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Reactivation of herpesviruses and cardiovascular and cerebrovascular risk factors in an African ART population

Submission date 10/10/2017	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 15/05/2018	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 10/05/2022	**Condition category** Circulatory System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cerebrovascular disease (CBD, e.g. stroke) and cardiovascular disease (CVD, e.g. myocardial infarction and heart failure) are increasing in the general adult population in low-income countries, including those in Sub Saharan Africa (SSA). This growing CBD/CVD epidemic intersects with an ageing HIV-infected population in countries such as Malawi where successful scale-up of antiretroviral therapy (ART) has led to a rising HIV prevalence due to increased life expectancy. In Europe and the USA, HIV is associated with a 50% increased risk of CVD. Studies are now urgently needed to find modifiable CVD/CBD risk factors in HIV-infected patients in SSA. In people with chronic viral infection (such as HIV and herpesviruses) products from ongoing virus replication cause inflammation which may lead to damage to the arteries. This arterial damage may then lead to an increased risk of CBD/CVD. The main aim of this study is to find out whether ongoing inflammation from uncontrolled chronic viral infection increases the risk of CBD/CVD in HIV-infected patients on ART. The study's other aims are to find out whether CBD/CVD is more common in people with an uncontrolled chronic viral infection and ongoing inflammation.

Who can participate?
Patients aged 35 and over with HIV who are starting ART, and HIV-uninfected adults

What does the study involve?
Participants are interviewed regarding their medical history and risk factors for vascular disease. They also have a physical examination, which includes an assessment of blood pressure and a scan of the blood vessels. A 30 ml blood sample is taken for assessment of viral load, Herpeseviruses infection, blood glucose, creatinine, cholesterol and immune markers of inflammation and senescence. Follow-up visits are conducted at months 6, 12, 18, 24, 30 and 36, and include some of the assessments done at the first visit. The first visit takes about 2 hours, while follow-up visits take about 1 hour. Participants are asked to come into the study clinic at any time that they are unwell. The study team help to manage their clinical care by providing extra tests that may not be readily available under standard care.

What are the possible benefits and risks of participating?
Participants may benefit from this study by gaining knowledge of their risk factors for illnesses like stroke and heart disease, which may enable them to change their lifestyle or receive medication to reduce that risk. Participants who experience a clinical event are expected to receive improved access to tests and follow-up by the study team, compared to normal standard of care. Participants receive a refund of the cost of travelling to attend study visits. Risks to participants are minimal. However, participants may experience pain and risk of hematoma with blood samples. The amount of blood drawn is within the WHO recommended allowable amounts. Participants may also be inconvenienced by spending longer than normal at their ART appointment.

Where is the study run from?
Malawi Liverpool Wellcome Trust (Malawi)

When is the study starting and how long is it expected to run for?
May 2015 to November 2021 (updated 02/06/2020, previously: May 2021)

Who is funding the study?
GlaxoSmithKline (UK)

Who is the main contact?
1. Dr Ingrid Peterson
ipeterson@som.umaryland.edu
2. Dr Laura Benjamin
L.Benjamin@liverpool.ac.uk

Contact information

Type(s)
Public

Contact name
Dr Ingrid Peterson

Contact details
Malawi Liverpool Wellcome Trust
PO 30096, Chichiri
Blantyre
Malawi
3
+265 1874628
ingrid.peterson@lstmed.ac.uk

Type(s)
Public

Contact name
Dr Laura Benjamin

ORCID ID
https://orcid.org/0000-0002-9685-1664

Contact details
Stroke Research Centre
UCL Institute of Neurology
First Floor
Russell Square House
10-12 Russell Square
London
United Kingdom
WC1B 5EH
+44 (0)20 3108 6255
l.benjamin@ucl.ac.uk

Additional identifiers

Protocol serial number
P02161874

Study information

Scientific Title
Protocol for a longitudinal, cohort study to evaluate Reactivation of Herpesviruses and Inflammation as Cardiovascular and Cerebrovascular risk factors in Antiretroviral initiators, in an African HIV population (RHICCA)

