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# Investigating chronic breathlessness in people living with HIV

**Submission date**
21/11/2018

**Recruitment status**
No longer recruiting

**Registration date**
23/11/2018

**Overall study status**
Completed

**Last Edited**
23/11/2018

**Condition category**
Infections and Infestations

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

## Plain English summary of protocol

Background and study aims
A previous study in our centre has shown that reported breathlessness is more common in HIV positive compared to matched HIV negative people. However, over two thirds of those who reported breathlessness did not have a substantiated diagnosis to explain their symptoms. We are aiming to explore the causes of breathlessness in 30 HIV positive and 30 matched HIV negative participants, all of whom should be at least breathless on walking up a slight incline. We will explore physical and psychological causes of breathlessness.

Who can participate?
Adult participants who are breathless on walking up a slight incline

What does the study involve?
The initial visit will take at most 1 hour. Consent will be taken and information on past medical history, social history and medications will be collected. Participants will complete six clinical questionnaires about respiratory symptoms, breathing pattern, health-related quality of life, anxiety, depression and sleepiness. The following tests will be performed on all participants:
1. Routine blood tests: basic blood count, your kidney function and also measure levels of proteins that are released from the heart.
2. ECG (a quick non-invasive test to check the electrical activity of the heart).
3. Chest x-ray if not done in the last 3 months.
4. Full lung function tests (breathing tests). This will involve spirometry and gas diffusion tests. Spirometry tests how much air can be emptied out of the lungs and how quickly. Participants will be asked to take a very deep breath in and to blow out as hard and fast as they can in to a mouthpiece until no more air is left. To get the best result, this is repeated three times with a rest in between. Participants may be required to repeat this test 20 minutes after taking an inhaler to see if this gives benefit. Gas diffusion tests are performed to see how well participants are able to move oxygen from their lungs in to their blood supply. This test has a number of stages: first participants will be asked to breathe normally in to the mouthpiece; then take deep breath in and gently blow out as far as possible; and then take a quick deep breath in as far as they can, hold their breath for 10 seconds and then breathe out.
5. Echocardiogram (heart scan): this is a simple, non-invasive way of looking at the structure and function of the heart using an ultrasound machine. A small probe with cold jelly on it will be

placed in different positions on the chest in order to obtain pictures of the structure and function of all parts of the heart. It will take approximately 30 minutes.
6. CT scan of the chest (some participants only) If there is a significant abnormality on chest x-ray or lung function tests, CT scan of their chest will be performed.
The results of these initial tests will be discussed by a group of lung and heart doctors to decide if a definite cause for breathlessness has been found. The results of the initial tests will be discussed in a multidisciplinary team meeting with heart and lung doctors. If the cause of breathlessness has been found then the appropriate referral for treatment will be made.
If the initial tests are inconclusive, further tests will be performed; in particular, a cardiopulmonary exercise test: This is a supervised exercise test on a stationary bike. During the exercise, oxygen levels, heart tracing, blood pressure and breathing pattern will be measured. At the end of the test a blood sample will be taken to measure oxygen and carbon dioxide levels.
We will arrange to meet participants again to explain all of the results and repeat the same six clinical questionnaires that they were asked to complete at the beginning of the study.

What are the possible benefits and risks of participating?
There is no direct benefit to participants in taking part in this study but we hope that it will be a positive experience for participants as it will explore all the likely causes of breathlessness, including asking about psychological symptoms and sleep, factors that are not always considered in routine care. We will report any significant findings back to participants to ensure they get the best possible medical care.
We do not anticipate any significant risks of taking part in this study. We are asking participants to attend for an additional two visits on top of routine clinical care at the beginning and the end of the study.
The blood test may cause mild discomfort. Lung function tests can provoke a bout of cough or minor breathlessness but are supervised at all times and the procedure can be stopped if the participant or the technician has any concerns. The cardiopulmonary exercise test is medically supervised at all times and has been demonstrated to be a safe procedure, even in those with severe heart or lung disease. As with any exercise, it may cause the participant to feel breathless, but this settles quickly after the test has finished.
X-rays and CT scans use ionising radiation in order to obtain images. The radiation of a chest X-ray is very low and comparable to only 2-3 days of background radiation (the radiation naturally occurring in the environment). A CT chest will only be performed if an abnormality has been found on the participant's chest x-ray or lung function (breathing tests) that means we need to know more detailed information about the lungs. It will only be performed if it would be indicated in routine clinical care. The radiation dose is equivalent to up to 400 chest X-rays, although the risk of any harm from this scan is still very low.

Where is the study run from?
Royal Free London NHS Trust (UK)

When is the study starting and how long is it expected to run for?
July 2018 to July 2019

Who is funding the study?
Department of Respiratory Medicine, Royal Free Hospital (UK)

Who is the main contact?
Dr Amina Jaffer
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# Contact information

### Type(s)
Public

### Contact name
Dr Amina Jaffer

### Contact details
Department of Respiratory Medicine, Royal Free Hospital, Pond Street,
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# Additional identifiers

### EudraCT/CTIS number

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers
11473

# Study information

### Scientific Title
What are the causes of chronic breathlessness in people living with and without HIV in the ART era? A pilot study

### Study objectives
1. The distribution of causes of breathlessness will be different in HIV positive and HIV negative groups
2. The prevalence of anxiety and depression will be higher in the HIV positive than HIV negative group

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
London- West London & GTAC Research and Ethics Committee, 13/07/2018, 18/LO/0819

### Study design
Observational cross sectional cohort study

### Primary study design
Observational

## Secondary study design
Cross sectional study

## Study setting(s)
Hospital

## Study type(s)
Other

## Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

## Health condition(s) or problem(s) studied
Breathlessness in HIV positive and HIV negative participants

## Interventions
Part 1
There will be an initial visit specifically for the study, in addition to routine clinical care. At this visit informed consent will be taken by a qualified study team member. Anthropometric data and basic observations will be collected including height, weight, blood pressure, pulse and oxygen saturations. The MRC Breathlessness Scale will be used to determine eligibility. Participants will also be asked to complete 6 clinical questionnaires during this visit.
Case notes and electronic records will also be reviewed to obtain information on Nadir CD4 count, duration of known HIV infection, HIV tropism (if known), risk for HIV acquisition, any AIDS diagnosis, plasma CD4 count and HIV viral load at baseline.
The results of the following routine clinical investigations performed as part of routine clinical care will be systematically collected for all participants:
1. Chest X-ray (walk in service)
2. ECG
3. Lung function tests (spirometry and gas transfer) to look for evidence of obstructive or restrictive lung disease or impairment of gas exchange
4. Transthoracic Echocardiogram (to assess left and right ventricular function, look for evidence of pulmonary hypertension, valvular abnormalities or pericardial disease)
5. Blood tests including FBC, renal profile and nT-proBNP
These investigations will be undertaken and reported by qualified personnel in the relevant departments with appropriate training and quality control in place.

Part 2
Once the initial investigation results have been collected, the results will be reviewed in an MDT consisting of a Consultant Respiratory physician and a Consultant Cardiologist (in addition to routine clinical care). All patients will have a follow-up consultation with their clinical team to explain the results of the initial investigations. The patients will then be stratified into those with:
1. Respiratory disease only: Definite impairment on lung function (as defined as value under 50% predicted for FEV1, FVC or TLCO) and/or abnormal chest X-ray indicative of lung disease. Normal ECG and echocardiogram. In some patients, sufficient information will be available at this point to make a definitive diagnosis. For example, asthma (compatible history and examination, airflow obstruction with bronchodilator reversibility). In other patients with a significantly abnormal CXR and/or lung function, the definitive diagnosis will not be clear. These patients will undergo a CT chest as part of routine care and will be followed up in respiratory clinic. Consent

will be obtained to record the results of subsequent investigations.
2. Cardiac disease only: Definite abnormality on echocardiogram (left ventricular dysfunction, valvular disease or pulmonary hypertension of at least moderate severity by standard echocardiogram criteria). Normal lung function, CXR not suggestive of respiratory disease. These patients will be referred to specialist cardiology clinic and undergo further specialist investigations as indicated. Consent will be obtained to record the results of these subsequent investigations and details of treatment received.
3. Cardiac and respiratory disease: Definite abnormality in CXR/lung function and echocardiogram. Participants will be jointly managed by cardiology and respiratory team. The results of subsequent investigations and details of treatment received will be recorded.
4. Unclear predominant cause of breathlessness: Basic investigations normal or with only minor abnormalities that may not be clinically significant. These patients will move to part 3.
It is estimated that up to 20 of our 60 participants will move to part 3 of the study.

Part 3
Cardiopulmonary exercise testing (CPET) is a recognised, validated tool for investigating breathlessness, especially when basic investigations have not identified a cause, or the predominant cause is not clear. It involves supervised exercise (cycling on an exercise bike or running on a treadmill) with continuous measurement of oxygen saturations, ECG trace, oxygen consumption, carbon dioxide production and minute ventilation; and periodic assessment of symptoms and blood pressure. An arterial blood gas measurement is taken at the end of the test. CPET is able to identify when exercise is predominantly limited by cardiac disease, respiratory disease, neuromuscular disease or deconditioning. It is also able to identify dysfunctional breathing patterns as a cause of breathlessness.
Participants who are identified to have cardiac or respiratory limitation on CPET who have not yet been referred for onward specialist investigation and management will be referred at this stage.
Participants identified to have deconditioning will be encouraged to increase physical activity levels and offered advice from physiotherapists about exercise programmes.
Those with dysfunctional breathing (with likely coexistent anxiety and/or depression) will be referred to a specialist respiratory physiotherapist for guidance on control of breathing patterns and will be offered referral to the clinical psychology team.
All of the data will be collected for each participant and a definitive cause of breathlessness recorded (where possible). We anticipate from previous studies that it will be possible to identify a cause or multiple causes of breathlessness in over 95% of participants (Pratter et al., 2011).

All participants will be asked to attend for an end of study visit after they have completed their diagnostic investigations. This visit will be specifically for the study and not part of routine clinical care. They will be asked to complete the same six clinical questionnaires as at the initial visit. Details of any new investigations that they have undertaken and treatments that they have received will be documented. Participants will be informed of any clinically significant findings on their clinical questionnaires (such as high levels of anxiety or depression) and will be offered referral to the department's clinical psychology team (HIV positive participants) or asked to see their GP for referral to local services (HIV negative participants). They may be asked at this visit if they would be prepared to be followed up for a longer period of time to see how their symptoms and general health change over time.

## Intervention Type
Mixed

## Primary outcome measure

Proportion of participants with breathlessness in HIV positive and HIV negative groups due to:
1. Cardiac disease
2. Respiratory disease
3. Psychological causes
4. Deconditioning
5. Other
For each participant group, the causes of breathlessness will be reported as a proportion due to each of the causes above at the end of the study.

### Secondary outcome measures
The following are assessed at the baseline and at the end of the study?
1. Prevalence of depression in HIV positive and negative groups as defined by Patient Health Questionnaire (PHQ-9) score ≥5, assessed using the PHQ-9
2. Prevalence of severe depression in HIV positive and negative groups as defined by PHQ-9 score ≥20, assessed using the PHQ-9
3. Prevalence of anxiety in HIV positive and negative groups as defined by Generalised Anxiety Disorder assessment (GAD-7) score ≥5, assessed using the GAD-7
4. Prevalence of severe anxiety in HIV positive and negative groups as defined by GAD-7 score ≥15, assessed using the GAD-7

### Overall study start date
01/07/2018

### Completion date
01/07/2019

## Eligibility

### Key inclusion criteria
HIV positive participants:
1. HIV positive
2. Aged 18 years or older
3. Informed consent given
4. Chronic breathlessness (defined as MRC breathlessness score ≥2 persisting for at least 4 weeks and not due to an acute illness)
5. No definitive diagnosis to explain breathlessness (definitive diagnosis defined as patient or physician reported diagnosis substantiated by recent physiological investigations)
6. Able to participate for the duration of the study

HIV negative participants:
1. Negative HIV test (performed as part of routine care)
2. Aged 18 years or older
3. Informed consent given
4. Chronic breathlessness (defined as MRC breathlessness score ≥2 persisting for at least 4 weeks and not due to an acute illness)
5. No definitive diagnosis to explain breathlessness (definitive diagnosis defined as patient or physician reported diagnosis substantiated by recent physiological investigations)
6. Able to participate for the duration of the study

### Participant type(s)
Mixed

### Age group
Adult

### Lower age limit
18 Years

### Sex
Both

### Target number of participants
60

### Key exclusion criteria
All participants:
1. Unable to perform lung function tests.
2. Physical disability precluding the ability to complete a cardiopulmonary exercise test (for example wheelchair bound)
3. Pregnant
4. Unable to attend for investigations and review

### Date of first enrolment
24/09/2018

### Date of final enrolment
24/01/2019

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre
**Royal Free London NHS Trust**
Pond Street
London
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## Sponsor information

### Organisation
Royal Free London NHS Trust

### Sponsor details
Department of Research and Development, Royal Free Hospital, Pond Street, London
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### Sponsor type
Hospital/treatment centre

### ROR
https://ror.org/04rtdp853

## Funder(s)

### Funder type
Hospital/treatment centre

### Funder Name
Existing departmental funds, Department of Respiratory Medicine, Royal Free Hospital

## Results and Publications

### Publication and dissemination plan
We intend to present our results at relevant conferences (primarily HIV medicine related) and publish in peer reviewed journals.

### Intention to publish date
01/10/2019

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to GDPR requirements.

### IPD sharing plan summary
Not expected to be made available

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |