome measures as of 07/04/2020:

1. Efficacy:
1.1. Proportion of participants with HIV-RNA ≥50 copies/mL at 48 and 96 weeks using the FDA snapshot algorithm
1.2. Proportion of participants with HIV-RNA ≥1000 copies/mL (confirmed) by week 96
1.3. The number and type of HIV mutations at confirmed virological rebound
1.4 HIV-RNA <50 copies/mL and no switch to second-line ART for treatment failure at 24, 48, 64 and 96 weeks
2. Safety:
2.1. Change in toxicity profile including change in metabolic parameters (lipids, HbA1C, phosphate), renal function (eGFR) from baseline to 96 weeks; change in anthropometric measures from baseline to 48 and 96 weeks
2.2. Time to any new or recurrent WHO grade 3 or WHO grade 4 event or death
2.3. Incidence of serious, grade 3 and 4, and treatment-modifying grade 1-2 adverse events
2.4. The proportion of participants with any change from baseline ART regimen
2.5. Change in CD4+ and CD8+ T-cell count from baseline to 48 and 96 weeks

3. Patient-reported outcomes:
3.1. Adherence, acceptability, well-being, and neuropsychiatric problems (e.g. depression, anxiety and sleep disturbance)
3.2. Healthcare resource utilisation (as a sub-study outcome)
3.3. Health-related quality-of-life (as a sub-study outcome)

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Previous secondary outcome measures:

1. Efficacy
1.1. Proportion of participants with HIV-RNA ≥50 copies/mL at 48 and 96 weeks using the FDA snapshot algorithm
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1.3. The number and type of HIV mutations at confirmed virological rebound
1.4 HIV-RNA <50 copies/mL and no switch to second-line ART for treatment failure at 24, 48, 64 and 96 weeks

2. Safety
2.1. Change in toxicity profile including change in metabolic parameters (lipids, HbA1C, phosphate), renal function (eGFR) from baseline to 96 weeks; change in anthropometric measures from baseline to 48 and 96 weeks
2.2. Incidence of clinical events (WHO 3 and 4 events; death)
2.3. Incidence of serious, grade 3 and 4, and treatment-modifying grade 1-2 adverse events over 96 weeks
2.4. The proportion of participants with any change from baseline ART regimen by week 96
2.5. Change in CD4+ and CD8+ T-cell count from baseline to 48 and 96 weeks

3. Patient-reported outcomes
3.1. Adherence, acceptability, well-being, and neuropsychiatric toxicities
3.2. Healthcare resource utilisation (as a sub-study outcome)
3.3. Health-related quality-of-life (as a sub-study outcome)

Completion date
27/05/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/04/2020:
1. HIV-1-infected
2. Aged 12-19 years
3. Aware of HIV status
4. On ART for ≥1 year, with no previous regimen change for treatment failure
5. On ART consisting of DTG, tenofovir and lamivudine/emtricitabine for ≥1 month prior to screening
6. Virologically suppressed with all HIV-1 RNA viral loads < 50copies/ml* in the last 12 months up to and including screening. Additionally there must be one result < 50copies/ml* at least 12 months prior to screening and the viral load at trial screening must be < 50 copies/ml*
7. Girls who are sexually active must be willing to adhere to highly effective methods of contraception**

8. Written informed consent/assent provided by participant (if aged 18 to 19 years) and/or carer /legal guardian (if participate aged 12 to 17 years) as appropriate
9. Written informed assent in participates aged 12 to 17 years

*VL <100 copies/ml is allowed for diluted samples with maximum dilution 1:5, except for the screening sample where the VL must be < 50 copies/ml in an undiluted sample
**Highly effective contraception are injectable, implantable, oral and intrauterine contraceptives which have an expected failure rate <1% per year

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Previous inclusion criteria:

1. HIV-1-infected
2. Aged 12-19 years
3. Aware of HIV status
4. On ART consisting of 2NRTI and a third agent (with no previous regimen change for treatment failure)
5. On ART for ≥1 year
6. On DTG-based ART for ≥1 month prior to screening
7. Virologically suppressed with all HIV-1 RNA viral loads <50copies/mL* in the last 12 months up to and including screening. Additionally there must be one result <50copies/ml* at least 12 months prior to screening and the viral load at trial screening must be <50 copies/mL
9. Written informed consent/assent provided by participant and/or carer/legal guardian as appropriate

*VL <100 copies/ml is allowed for diluted samples with maximum dilution 1:5, except for the screening sample where the VL must be <50 copies/ml in an undiluted sample

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 Years

Upper age limit
19 Years

Sex
All

Total final enrolment
470

Key exclusion criteria

Current exclusion criteria as of 07/04/2020:

1. Females who are pregnant or breastfeeding
2. Females who plan to become pregnant during the trial follow-up or are unwilling to use a highly effective method of contraception** for the duration of the trial if sexually active
3. Moderate or High risk score on the Columbia-Suicide Severity Rating Scale
4. On treatment for any active TB
5. Contraindication to continued receipt of dolutegravir or any formulation of tenofovir, emtricitabine/lamivudine
6. Underlying medical condition that in the opinion of the Investigator precludes participation
7. Previous randomisation in the LATA trial

**Highly effective contraception are injectable, implantable, oral and intrauterine contraceptives which have an expected failure rate <1% per year

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Previous exclusion criteria:

1. Females who are pregnant or breastfeeding
2. Females who plan to become pregnant during the trial follow-up or are unwilling to avoid pregnancy* for 96 weeks
3. Moderate or High risk score on the Columbia-Suicide Severity Rating Scale **
4. On treatment for any active TB
5. Contraindication to receipt of dolutegravir, any formulation of tenofovir, emtricitabine /lamivudine
6. Previous randomisation in the LATA trial

*methods of avoiding pregnancy include the following: use depot or implant hormonal contraception, oral contraception or intrauterine device.
**Participants initially ineligible on the basis of a moderate or high risk score on the Columbia-Suicide Severity Rating Scale if in the opinion of the Investigator it is safe for them to be rescreened

Date of first enrolment
17/06/2022

Date of final enrolment
10/05/2023

Locations

Countries of recruitment
Kenya

South Africa

Uganda

Zimbabwe

Study participating centre
Baylor College of Medicine Children's Foundation
Block 5 Mulago Hospital
P.O Box 72052
Kampala
Uganda
N/A

Study participating centre
Joint Clinical Research Centre (JCRC)
Plot 101 Lubowa Estates,
off Entebbe road,
P.O. Box 10005
Wakiso District,
Kampala
Uganda
N/A

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

Study participating centre
Moi University, AMPATH Centre
Nandi Road
Eldoret
Kenya
4606-30100

Study participating centre
Durban International Clinical Trials Research Site, Enhancing Care Foundation
Parkhome
King Edward VIII Hospital
Umbilo Road
Congella
Durban
South Africa
4013

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)
The European & Developing Countries Clinical Trials Partnership, The European & Developing Countries Clinical Trials Partnership (EDCTP), European and Developing Countries Clinical Trials, 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, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Funder Name
Medical Research Council

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository. The EDCTP2 programme is funded under the Horizon 2020 programme (H2020) and is committed to open
access. Open access refers to the practice of providing online access to scientific information that is free of
charge to the end-user and reusable. This encompasses:
- Peer-reviewed scientific research articles (published in scholarly journals)
- Research data (data underlying publications, curated data and/or raw data).

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/04/2026	13/04/2026	Yes	No
Protocol article		29/05/2025	11/08/2025	Yes	No
Protocol file	version 3.0	24/03/2023	22/05/2026	No	No
Statistical Analysis Plan	version 2.0	17/06/2024	22/05/2026	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes