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The impact of HIV infection on bone and muscle development in Zimbabwean children

Submission date
19/07/2019

Recruitment status
No longer recruiting

Registration date
22/07/2019

Overall study status
Completed

Last Edited
18/08/2023

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Increasing numbers of children with HIV are surviving to adulthood due to global roll-out of HIV treatment. However, nearly 50% of children have impaired growth, including stunting and delayed puberty, due to HIV. Poor growth directly affects bone development, particularly during adolescence when the pubertal 'growth-spurt' occurs, which makes adolescence such a critical period for bone development. Currently, the extent to which HIV infection affects the growing skeleton through puberty is unknown. This is important to understand because poor bone growth is a key risk factor for adult osteoporosis and hence a person's future risk of sustaining a fracture; fractures can be lifechanging leading to pain and disability.
We aim to understand how HIV affects bone growth in children during the pubertal period. We will conduct a study in Harare, Zimbabwe to assess the differences in bone density (the amount of bone mass for a given bone size) between HIV-infected and uninfected children (aged 8-16 years) and measure how bone grows differently in these two groups over the course of a year. Our findings will determine how HIV impacts bone growth and whether HIV-infected children will require interventions to enhance bone development to try to avoid premature osteoporosis in adulthood.

Who can participate?
Children living in Harare aged 8-16 with vertically acquired (mother-to-child) HIV who are aware of their condition.

What does the study involve?
If a parent and child agree to take part in the research, they will be invited to our study centre where we will go through a questionnaire about the participant's health. We will examine muscle function by measuring hand grip strength and taking long jump measurements. We will take a blood test, special bone scans and a hand x-rays to assess how well the bones are growing. This will all be carried out in one session and then we will request for participants to return after a year to have all these assessments repeated.

What are the possible benefits and risks of participating?
Potential benefits to participants:
Children and guardians who take part in the study will benefit from gaining knowledge about

their growth and development.
A small number of children will benefit from the identification of musculoskeletal conditions and will be referred on to specialists for further management.
All transport costs for visits will be covered and all the tests will be done free of charge.
Potential benefits to society:
Determining the risk factors for low bone density in children with HIV will highlight which risk factors doctors and other health professionals should focus on for screening and treatment. For example, we may find that low muscle strength is a risk factor for low bone density. Therefore, targeted physiotherapy may be included in the treatment of HIV in addition to medications. This is important because adolescence provides a unique window of opportunity to improve the maximum amount of bone mass that can be reached in adulthood and therefore reduce the chances of osteoporosis and fractures in adulthood.
This project will also develop measurement standards for DXA, pQCT, bone age and muscle strength for Zimbabwean children which are currently lacking and form a bank for future research, for example, genetic studies.
Risk to participants:
Children who do not know their HIV status will be eligible to take part in the research and there is the possibility that children will be newly identified as HIV positive on testing. This can be a psychologically difficult time for children and their guardians. Staff will be trained to provide counselling and how to explain the new diagnosis in an age-appropriate manner and involve the caregiver in the process. The HIV status of children will not be disclosed to any health care workers without the consent of the guardian and child.
There is a low risk of radiation from being near X-rays. Every person is naturally exposed to small levels of radiation from the sun and the bedrock of the earth (background radiation). High levels of radiation can lead to cancer. However, the level of radiation used in a DXA and pQCT scan are much lower than the levels that may cause cancer. This study is considered a minimal level risk. Trained radiographers will perform bone scans using the smallest amount of radiation possible. As ionising radiation can be more harmful during pregnancy, a urine pregnancy test will be done before scanning.
Up to 15ml of blood will be taken from study participants. This may be associated with discomfort, pain or bruising at the venepuncture site. Staff will be trained in how to take blood to minimize these risks.
No serious adverse events are anticipated but there is a small risk of incidents such as breaches of confidentiality following HIV diagnosis, negative life-events following study participation or HIV diagnosis and needle stick injuries. Procedures will be in place to deal with any adverse events that may arise and will be reported back to local ethics committees. Staff will receive training on how to handle any of these events in case they arise.

Where is the study run from?
1. Parirenyatwa Hospital, Zimbabwe
2. Harare Central Hospital, Zimbabwe

When is the study starting and how long is it expected to run for?
May 2018 to October 2020

Who is funding the study?
Wellcome Trust, UK

Who is the main contact?
Dr Ruramayi Rukuni
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
MRCZ/A/2297

Study information

Scientific Title
The IMpact of Vertical HIV infection on child and Adolescent Skeletal development in Harare (IMVASK) study

Acronym
IMVASK

Study objectives
We hypothesize that HIV infection affects skeletal development, such that children with HIV, despite antiretroviral therapy, accrue less bone mass during skeletal development and achieve lower bone mineral density, and ultimately lower peak bone mass, compared to children who are not infected, therefore putting them at increased risk of osteoporosis and fractures in adulthood.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 14/05/2018, London School of Hygiene and Tropical Medicine Ethics Committee (Keppel Street, London, WC1E 7HT, UK; ethics@lshtm.ac.uk; +44(0) 20 7636 8636), ref: 15333
2. Approved 20/02/2018, Institutional Review Board of the Biomedical Research and Training Institute (BRTI, 10 Seagrave Road, Avondale, P.O. Box CY 1753, Causeway, Harare, Zimbabwe; admin@brti.co.zw; +263 242 333 091), ref: AP 145/2018
3. Approved 01/03/2018, Joint Research Ethics Committee for University of Zimbabwe College of Health Sciences and the Parirenyatwa Group of Hospitals (JREC) (JREC Office No 4, 5thFloor College of Health Sciences Building, Parirenyatwa Hospital, Mazowe Street, Harare, Zimbabwe; jrec@medsch.uz.ac.zw; +263 242 708 140 extension 2241), ref: 11/18
4. Approved 23/02/2018, Harare Central Hospital Ethics Committee (HCHEC) (Harare Central Hospital, Lobengula Road, P.O. Box ST 14, Southerton, Harare, Zimbabwe; pasic@bechr.co.zw; +263 242 621 100-19), ref: 170118/04
5. Approved 10/04/2018, Medical Research Council of Zimbabwe (Medical Research Council of Zimbabwe, Josiah Tongogara/Mazowe Street, P.O. Box CY 573, Causeway, Harare, Zimbabwe; mrcz@mrcz.org.zw; +263 242 791 792), ref: MRCZ/A/2297
6. Approved 13/02/2018, Ministry of Primary and Secondary Education Zimbabwe (Ambassador House, 88 Kwame Nkrumah Avenue/Second Street, Harare, Zimbabwe; admin@mopse.gov.zw), ref: C/426/Harare

Study design
Frequency-matched prospective cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Other

Study type(s)
Prevention

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
HIV, musculoskeletal health

Interventions
The following data will be collected from participants at baseline and follow-up (after one year):
• An interviewer-administered questionnaire
• A standardised musculoskeletal examination including a screening musculoskeletal examination (pGALS), anthropometry (standing and sitting height with mid-upper arm circumference), pubertal staging (Tanner) and assessment of muscle strength and function of

the upper limb and lower limb using grip strength dynamometry, standing long jump respectively.
• DXA scans will be performed to measure lumbar spine, left hip and total body bone mineral density.
• pQCT scans of the left tibia will be taken at distal and proximal sites to measure cortical and trabecular bone density.
• An X-ray of the non-dominant hand will be taken to quantify skeletal maturation as bone age.
• A blood sample (up to 15ml) will be collected for HIV markers (CD4 and viral load) from HIV-infected children only. Children without HIV will have a diagnostic HIV test. Serum will be stored and frozen to measure of bone biochemistry in the future. DNA will also be stored frozen will form a biobank supporting future studies.

Intervention Type
Other

Primary outcome measure
1. Total-body less-head (TBLH) Bone Mineral Content (BMC) for lean mass adjusted-for-height (TBLH-BMCLBM) Z-scores) measured using DXA (dual-energy X-ray absorptiometer) at baseline and one year
2. Lumbar spine (LS) Bone Mineral Apparent Density (BMAD) (LS BMAD) Z-score measured using DXA at baseline and one year

Secondary outcome measures
1.1 Prevalence of low muscle function; grip strength (Z-score < -2) measured using grip strength meter (dynamometer) at baseline
1.2 Prevalence of standing long jump-for-age (Z-score < -2) measured using standing long jump distance measurement at baseline
1.3 Musculoskeletal abnormalities/disabilities by HIV status at baseline measured using questionnaire and screening musculoskeletal exam (pGALS) at baseline
2.1 Mean percentage change in TBLH BMCLBM (g) and LS BMAD (g/cm3) measured using DXA at baseline and one year
2.2 Tibial cortical and trabecular volumetric BMD (g/cm3), total cross sectional area, cortical thickness and bone strength measured using pQCT at baseline and one year
2.3 Muscle mass measured using DXA at baseline and one year
2.4 Muscle function at baseline and one year, by HIV status measured using hand grip strength meter (dynamometer) and standing long jump distance measurement at baseline and one year
3. Assessment of the extent to which pubertal delay (chronological age - bone age> 2 years) explains changes in these bone and muscle outcomes measured using hand x-ray (to measure bone age) and questionnaire (to measure chronological age) at baseline and one year

Overall study start date
01/08/2017

Completion date
31/10/2020

Eligibility

Key inclusion criteria
1. Age 8-16 years (includes pre- and peri-pubertal children)
2. Living in Harare

3. With HIV only if:
3.1 Vertically-acquired HIV and taking ART for at least two years (as adult studies demonstrate ART initiation is followed by an initial decline in BMD which stabilizes after 2 years)
3.2 The child is aware of their HIV status, to avoid inadvertent disclosure as a result of study participation

Participant type(s)
Mixed

Age group
Child

Lower age limit
8 Years

Upper age limit
16 Years

Sex
Both

Target number of participants
300 children (8-16 years) with HIV and 300 children (8-16 years) without HIV

Key exclusion criteria
1. Acute illness (requiring immediate hospitalisation) and lack of consent

Date of first enrolment
14/05/2018

Date of final enrolment
31/10/2019

Locations

Countries of recruitment
Zimbabwe

Study participating centre
Parirenyatwa Hospital
Mazowe Street
Harare
Zimbabwe
P. O. Box CY 198, Causeway

Study participating centre

Harare Central Hospital
Lobengula Street
Southerton
Harare
Zimbabwe
P.O. Box 14, Southerton

Sponsor information

Organisation
Biomedical Research and Training Institute

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P.O.Box CY 1753 Causeway
+263 242 333 091
admin@brti.co.zw

Sponsor type
Research organisation

Website
www.brti.co.zw

ROR
https://ror.org/0130vhy65

Organisation
London School of Hygiene

Sponsor details
Clinical Research Department
Keppel Street
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United Kingdom
WC1E 7HT
+44 (0)20 7636 8636
study@lshtm.ac.uk

Sponsor type

University/education

Website
https://www.lshtm.ac.uk

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Results of interim data analysis will be presented at national and international research meetings and conferences. Study findings will be published in international peer reviewed scientific journals and disseminated to research communities at the end of study.

Planned publications:
Study protocol - Bone Density and Muscle Function in Zimbabwean Children: A Study Protocol for the IMVASK Project (December 2019).
Literature review - Bone Density and Muscle Function in African Children and Adolescents: Gaps in the literature and progress towards establishing African reference data sets (November 2019)
Baseline data analysis - Prevalence of and risk factors for low bone density and reduced muscle function in HIV-infected African Children (December 2019)
Follow up data analysis - Comparative changes in bone mass accrual between HIV-infected and uninfected children (September 2020)

Intention to publish date
01/09/2020

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.
Anonymised research data will be made available for sharing through the open access data repository established by the LSHTM Data Management Support Service at the time of publication (https://datacompass.lshtm.ac.uk). This will allow other research groups to request access to study data and tools. Consent has been obtained from participants to share anonymised research data with other researchers.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		09/02/2020	30/11/2021	Yes	No
Results article		25/11/2022	18/08/2023	Yes	No
Results article		01/04/2023	18/08/2023	Yes	No
Results article		01/08/2021	18/08/2023	Yes	No