Acronym
RHICCA

Study objectives
Immune activation, and in turn dysfunction, driven by HIV and reactivation of latent herpesvirus infections leads to increased cardiovascular and cerebrovascular risk in adults aged > 35 years in SSA.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. University of Malawi College of Medicine Ethics Committee, 05/30/2016, ref: P02/16/1874
2. Liverpool School of Tropical Medicine Research Ethics Committee, 08/10/2016, ref: 16-014

Study design
Single-centre 36-month observational prospective cohort study

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Cardiovascular and cerebrovascular disease

Interventions
The primary study exposures are HIV infection, CMV reactivation, and markers of inflammation and endothelial dysfunction. HIV tested at baseline in all participants (ART patient and HIV uninfected community controls). HIV status will be assessed yearly by rapid test in HIV-uninfected participants to detect sero-conversion. Reactivated latent herpes viral infections will be assessed by quantification of IgG VZV, CMV and HHV-8 antibodies at baseline in HIV uninfected controls and at baseline and 6 months in HIV infected participants. In all participants, at baseline, 6, 12, 24 and 36 months we will measure soluble markers in plasma , which are associated with systemic inflammation (plasma IL-6, hsCRP), and activation of coagulatory pathways (D-Dimers) and endothelial activation (sICAM-1 and sVCAM-1).

Intervention Type
Other

Primary outcome(s)
1. Carotid intima media thickness (cIMT) is assessed by ultrasonography at baseline and 24 months
2. Carotid femoral pulse wave velocity (PWV) is assessed using a Vicorder at baseline, 6, 12, 18, 24, 30 and 26 months

Key secondary outcome(s))
All secondary outcomes are reviewed by an Endpoint Review Committee, comprised of medical experts. Retrospective assessment of outcomes deceased cases is done by medical record review, or by verbal autopsy if the individual died > 4 weeks after hospital discharge (or with no hospital admission). Verbal autopsy is conducted using a standardized WHO assessment tool
1. Stroke is measured at all occurrences by clinical assessment with standard protocols with MRI confirmation
2. Myocardial infarction (MI) is measured at all occurrences by clinical assessment with standard protocols, and ECG confirmation
3. Unstable angina is measured at all occurrences by clinical assessment with standard protocols, and ECG confirmation
4. Peripheral vascular disease (PVD) is measured at baseline, 6, 12, 18, 24, 30 and 36 months by calculation of ankle brachial pressure index (ABPI), which is assessed by sphygmomanometer and doppler ultrasound. A change of >0.15 ABPI from baseline is considered clinically significant PVD
5. All cause death or vascular death is measured at all occurrences. For deaths occurring within 4 weeks of hospital admissions, cause of death will be assessed by medical record review using standardized protocols. Deaths occurring >4 week post hospital discharge (or with no hospital admission) will be assessed by verbal autopsy
6. Immune Reconstitution Syndrome [IRIS] vasculopathy is measured at all occurrences within 6 months of the baseline visit. It is defined as a vascular event (ex. stroke, MI or unstable angina) accompanied by a decrease in viral load >1 log10 copies from baseline

Completion date
30/11/2021

Eligibility

Key inclusion criteria

1. Aged => 35 years
2. Resident in Blantyre
3. HIV-infected patients must further be ART-naïve or initiated ART <10 days prior to enrolment
4. Initiating standard first-line ART (in Malawi this is: TDF/3TC/EFV)
5. Adult controls must further be HIV uninfected

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Clinical history of CVD/CBD
2. Pregnant
3. Critically ill or have symptomatic anaemia at enrolment
4. Enrolled in an intervention study

Date of first enrolment
17/05/2017

Date of final enrolment
30/11/2020

Locations

Countries of recruitment
Malawi

Study participating centre
Malawi Liverpool Wellcome Trust
PO 30096, Chichiri
Blantyre
Malawi
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Sponsor information

Organisation
GlaxoSmithKline

ROR

https://ror.org/01xsqw823

Funder(s)

Funder type
Industry

Funder Name
GlaxoSmithKline

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Participant level data for sub-analyses will be available upon request conditional upon approval by study committee approval of proposed sub-study. Please contact Ingrid Peterson (idpet2@gmail.com) or Laura Benjamin (L.Benjamin@liverpool.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	12/09/2019	05/10/2020	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes