ISRCTN44453201 https://doi.org/10.1186/ISRCTN44453201

Will HIV-positive individuals who have drug resistance and have suppressed amount of virus in the blood on protease inhibitor regimen still remain suppressed if switched to a regimen containing bictegravir, emtricitabine and tenofovir alafenamide?

Submission date
10/06/2019

Registration date
19/06/2019

Last Edited
20/09/2023

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
As HIV multiplies in the body, the virus sometimes changes form (mutates). Some HIV mutations that develop while a person is taking HIV medicines can lead to drug-resistant strains of HIV. Once drug resistance develops, HIV medicines that previously controlled a person's HIV are no longer effective. In other words, the HIV medicines can't prevent the drug-resistant HIV from multiplying. Drug resistance can cause HIV treatment to fail. The aim of this study is to find out whether a new integrase inhibitor-based drug regimen is as effective as a regimen containing a protease inhibitor in controlling the multiplication of HIV virus which harbours resistance.

Who can participate?
Patients aged 18 and over who are HIV-positive and on effective antiretroviral treatment containing a protease inhibitor. Patients must have evidence that the virus is resistant to antiretroviral therapy.

What does the study involve?
Participants are randomly allocated to either continue on their current protease inhibitor-based regimen or switch to an integrase inhibitor-based regimen (tenofovir alafenamide/emtricitabine /bictegravir (Biktarvy) single tablet regimen). Participants continue on their allocated treatment for 24 weeks. At this point, if there is no difference in the response to both the regimens, all those who had remained on their protease-inhibitor based regimen are then switched to the new treatment and all participants are followed up for a further 24 weeks. No one in this study takes dummy tablets. All participants are on active treatment throughout the study. There are a total of eight scheduled study visits during the 48 weeks of the study, with a 30-day post-study treatment follow up call or standard of care visit.

What are the possible benefits and risks of participating?
The possible benefits include reduced cardiovascular risk (reduced risk of heart attacks and strokes) with continued suppression of the amount of virus in the blood, lower likelihood of interactions with other medications, and reduced number of tablets taken for HIV. Information gained from this study could lead to change in how doctors use the medication. Blood tests may cause discomfort and may leave a temporary bruise. Every effort will be made to minimise this. Because the study involves additional visits to the clinic, the researchers can reimburse reasonable travel expenses for those extra visits. When switching from one antiviral regimen to another, there is a small risk that the virus will not be controlled with the new regimen, hence the virus could develop resistance to the medications. Furthermore, the new regimen could cause new side effects. Viral load and side effects will be frequently and carefully monitored during this study to minimise these risks

Where is the study run from?
1. University Hospitals Sussex NHS Foundation Trust
2. Barts Health NHS Trust
3. Central and North West London NHS Trust
4. King's College Hospital NHS Foundation Trust
5. Chelsea and Westminster NHS Trust
6. Royal Free London NHS Foundation Trust
7. Guy's and St Thomas' NHS Foundation Trust

When is the study starting and how long is it expected to run for?
November 2018 to February 2023

Who is funding the study?
Gilead Sciences (USA)

Who is the main contact?
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2. Dr Collins Iwuji
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-004732-30

Integrated Research Application System (IRAS)
257865

Protocol serial number
CPMS 42164, IRAS 257865

Study information

Scientific Title
A Phase IV, randomised, open-label pilot study to evaluate switching from protease-inhibitor based regimen to bictegravir/emtricitabine/tenofovir alafenamide single tablet regimen in virologically suppressed HIV-1 infected adults harbouring drug resistance mutations

Acronym
PIBIK

Study objectives
Current study hypothesis as of 23/07/2021:
This is a phase IV, multicentre, open-label, randomised two-arm pilot study to assess the safety and efficacy of switching from boosted protease inhibitor regimen to B/F/TAF single-tablet regimen in virologically suppressed HIV-1infected adults harbouring drug resistance mutations.

Previous study hypothesis:
This is a phase IV, multicentre, open-label, randomised two-arm pilot study to assess the safety and efficacy of switching from boosted protease inhibitor regimen to B/F/TAF single-tablet regimen in integrase Inhibitor-naïve, virologically suppressed HIV-1infected adults harbouring drug resistance mutations.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/06/2019, London – Brighton & Sussex Research Ethics Committee (Health Research Authority, Ground Floor, Skipton House, 80 London Road, London SE1 6LH; Tel: +44 (0)20 797 22567; Email: NRESCommittee.SECoast-BrightonandSussex@nhs.net), ref: 19/LO/0905

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Human immunodeficiency virus [HIV] disease

Interventions
HIV-positive individuals who meet the eligibility criteria for the trial will be identified by their doctor and informed about the study. They will be referred to the doctor in charge of the research in each site where they will be given more information about the study and be given the opportunity to study the patient information leaflet and ask questions. Only after that will patients be consented and recruited into the study.

HIV-positive individuals will be randomised to either continue on their current protease inhibitor-based regimen or switch to an integrase inhibitor-based regimen (tenofovir alafenamide /emtricitabine/bictegravir (Biktarvy) single-tablet regimen). Participants will know which arm they fall into after the randomisation and which treatment they are taking. Participants will continue on their allocated treatment for 24 weeks. At this point, if there is no difference in the response to both the regimens, all those who had remained on their protease-inhibitor based regimen will then be switched to the new treatment and all participants will be followed up for a further 24 weeks. The study will continue until each person enrolled in the study has been followed up for 48 weeks from the time they joined the study. This will occur at different times for those involved depending on when they joined the study. No one in this trial will be on dummy tablets. All participants will be on active treatment throughout the study. There will be a total of eight scheduled study visits during the 48 weeks duration of the trial.

Updated 15/01/2020:
There will be a total of eight scheduled study visits during the 48 weeks duration of the trial, with a 30-day post-study treatment follow up call or standard of care visit.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Tenofovir alafenamide, emtricitabine, bictegravir

Primary outcome(s)
Proportions of individuals with HIV RNA <50 copies/mL at 24 weeks will be estimated using pure virologic response (PVR). The percentage of participants with PVR for HIV-1 RNA cut-off at 50 copies/mL at Week 24 will be summarized. PVR will be assessed as follows:
1. On study treatment
2. No confirmed virologic rebound defined as:
2.1. HIV RNA ≥ 50 copies/mL on 2 consecutive visits
2.2. HIV-1 RNA ≥ 50 copies/mL during study followed by premature discontinuation
Discontinuation prior to week 24 for reasons other than virologic rebound (i.e. no data in window and last HIV RNA < 50 copies/mL) are considered PVR
Timepoint(s): End of the study

Key secondary outcome(s))
1. Proportion of patients with HIV RNA <50 copies/mL at week 48 using PVR
2. Proportion of patients with HIV-1 RNA <50 copies/mL at weeks 24 and 48 using PVR in those with any archived resistance detected in proviral DNA
3. Emergence of new resistance mutations measured by population sequencing in participants with two consecutive viral load >50 copies/mL 2-3 weeks apart
4. Safety and tolerability of B/F/TAF FDC in participants switching from bPI-based regimens measured using laboratory parameters and clinical assessments at 48 weeks
5. Patient-reported outcomes: sleep quality measured using the Pittsburgh Sleep Quality Index and bothersome symptoms measured using the HIV symptom distress scale at baseline, weeks 24 and 48
6. Serum lipid concentrations measured using blood samples at baseline, weeks 24 and 48
7. HBA1c measured using blood samples at baseline, weeks 24 and 48

8. Weight and BMI measured using weighing scale for weight and measuring tape for height at baseline, weeks 24 and 48

Completion date
28/02/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 23/07/2021:
1. 18 years and above
2. On a bPI-based ART regimen with documented HIV-1 RNA <50 copies/mL for at least 6 months on current regimen and at screening (A switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF), lamivudine (3TC) to emtricitabine (FTC), or splitting co-formulated tablets to their individual component or vice versa will not be considered true regimen changes)
3. Must have a historical genotype
4. Eligible drug resistance mutations in historical genotype include at least one of the following:
4.1. M184V/I with or without any nucleoside analogue mutation (e.g. L74I/V, Y115F, K70E/G/Q/T/N/S)
4.2. M184V/I alone (maximum of 20 participants with isolated M184V/I mutation with or without NNRTI mutations)
4.3. Up to 2 TAMs (M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/N/R) with or without M184V/I
4.4. Any of the above with or without NNRTI mutations
5. If previous INSTI exposure, participants should not have experienced virological failure on the INSTI regimen. Site must provide viral load history during the time participant was on INSTI for Chief Investigator review and confirmation of eligibility. Participants who experienced one of the following whilst on INSTI regimen will be excluded:
5.1. Viral load ≥50 copies/ml on two consecutive occasions
5.2. A single “blip” viral load ≥500 copies/ml
5.3. 3 or more “blips” (viral load 50 -500 copies/ml)
6. No known INSTI mutations
7. Estimated GFR ≥ 50 mL/min (Cockcroft-Gault formula)
8. Have the following laboratory values at screening within 30 days prior to baseline (note: a single repeat of a laboratory screening test will be allowed for test results that are unexpected based on documented prior laboratory results):
8.1. Alkaline phosphatase ≤ 3.0 x upper limit of normal (ULN)
8.2. AST and ALT ≤ 5.0 x ULN
8.3. Haemoglobin ≥9.0 g/dL (female) or ≥10.0 g/dL (male)
9. Provides written, informed consent to participate
10. Is willing to comply with the protocol requirements
11. If female and of child bearing potential and are willing to continue practising one of the following:
11.1. Must be using effective birth control methods, that is has an expected failure rate of <1% per year and willing to continue practicing these birth control measures during the trial and for at least 30 days after the end of the trial. Effective methods include IUD, combined pill, contraceptive injection, implant, IUS, contraceptive vaginal ring, contraceptive patches etc.
11.2. Must be truly abstinent from penile-vaginal intercourse from 2 weeks prior to administration of study drug, throughout the study, and for at least 30 days after the end of the trial (When this is in line with the preferred and usual lifestyle of the participant.) Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal

are not
acceptable methods of contraception. Note: women who are postmenopausal for least 2 years, women with a total hysterectomy, and women who have a tubal ligation are considered of non-childbearing potential.
12. If male, and sexually-active with female partners of child bearing potential, is using effective barrier contraception, and willing to continue using this during the trial and for at least 30 days after the end of the trial.

Previous participant inclusion criteria as of 15/01/2020:
1. 18 years and above
2. On a bPI-based ART regimen with at least one documented HIV-1 RNA < 50 copies/mL within the previous 6 months and at screening
3. Eligible drug resistance mutations in historical genotype include at least one of the following:
3.1. M184V/I with or without any nucleoside analogue mutation (e.g. L74I/V, Y115F, K70E/G/Q/T /N/S)
3.2. M184V/I alone (maximum of 20 participants with isolated M184V mutation with or without NNRTI mutations)
3.3. Up to 2 TAMs (M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/N/R) with or without M184V /I
3.4. Any of the above with or without NNRTI mutations
4. No previous use of any approved or experimental integrase strand transfer inhibitor (INSTI)
5. No known INSTI mutations
6. Must have historical genotype
7. Estimated GFR > = 50 mL/min (Cockcroft-Gault formula)
8. Have the following laboratory values at screening within 30 days prior to baseline
8.1. Alkaline phosphatase < = 3.0 x upper limit of normal (ULN)
8.2. AST and ALT < = 5.0 x ULN
8.3. Hemoglobin > = 9.0 g/dL (if female) or > = 10.0 g/dL (if male)
9. Provides written, informed consent to participate
10. Is willing to comply with the protocol requirements
11. If female and of childbearing potential, is using effective birth control methods (as agreed by the investigator) and willing to continue practising these birth control measures during the trial and for at least 30 days after the end of the trial
12. If male, and sexually-active with female partners of childbearing potential, is using effective barrier contraception, and willing to continue using this during the trial and for at least 30 days after the end of the trial

Previous inclusion criteria:
1. 18 years and above
2. Any nadir CD4 count and baseline VL
3. On a bPI-based ART regimen with at least one documented HIV-1 RNA < 50 copies/mL within the previous 6 months and at screening
4. Eligible drug resistance mutations in historical genotype include the following:
4.1. M184V/I with or without any nucleoside analogue mutation (e.g. L74I/V, Y115F, K70E/G/Q/T /N/S)
4.2. M184V/I alone
4.3. Up to 2 TAMs (M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/N/R) with or without M184V /I
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10. Provides written, informed consent to participate
11. Is willing to comply with the protocol requirements
12. If female and of childbearing potential, is using effective birth control methods (as agreed by the investigator) and willing to continue practising these birth control measures during the trial and for at least 30 days after the end of the trial
13. If male, and sexually-active with female partners of childbearing potential, is using effective barrier contraception, and willing to continue using this during the trial and for at least 30 days after the end of the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria as of 23/07/2021:
1. Exclusion under drug resistance mutations include:
1.1. Presence of any of the following mutations: K65R/N/E
1.2. Presence of multidrug resistance mutations: T69ins, Q151M with or without A62V, V75I, F77L, F116Y
1.3. Presence of INSTI mutations: H51Y, T66AIK, E92QGV, G118R, F121Y, E138KAT, G140ASC, Y143CRHKSGA, P145S, Q146P, S147G, Q148HKRN, S153YF, N155HSTD, S230R, R263K
1.4. Three or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/N/R)
2. Individuals experiencing decompensated cirrhosis (e.g., ascites, encephalopathy, or variceal bleeding)
3. An opportunistic illness within the 30 days prior to screening
4. Active tuberculosis infection
5. Have been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents or systemic steroids during the study (e.g., corticosteroids, immunoglobulins, and other immune- or cytokine based therapies)
6. Current alcohol or substance use judged by the Investigator to potentially interfere with participants’ adherence to study procedure.
7. A history of malignancy of less than 2 years or ongoing malignancy (including untreated carcinoma in-situ) other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Individuals with biopsy-confirmed cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Day 1 and

are not anticipated to require systemic therapy during the study.
8. Active, serious infections (other than HIV 1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Day 1 (except if the parenteral therapy is for syphilis infection)
9. Any pre-existing physical or mental health condition which, in the opinion of the Investigator, may interfere with the subject's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participants. Subjects considered to pose a significant risk of suicide should be excluded.
10. Any known allergies to the excipients of B/F/TAF FDC
11. Females who are pregnant (as confirmed by positive urine pregnancy test)
12. Females who are breastfeeding
13. Women of child bearing age not using any reliable form of contraception (e.g. intrauterine device/intrauterine system, long-acting contraceptive injection)
14. Acute hepatitis in the 30 days prior to study entry, anyone with HCV who is likely to need direct acting antivirals in study
15. Any concomitant medications that cannot be administered with TAF (i.e strong inducers of p-glycoprotein) or bictegravir (dofetilide, rifampins)

Previous participant exclusion criteria as of 15/01/2020:
1. Exclusion under drug resistance mutations include:
1.1. Presence of any of the following mutations: K65R/N/E
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6. Current alcohol or substance use judged by the Investigator to potentially interfere with participants’ adherence to study procedure
7. A history of malignancy of less than 5 years or ongoing malignancy (including untreated carcinoma in-situ) other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Individuals with biopsy-confirmed cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Day 1 and are not anticipated to require systemic therapy during the study
8. Active, serious infections (other than HIV 1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Day 1 (except if the parenteral therapy is for syphilis infection)
9. Any other clinical condition or prior therapy that will, in the opinion of the investigator, make the participant ineligible
10. Any known allergies to the excipients of B/F/TAF FDC
11. Females who are pregnant (as confirmed by positive urine pregnancy test)
12. Females who are breastfeeding
13. Women of childbearing age not using any reliable form of contraception (e.g. intrauterine device/intrauterine system, long-acting contraceptive injection, in addition to barrier methods)
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3. An opportunistic illness within the 30 days prior to screening
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5. Have been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents or systemic steroids during the study (e.g., corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)
6. Current alcohol or substance use judged by the Investigator to potentially interfere with subjects' adherence to study procedure
7. A history of or ongoing malignancy (including untreated carcinoma in-situ) other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Individuals with biopsy-confirmed cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Day 1 and are not anticipated to require systemic therapy during the study
8. Active, serious infections (other than HIV 1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Day 1 (except if the parenteral therapy is for syphilis infection)
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14. Acute hepatitis in the 30 days prior to study entry, anyone with HCV who is likely to need direct-acting antivirals in study
15. Any concomitant medications that cannot be administered with TAF (i.e. strong inducers of p-glycoprotein) or bictegravir (dofetilide, rifampins)

Date of first enrolment
16/09/2019

Date of final enrolment
28/02/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University Hospitals Sussex NHS Foundation Trust
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Eastern Road
Brighton
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Study participating centre
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The Royal London Hospital
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Study participating centre
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Royal Free Hospital

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Study participating centre
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Sponsor information

Organisation
University of Sussex

ROR
https://ror.org/00ayhx656

Funder(s)

Funder type
Industry

Funder Name
Gilead Sciences

Alternative Name(s)
Gilead, Gilead Sciences, Inc., Oligogen

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

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 Dr Collins Iwuji (c.iwuji@bsms.ac.uk).
Type of data: fully anonymised raw dataset
When the data will become available and for how long: for 5 years from 01/01/2024
By what access criteria data will be shared including with whom:
1. The researcher requesting the data will need to sign a data use agreement
2. The data will only be processed for the stated statistical and research purposes
3. Data will not in any way be used for any administrative, proprietary or law enforcement purposes
For what types of analyses, and by what mechanism: analysis will be for non-commercial use
Whether consent from participants was obtained: PIBIK participants provide consent to the following statement during the informed consent process prior to study registration
Comments on data anonymisation: all data provided will be anonymised
Any ethical or legal restrictions: no, only fully anonymised data will be shared

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	20/07/2020	22/07/2020	Yes	No
HRA research summary			20/09/2023	No	No