NEWSLETTER #3 4 DECEMBER 2024

IMPALA NEWS

IMPROVING HIV OUTCOMES IN AFRICA WITH LONG ACTING ANTIRETROVIRALS

WELCOME TO THE THIRD IMPALA NEWSLETTER

What an action-packed year it has been! We hope that you have a peaceful festive period ahead to rest, rejoice and reflect. This year has seen the exciting milestone of completion of recruitment on 6th May 2024 and the interim analysis in September 2024. You should all feel incredibly proud of the commitment and teamwork undertaken to achieve these milestones. We celebrated these achievements at the Investigator meeting in Nairobi on 1st and 2nd October. It was such a joy to be together in person and the meeting really cemented the value and importance of these face-to-face gatherings in an increasingly virtual world. More on the meeting in the pages ahead.

As we look to the year ahead, we can focus our minds on the analysis and presentation of the primary outcome data, hopefully at the International AIDS Society conference in Rwanda on 13-17th July. We hope that as many of us as possible may be able to attend. To deliver on this next milestone we trust that we will continue to work closely with the coordinating centre team to ensure that the trial conduct aligns with the protocol, the data is complete and correct, and that participant safety is centre stage.

Amidst the daily grind we mustn't lose sight of the reason why we are doing this study, because people living with HIV in Africa are eager for better treatment options that are free of the daily pill burden and stigma. Let's ensure that one day, in the not-too-distant future, through science, collaboration and advocacy their wishes will be answered.

Warm wishes to you and your loved ones for the festive season.

Fiona and Eugene

Dr Fiona Cresswell
Chief Investigator

MRC/UVRI-LSHTM Uganda Research Unit

Associate Professor, Brighton & Sussex Medical School

Dr Eugene Ruzagira
Principal Investigator

Head HIV Interventions, MRC/UVRI-LSHTM Uganda Research Unit

Associate Professor, LSHTM

Victoria Tumusiime

Trial manager

SCENES FROM THE 2ND INVESTIGATOR MEETING IN NAIROBI

STUDY PROGRESS

After a concerted efforts from all sites we reached the 100% enrolment target of 540 study participants on 6th May 2024. So far retention in study has been excellent with 99% of participants remaining in follow-up. The enrolment numbers by site are shown here:

IMPALA site updates	MUL	IDI	JCRC	KNH	JOOTRH	CAPRISA	DTHF	Total
Enrolments	79	81	80	80	80	50	90	540
Active	79	79	79	78	80	50	89	534
Withdrawn	0	2	1	2	0	0	1	6

MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda; IDI: Infectious Disease Institute, Kampala, Uganda; JCRC: Joint Clinical Research Centre, Fort portal, Uganda; KNH: Kenyatta National Hospital, Nairobi, Kenya; JOOTRH: Jaramogi Oginga Odinga Teaching & Referral Hospital, Kisumu, Kenya; CAPRISA: Centre for the AIDS Programme of

We appreciate the dedication in reaching this important milestone. Having completed enrolment it means that we are on track to be able to deliver the primary endpoint results, and hopefully publish the primary manuscript, in the middle of 2025. Further updates on study progress will be shared in due course.

STUDY MONITORING VISITS

You will all be familiar with the study monitors Charles Ogwang and Miriam who are working hard to deliver the trial monitoring plan. As you know the regulations that oversee clinical trials are extensive and they do a fantastic job ensuring that day to day activities on the ground align with those regulations. Central monitoring is also being performed by Paddy Kafeero, Jonathan Kitonsa, Jane Nabbuto and Claire Norcross and and you are now well versed with the queries via REDCap.

Site Name	Interim Visit 03	Interim Visit 04	Interim Visit 05
MUL	Completed	Completed	April/May 2025
IDI	Completed	Completed	May/June 2025
JCRC	Completed	Completed	April/June 2025
JOOTRH	Completed	March/April 2025	August/September 2025
KNH	Completed	March/April 2025	August/September 2025
DTHF	Completed	June/July 2025	December 2025
CAPRISA	Completed	June/July 2025	December 2025

PROTOCOL AMENDMENT

Protocol amendment, key changes

- To allow for the use of alternative oral bridging treatment (e.g. TLD)
- Deletion of Month 19 visit, which was not required
- Specifying start of suppressive oral therapy for participants discontinuing injectable cabotegravir/ rilpivirine after the first dose
- Changes to the list of adverse events of special interest (AESI). Now only *systemic* post-injection reactions are considered an AESI.
- Clarification on the definition of participants lost to follow-up
- Addition of questions on changes in appetite
- Inclusion of participants with confirmed virological failure in the qualitative sub-study
- Inclusion of peak drug level pharmacokinetics sampling
- Clarification of procedures for pregnant participants who continue CAB + RPV LA in the study
- Collection of infant HIV status

Informed consent forms

The pregnancy follow-up consent form has been updated to include emerging evidence on cabotegravir and rilpivirine drug levels in pregnancy from physiologically-based pharmacokinetic modelling and a single case report. In light of this recently published research, we have recommended increased frequency of HIV viral load monitoring to 2-monthly for the duration of pregnancy and up to 6 months post-partum, in women continuing CAB + RPV LA.

A new peak pharmacokinetic (PK) sub-study consent form has been provided for collection of peak PK samples (1 week post injection) to enable paired peak and trough values to be used in PK modelling work. The informed consent form (ICF) informs participants about the rationale for the sub-study, the need to attend for a blood sample 1 week (+/- 2 days) post-injection and the reimbursement involved. Plasma is already being routinely collected and stored at the time of HIV viral load testing in the main study which aligns with the trough drug level time points. So, additional consent is required only for the additional visits and samples collected relating to the peak PK samples.

eCRFs

There have been a number of minor observations made during the cleaning of the data which has led to rephrasing some points for clarity. Changes were made on a variety of CRFs to align them with amendments in the protocol.

Notable changes include the following:

- **Adverse event CRF –** items on adverse events of special interest (except systemic post-injection reactions) have been removed from the CRF
- **Month 12 and 24 outcome CRF –** for participants who discontinue the originally assigned regimen due to an adverse event, the option of 'definitely / probably / possibly drug-related' and 'unlikely / not drug-related' have been added
- **Pharmacy drug accountability CRF –** questions have been added about batch number
- **Pregnancy notification and outcome CRF –** options have been added to pregnancy outcome including 'elective termination', 'therapeutic termination', or 'other'. Additionally, a question about neonate/infant HIV testing and the result has been added.
- **Visit contact CRF –** questions on change in appetite, family history and smoking history have been added.
- **Sample storage CRF –** this is a new CRF which needs to be completed every time that plasma is stored. The essence of this form is to ensure collection of information on storage of plasma for peak drug level PK, tuberculosis therapy PK, pregnancy PK, virological failure PK and overdose PK.

A MEMO indicating the latest changes to the CRFs was shared with the sites who have moved over to the updated version of the eCRFs on 05th November 2024 (for the Uganda and South African sites), and 26th November 2024 (for Kenya).

INSPECTIONS

On the 5th of August 2024 a regulatory inspection was conducted at Entebbe hospital site by Uganda National Council of Science and Technology (UNCST). The team was comprised of Mr. Makhuwa Isaac (UNCST), Haruna Muwonge and Eve Namitala (Bioethicist). The team reviewed the trial documentation, study procedures or processes and interacted with study participants. This was done to ensure that the study team complied with the approved protocol, ICH-GCP, and GDPR. The findings were positive and the team recommended continuation of the study.

Entebbe Site team members during the UNCST inspection

TRIAL OVERSIGHT

Trial Steering Committee (TSC) Meetings

This year began with a TSC meeting on the 22nd January 2024. We discussed the planned protocol and ICF amendments and concerns about minor differences within the different sites' ICFs. It was agreed that local adaptations to wording in the IMPALA ICFs across the different sites are acceptable if the meaning aligns with the master ICF template. This flexibility helps manage terminological differences between countries without affecting the content.

Thereafter, we had an *ad hoc* TSC meeting on the 9th April 2024 for discussions about the findings presented at the Conference on Retroviruses and Opportunistic Infections in Denver in March 2024 and their relevance to the implementation of the IMPALA protocol. The members concluded that the findings from these trials are reassuring, the high efficacy of LA ART strengthens confidence in the use of CAB + RPV LA, particularly in harder to treat populations. The meetings reaffirmed the IMPALA study's current direction.

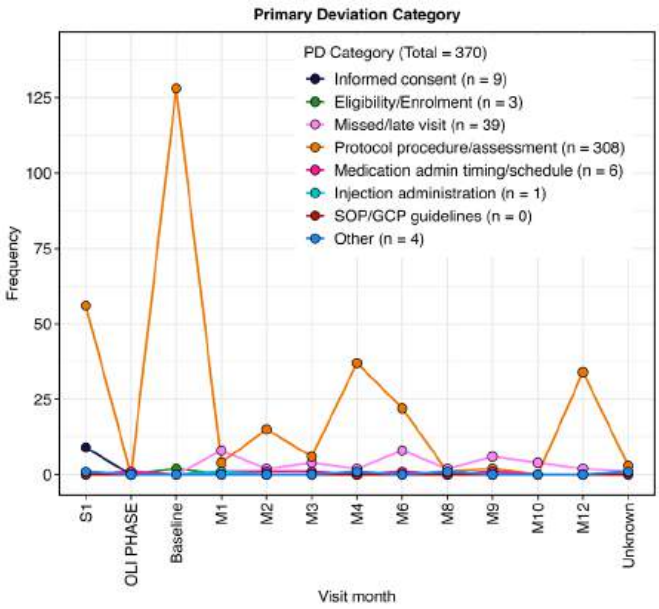
We would like to thank the TSC for their ongoing support and look forward to the next meeting in early 2025.

Independent Data Safety Monitoring Committee (IDMC) Meetings

This year's IDMC meeting took place on the 4th July 2024 where trial progress and safety aspects were discussed. The IDMC recommended that the study should continue as planned. Another IDMC meeting to review interim analysis efficacy data took place in September 2024. This also recommended the study should continue. We look forward to the next IDMC meeting in early 2025 and would like to sincerely thank the IDMC members for the time that they generously give in ensuring that the trial is conducted safely.

PROTOCOL DEVIATIONS

The graph below indicates that the majority of the protocol deviations were associated with protocol procedures or assessments, with most occurring around the baseline visit, followed by the month 4 (M4) and month 12 (M12) visits. The baseline visit deviations were minor and largely related to an AST being done in addition to ALT, which was not specified in the protocol. Overall, protocol deviations have decreased with time. We thank the teams for their efforts in minimizing deviations.



CLARIFICATION MEMOS

Clarification memos are designed to share relevant emergent data from the field or systematic observations about trial conduct that apply to all sites. By documenting evolving observations, these memos serve as dynamic tools that not only guide the research process but also preserve the context in which findings are interpreted. We have two memos that are still relevant at this stage of the study.

Memo #3 *Hyperglycaemia – this memo contained guidance aimed at ensuring consistent management of abnormal HbA1c and diagnosis of prior or incident diabetes mellitus study-wide.*

Memo #4 *Pregnancy sub-study - New information from a recent case report and from a physiologically-based pharmacokinetic modelling study is shared. This information is of relevance for the informed consent process for the pregnancy sub-study. The information is to be shared with relevant participants shared pending approval of the amended ICF for the pregnancy study.*

These memos are on file and can be referenced at any time while conducting the study.

LABORATORY ASPECTS

Routine sample collection, processing and testing is currently ongoing as planned across all sites. These samples are collected for routine clinical management of participants or for research purposes. Collaborating site staff continue to enter results for routine lab tests in the lab eCRFs, and where appropriate lab abnormalities (AEs/SAEs) are recorded once detected. The IMPALA protocol safety team continues to ensure that clinically significant lab abnormalities are followed up until resolution. Furthermore, additional safety tests are conducted as necessary to monitor and address previously abnormal values.

Study teams continue to collect additional samples for repeat HIV-1 RNA testing from participants with HIV-1 RNA ≥200 c/ml at any of the scheduled VL testing visits. Additional plasma samples are collected for storage in the following scenarios: 1) at the time of HIV VL testing; 2) drug level measurements in pregnant participants; 3) participants who develop TB; 4) those who experience treatment overdoses; 5) suspected virological failure.

For participants who consent to peak drug level testing, an additional sample will be collected one week post-injection in accordance with the Peak PK SOP. Shipment of samples to the central biorepository at MRC/UVRI and LSHTM Uganda Research Unit in Entebbe is ongoing. So far, a total of 4930 vials of plasma and 1123 vials of PBMC samples have been received from MUL, IDI, JCRC, and CAPRISA.

