NEWSLETTER #1 3rd MAY 2023

IMPALA NEWS

IMPROVING HIV OUTCOMES IN AFRICA WITH LONG ACTING ANTIRETROVIRALS

Welcome to the IMPALA study

Foreword by the Chief Investigator and Principal Investigator

Long-acting antiretroviral therapy is one of the most exciting breakthroughs in the last two decades of HIV treatment. Almost all participants who have received the injectable HIV treatment in clinical trials prefer it to oral therapy and the community are eager for access to injectable ART. Following a decade of research, the regimen of long-acting (LA) cabotegravir and rilpivirine given by 2-monthly intramuscular injections is now approved by the US Federal Drug Authority and European Medicines Agency and rollout is underway in several countries. However, robust data from Africa is needed to inform policy for the continent and to ensure that it can be safely used in programmatic HIV care settings using the public health approach.

The roll out of antiretroviral therapy (ART) across the globe over the last two decades has been a remarkable feat of the public health approach. However, advanced HIV disease (AIDS) and its associated opportunistic infections/illnesses continue to cause a huge burden of disease and suffering. In 2021, there were 650,000 deaths from AIDS-related illnesses, 187,000 deaths from HIV-associated TB and 250,000 cases of cryptococcal meningitis.

Dr Fiona Cresswell
Chief Investigator

Academic Clinical Lecturer

Honorary Research Fellow

MRC/UVRI-LSHTM Uganda Research Unit

Dr Eugene Ruzagira
Principal Investigator

Head of HIV Interventions programme

MRC/UVRI-LSHTM Uganda Research Unit

Assistant Professor, EPH, LSHTM

Nowadays, the majority of people with advanced HIV disease are ART-experienced but have struggled with the fastidious daily pill-taking required to suppress the HIV virus. In order to reach the UNAIDS 95-95-95 target, radical new approaches are needed to increase the proportion of people who remain virologically suppressed on ART. In 2021, of all people living with HIV worldwide, only 68% [60-78%] were virally suppressed. Injectable ART is a paradigm shift that may be life changing for people who do not engage with oral therapy.

CARES trial (Cabotegravir and Rilpivirine Efficacy and Safety) is investigating the LA regimen of 2-monthly cabotegravir and rilpivirine in people with good adherence to first-line oral ART in sub-Saharan Africa. IMPALA trial (IMProving HIV Control in Africa with Long-acting Antivirals) builds upon the evidence provided by CARES by further investigating the LA regimen in people with a history of sub-optimal adherence to first-line oral ART. Randomised clinical trials (RCTs) are the gold standard for evaluating new interventions as they minimise the risk of bias and confounding affecting the study findings.

Owing to their rigor, RCTs are also labour intensive, slow and costly, and therefore it is vital to maximise the scientific outputs from the trial by including qualitative work, maximising the generalisability of the results, sharing data and utilising samples wisely. We are grateful for the oversight of the Trial Steering Committee and Independent Data Safety Monitoring Committee who are ensuring that the trial is conducted ethically, safely and considers emerging data in the field and the views of the community.
All the trial collaborators and supporters deserve a deafening round of applause for all the hard work that has gone into getting the study off the ground. This newsletter summarises the achievements thus far and maps out the milestones on the road ahead.

IMPALA trial is funded by Janssen Pharmaceutical Companies of Johnson & Johnson. The trial is coordinated by MRC/UVRI-LSHTM Uganda Research Unit.

STUDY COLLABORATORS

Uganda
- Entebbe Hospital
- Joint Clinical Rearch Centre
- Infectious Diseases Institute

UK
- London School of Hygiene and Tropical Medicine

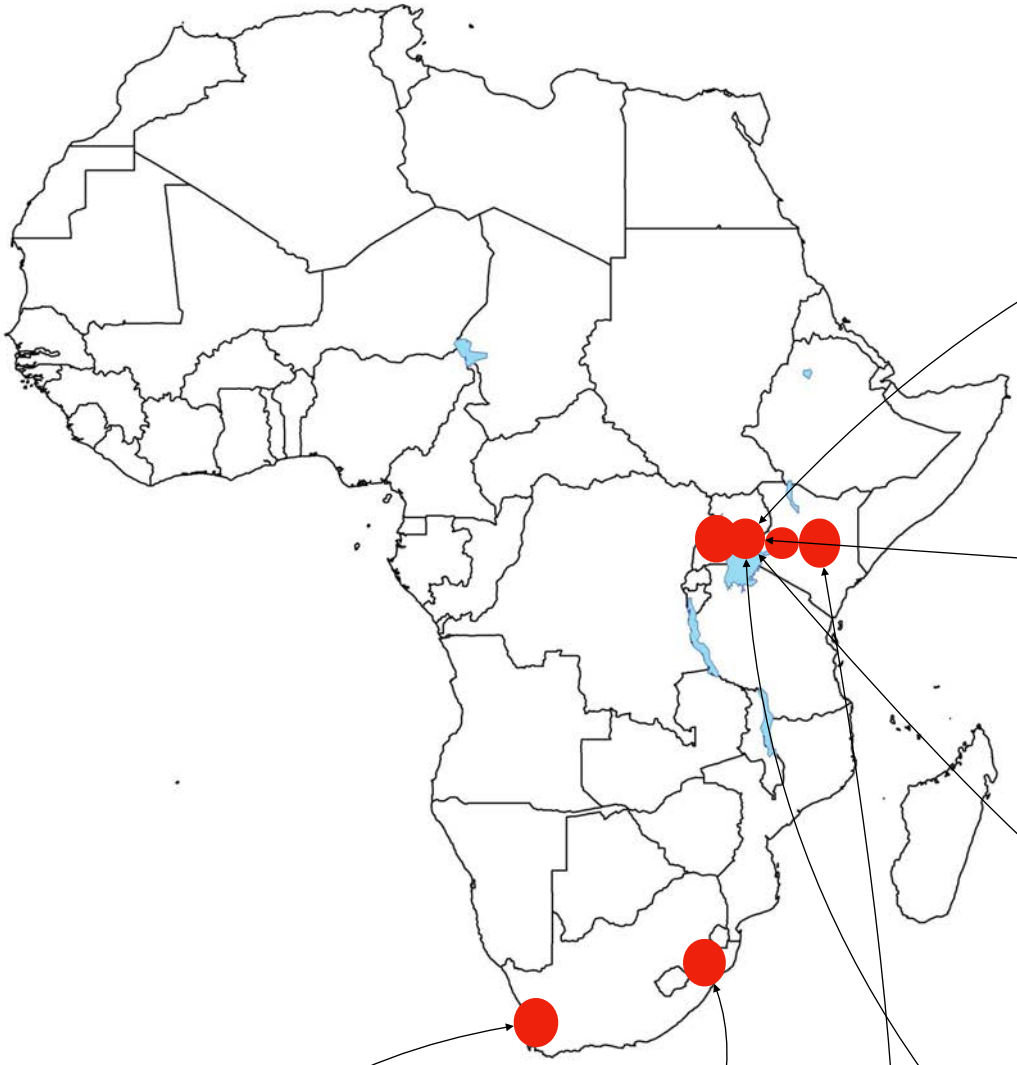
Kenya
- University of Nairobi

USA
- Harvard University

South Africa
- CAPRISA, Durban
- Desmonnd Tutu Health Foundation, Capetown

Belgium
- Janssen
- CCSM

Collaborators and Sites



PI: Dr Eugene Ruzagira
Collaborator: MRC/UVRI/ LSHTM Uganda Research Unit
Site: Entebbe Hospital

PI: Dr Gilbert Ategeka
Collaborator: Joint Clinical Research Center, Uganda
Site: JCRC Fort Portal

PI: Dr Noela Clara Owarwo & Evă Laker
Collaborator: Infectious Diseases Institute, Uganda
Site: IDI, Kampala

PI: Dr Henry Mugerwa
Collaborator: Joint Clinical Research center
Site: JCRC Lubowa (Backup site)

PI: Dr Sheetal Kassim
Collaborator: Desmond Tutu Health Foundation (DTHF), Cape Town, South Africa
Site: J52 Trials Unit

PI: Dr Sharana Mahomed & Dr Nigel Garret
Collaborator: CAPRISA, Durban, South Africa
Site: CAPRISA eThekwini Research Clinic

PI: Dr Loice Achieng Ombajo
Collaborator: University of Nairobi
Sites: Kenyatta National Hospital, Nairobi. Jaramogi Oginga Odinga Hospital

Funder & Collaborative Partner: Janssen Pharmaceutical companies of J&J

Virological suppression is dependent on adherence to safe and efficacious anti-retroviral treatment. Treatment simplification and long-acting alternatives can serve as an option to patients struggling with compliance to daily oral pills.

Johnson & Johnson, in collaboration with ViiV Healthcare, is proud to be working alongside the MRC/UVRI-LSHTM Uganda Research Unit and all participating sites to evaluate the use of cabotegravir and rilpivirine long-acting injection treatment in persons living with HIV, who struggle with adherence to daily oral pills and who may benefit from treatment options with reduced dosing frequency. We are excited to investigate the impact of this regimen on care and treatment outcomes for such patients in Africa, and are proud of the work done so far.

We wish the study team all the best as the Impala study progresses.

Sincerely
Dr. Fafa Addo Boateng
Director of Data and Evidence Generation
on behalf of Janssen Pharmaceutical Companies of Johnson & Johnson

Johnson & Johnson

Fafa Addo Boateng

Dr Fridah Mwendhia

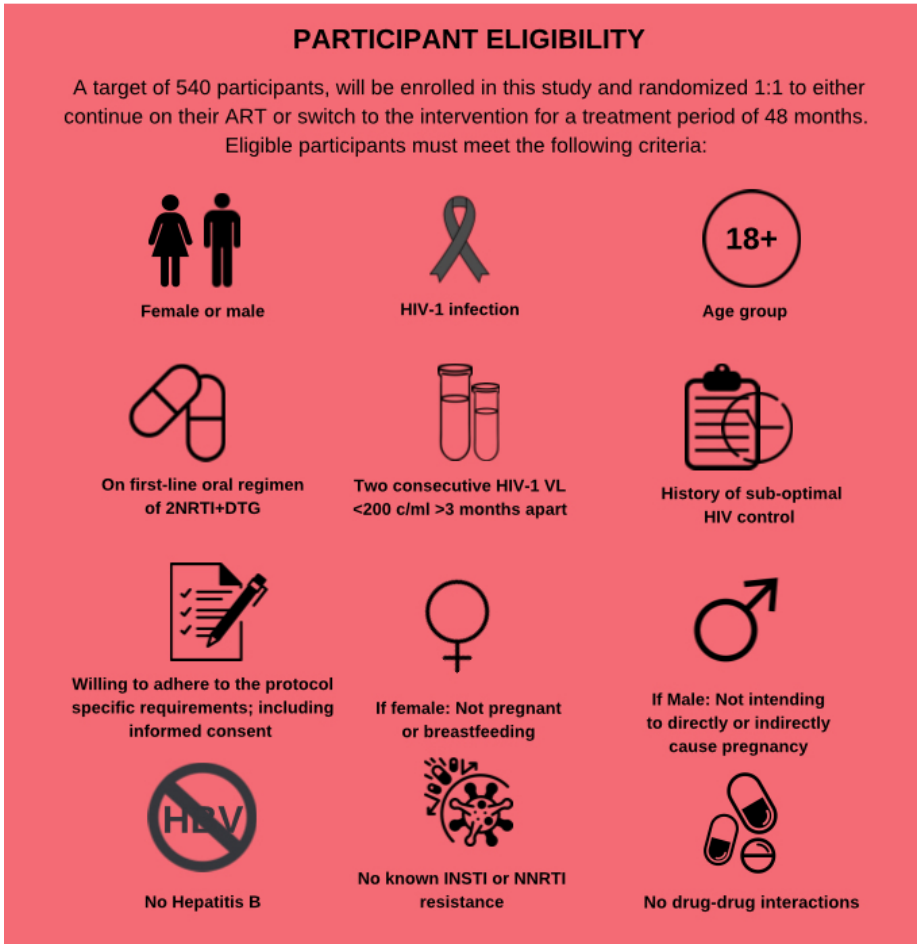
Stanislav Meshcheryakov

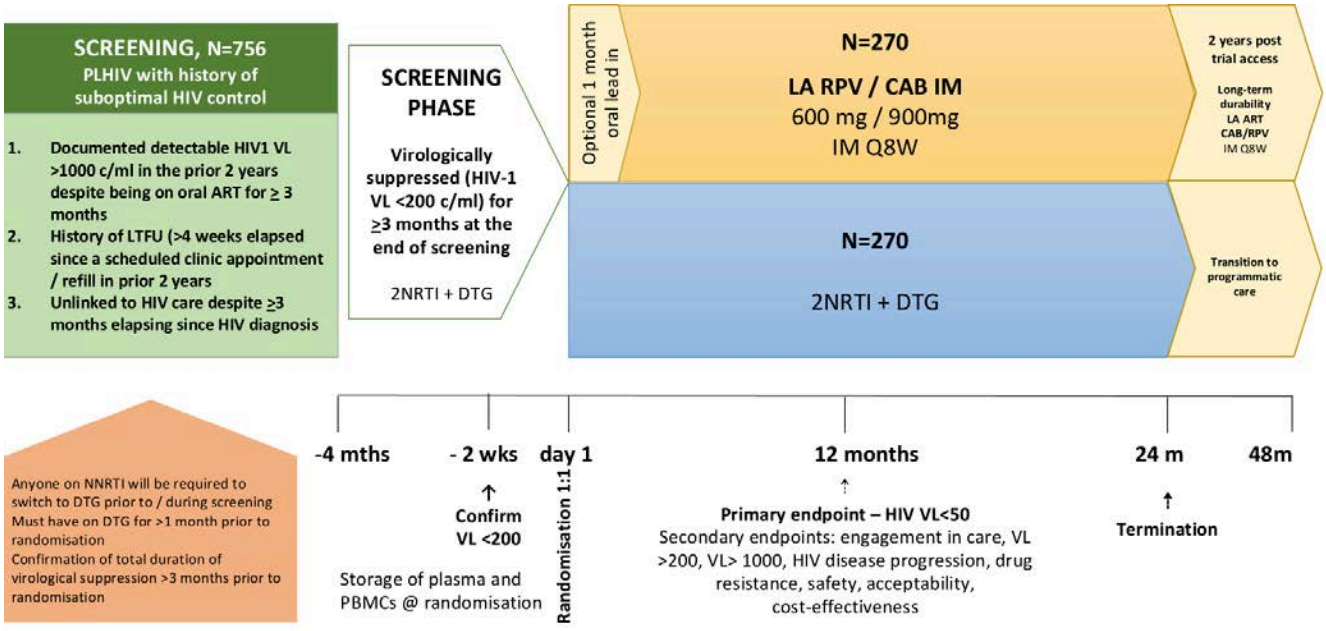
Ingrid-Eshun Wilsonova

Idahosa Awhonukeh

Study Design

IMPALA is an open-label 2-arm parallel design randomised clinical trial conducted amongst 540 virologically suppressed adults with a history of sub-optimal HIV control. The intervention arm is 2-monthly intramuscular LA cabotegravir and LA rilpivirine with a 1-month optional oral lead in. The control arm is a continuation of dolutegravir-based oral ART. The primary endpoint is HIV virological suppression (VL <50 copies/ml) at 12 months. Total duration of follow-up is 24 months.





SOCIAL SCIENCES

Alongside the clinical trial we will conduct a qualitative methods study with the aim of understanding the acceptability of the LA treatment compared to daily oral therapy. This study is led by Dr Agnes Ssali (MRC/UVRI/LSHTM) and Dr David Lawrence (LSHTM) and will involve in-depth interviews with participants from both treatment arms in Uganda and South Africa. These qualitative data will complement the survey data which include EuroQoL-5D-5L, Medical Outcomes Study HIV Health Survey (MOS-HIV), HIV Treatment Satisfaction Questionnaire (HIVTSQ), and a question on Treatment Preference. In addition, we will explore the feasibility of widespread implementation of LA treatment by conducting in-depth interviews with key stakeholders in all three recruiting countries, including those delivering HIV care within and outside of the IMPALA trial.

Dr David Lawrence
LSHTM

Dr Agnes Ssali
MRC/UVRI/LSHTM

OVERSIGHT - TSC & IDMC

The Independent Data and Safety Monitoring Committee periodically reviews recruitment progress and safety data by trial arm and ensures there is no signal of harm from the study. The IDMC Chair can suggest changes to the protocol or procedures based on accruing data.
The Trial steering Committee provides independent expert oversight and is a source of impartial advice regarding major decisions within the trial. The TSC takes into account the suggestions of the IDMC and other emerging data which affects scientific equipoise.

HEALTH ECONOMICS

Dr. Ruanne Barnabas serves as Chief of the Division of Infectious Diseases at Massachusetts General Hospital and holds joint appointments at Harvard Medical School and the Harvard T.H. Chan School of Public Health. She is the principal Investigator of clinical studies that aim to increase equity in health outcomes through client-centered approaches.

Her projects generate individual-level efficacy and cost data and use health economic models to estimate the potential population-level impact and cost-effectiveness of interventions beyond the scope of clinical trials. Dr. Jesse Heitner is a health economist working with Dr. Barnabas to cost proposed interventions, estimate future costs averted, and quantify projected health impacts.

Together, Drs. Barnabas and Heitner will lead the data collection and analysis to estimate the difference in medical resource utilisation between IMPALA's study arms due to differential patterns of medical encounters such as clinical visits for opportunistic infections and inpatient hospitalisations. They will also perform exploratory health economic analysis in a separate model- based analysis.

COMMUNITY ADVISORY BOARD

The purpose of community advisory board (CAB) is to act as a connection between the researchers and the community where research is conducted.
It is important that CAB members have information and accurate information about the study that is going on in the community. They report community perspectives to the study team and give correct information back to the community to allay fears or questions about the study.

On the 10th of February 2023, we had a meeting with the Uganda Virus Research Institute CAB and presented the IMPALA study to the CAB members. The CAB members were very receptive to the information and had existing knowledge of injectable antiretrovirals because of the cabotegravir pre-exposure prophylaxis studies that took place in their communities.
They had interesting and intelligent questions about the study, and all these were answered by the Chief Investigator Dr Fiona Creswell and Study Coordinator Dr Ubaldo Bahemuka. The study team will engage the CAB on a regular basis during the study.

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KEY ACHIEVEMENTS SO FAR

- Master agreement signed – 2nd August 2022
- Joint protocol review panel in Uganda – 25th Aug 2022
- Protocol amended – 30th Sept 2022
- Submissions to RAs in South Africa - 13th Oct 2022
- Submissions to RAs in Kenya - 20th Oct 2022
- Ugandan RA approvals in place- 7th Nov 22
- IDMC introductory meeting #1 - 25th Nov 22
- SIV MRC clinic, Entebbe - 29/30th Nov 22
- TSC introductory meeting #1 - 2nd Dec 22
- First participant screened, Entebbe - 8th Dec 22
- SIV IDI, Kampala - 8/9th Dec 22
- First participant randomised, Entebbe - 6th Jan 23
- SIV JCRC, Fort Portal - 7/8th Feb 23
- First participant randomised, JCRC FP - 16th March 23
- First participant randomised at IDI - 20th March 23

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MILESTONES AHEAD

Q2

- SIV University of Nairobi
- SIV CAPRISA and DTHF
- IDMC meeting #2

Q3

- TSC meeting #2
- Investigator meeting

Q4

- Complete enrolment of 540

2024

- Interim analysis
- IDMC meeting #3
- TSC meeting #3

2025

- Primary endpoint analysis

2026

- Database lock

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UPDATE ON 3RD MAY 2023:
Screened = 167
Recruited = 66

Introduction to Coordinating Centre

MRC/UVRI/ LSHTM Uganda Research Unit has a team of staff that is working with the IMPALA Trial sites to ensure patient safety, high quality data and consistency across sites.

Team

Victoria Babirye Tumusiime is the IMPALA Trial Manager at the MRC/UVRI/LSHTM Uganda Research Unit. She has a wealth of experience in clinical trial research, quality assurance, and study coordination especially in HIV vaccine, Ebola & Marburg clinical trials research. Victoria holds a Master of organisational psychology, a Bachelor of Community Psychology and a Diploma in Registered Comprehensive Nursing. She has recently completed her Master of Health Services Research and her research work was funded by the MAKBSSR an NIH funded program at Makerere University School of Public health. Victoria's strengths are in quality assurance and interpersonal skills, essentially competencies for clinical trials! Victoria is a mother of five and loves reading scientific and motivational literature books when she can find time.

Paddy Kafeero - Data Manager Paddy, a keen mathematician, built the database. He has been busy training all the site staff on how to use REDCap and the eCRFs. As the data manager for IMPALA trial he will be sending you plentiful friendly queries to ensure that the data is complete and of the highest quality.

Dr Geofrey Kimbugwe MBChB, MPH, MRQA is Head of Research Governance at the MRC/UVRI & LSHTM Uganda Research Unit, and is a member of the LSHTM Research Governance Committee. He is an experienced Medical Doctor and Clinical Researcher who has worked in several healthcare facilities and on research studies that span from HIV vaccine, high risk cohort and treatment studies, to Ebola and COVID-19 vaccines and drugs. Dr Geofrey is GCP Audit trained and oversees the multitude of interventional and observational studies conducted at the Unit to ensure absolute compliance to local and international standards of best practice including ICH-GCP, ISO15189, GCLP and LSHTM/Unit Standard Operating Procedures (SOPs) and Policies. He provides Sponsorship oversight and as well leads the Regulatory, Quality and Monitoring teams at the Unit and we are grateful to have him on the IMPALA study.

Charles Ogwang is a certified Clinical Research Associate, registered nurse and the lead monitor for the IMPALA study. He has been in the clinical research field since 2008 and is enthusiastic about quality with a keen eye for detail. He has worked on trials covering Ebola, COVID19, yellow fever, TB, diabetes, vaccines and HIV in the past so has many feathers in his cap. The IMPALA site teams will all get to know Charles well during monitoring visits over the coming 2 years.

University of Nairobi protocol training

The University of Nairobi team including site staff from Kenyatta National Hospital and Jaramogi Oginga Odinga Teaching and Referral Hospital convened on 3-5th April in Nairobi for protocol and REDCap training. The training was supported by Dr Claire Norcross, Victoria Tumusiime and Paddy Kafeero. The University of Nairobi team are hoping to begin enrolment in June.

CONTACTS

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MRC/UVRI and LSHTM Uganda Research Unit