Next generation sequencing of baseline peripheral blood mononuclear cells will begin in early 2025. The purpose of this is to investigate archived resistance and its relationship with treatment outcomes. We look forward to sharing the sequencing results in 2025.

DATA MANAGEMENT

Data query resolution for the study is expected in 7 calendar days from the time a query is raised. Queries will be closed by the individuals (Data Manager, Monitor, Clinical Reviewer, Site QC Personnel) who raised them. The cumulative number of queries raised and resolved from the study's initiation through 5th November 2024, is illustrated in the below figure.

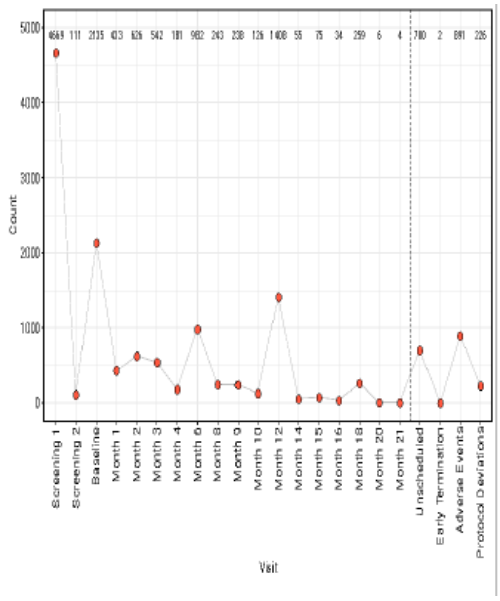


Figure illustrating the cumulative number of queries raised and resolved at each visit

During the screening phase, slightly more than 4500 queries were raised across all sites. However, these have significantly reduced during the follow up phase, with fewer than 1500 queries raised at the Month 12 visit.

The most common queries involve missing laboratory forms and clarifications needed to complete information on adverse events or previous conditions. Over the past year, the majority of queries across all sites have been addressed and resolved within the specified timeline outlined in the IMPALA Study Data Management Plan.

INVESTIGATOR MEETING 1ST & 2ND OCTOBER 2024, KWETU HILTON, NAIROBI

The The 2nd investigator meeting took place in early October at the Kwetu Hilton Hotel in Nairobi, bringing together representatives from all participating research centres (DTHF, CAPRISA, KNH, JOORTH, IDI, JCRC, MUL), collaborators from London School of Hygiene and Tropical Medicine, Massachusetts General Hospital and Johnson & Johnson, as well as the coordinating centre team. A special acknowledgement to the DTHF team – Dorothie, Viwe and Leah – whose patience and resilience were truly commendable after enduring a long and challenging journey from Cape Town to Nairobi that included two nights in Victoria Falls.

The two-day meeting featured a diverse and action-packed agenda. We began with updates from each team on the progress of the trial. Key administrative topics were also addressed, including updates on regulatory processes, monitoring and compliance, laboratory shipments and sample management, pharmacy operations, the publication plan, and the rollover study.

Additionally, the meeting covered a range of scientific topics in relation to the trial including social sciences, virology, cost effectiveness analysis, and clinical pharmacology, providing a comprehensive perspective on the trial's progress and future plans.

MEETING IN FULL SWING

DR LOICE ACHIENG OMBAJO KICKING OFF THE MEETING WITH AN ENERGIZER

DR FAFA ADDO BOATENG (J&J) WITH DR LOICE ACHIENG OMBAJO (UoN), DR FIONA CRESSWELL, AND DR EUGENE RUZAGIRA

DR EUGENE RUZAGIRA AND DR FIONA CRESSWELL INTRODUCING THE AGENDA FOR THE MEETING

PUBLICATION PLAN

We are pleased to introduce our publication plan, which outlines the strategic framework for disseminating the key findings and insights from our study. This plan has been designed to ensure our research reaches a broad audience across relevant academic, professional, and public platforms. By mapping out target journals, conferences, and potential collaborations, we aim to position our work to maximize impact, engagement, and visibility. The publication plan will also help us prioritize timelines, manage resource allocation, and coordinate team efforts to meet submission deadlines.

We invite all team members to familiarize themselves with the plan, as their contributions will be essential to achieving the IMPALA study publication goals. The publication plan and a list of planned publications can be found on the study Sharepoint.

SOCIAL SCIENCES

The IMPALA trial social science study has two components. The first targets trial participants while the second targets key stakeholders. Stakeholders include healthcare workers delivering the trial and working in routine care, policy makers and HIV program managers. The first study component is being carried in Ugandan and South Africa while the stakeholders' component will cover all the three countries (Uganda, Kenya and South Africa). Data from the trial participants is being collected through three repeat in-depth interviews. These interviews occur at baseline (post trial randomization but before the first injection), 6 and 12 months. In Uganda, all three repeat in-depth interviews with the trial participants have been conducted by PhD student Dominic Bukenya, an experienced social scientist. The study team in South Africa, led by Makhosazane Zondi, is conducting the final repeat in-depth interview with trial participants. Overall, this study component has recruited the target of 40 trial participants (18 female/22 male and 22 injectable/18 oral arm). The study component with stakeholders will start in early 2025. Data from the stakeholders will be collected through a single key informant interview.



IMPORTANT REMINDERS TO COLLEAGUES

Please submit all Serious Adverse Events (SAEs) to the sponsor within 24 hours and to the relevant Research Ethics Committees (RECs) in accordance with your country's requirements (see Safety Management Plan, SMP).

Please submit and file Protocol Deviations (PDs) as per the SMP and as locally required by your country.

Please send notification about missed visits via the protocol deviation eCRF with appropriate documentation

If a participant's injection schedule changes due to late injection this does not affect the date of the planned M12 or M24 HIV VL. The HIV VL window remains set from the time of randomization. This may mean that the participant needs to return for a separate HIV VL test within their originally planned HIV VL window.

Please upload all completed forms, including SAEs and PDs, to SharePoint.

NEWS ON LA INJECTABLES FROM CROI

3-6 March 2024

Several landmark studies involving long-acting cabotegravir and rilpivirine shared promising results at CROI 2024:

CARES study

The CARES study, conducted in Uganda, Kenya, and South Africa, involved 512 participants with suppressed HIV viral loads and investigated the use of long-acting injectable cabotegravir and rilpivirine as an alternative to first-line daily oral HIV therapy in the African public health approach. We salute Dr Cissy Kityo and the rest of the CARES team for delivering this pivotal study. After 48 weeks, 96% of those on the injectable therapy maintained viral suppression, closely matching the 97% success rate of those on oral therapy. Although two cases of drug-resistant virological failure were noted, the injectable treatment was found to be non-inferior to daily pills. This result is very encouraging given that no baseline drug resistance testing took place and HIV VL testing was done 6-monthly. The CARES findings build confidence in the injectable regimen and expand the potential for broader use of injectables. IMPALA study builds on the CARES data by focusing on patients with a history of suboptimal HIV control, addressing a population at-risk of poor treatment outcomes, HIV-related illness and death.

MOCHA study

The IMPAACT 2017 (MOCHA) study is a Phase I/II trial evaluating the safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir (CAB-LA) and rilpivirine (RPV-LA) in virologically suppressed adolescents (12 to 18 years old) with HIV-1. The study enrolled 144 participants across 18 sites in 5 countries. After a 4-week oral lead-in, participants received injections every 2 months. By Week 24, no virologic failures or deaths were reported, and SAEs were rare.

Injection site reactions were common but mild, resolving within 7 days. The study concludes that CAB-LA and RPV-LA are safe and effective for HIV-1 suppression in adolescents.

LATITUDE study

The LATITUDE (Long-Acting Therapy to Improve Treatment Success in Daily Life) study is across 31 sites in the U.S. including Puerto Rico, implemented through ACTG trials network. Participants with challenges taking daily oral ART as prescribed and evidence of viremia were screened to ensure the HIV in their blood was not resistant to the study drugs and that they met other health and safety criteria. Once enrolled, they received comprehensive and incentivised adherence support while taking guideline-recommended, three-drug regimen oral ART, including dolutegravir and bictegravir-based regimens, to achieve viral suppression. They were then randomised to receive LA ART (cabotegravir + rilpivirine) every four weeks or to continue taking daily oral ART. The Data Safety Monitoring Board performed a planned interim review in early 2024. They considered the totality of all the study endpoints together and concluded that the evidence indicated superior efficacy of long-acting ART over daily oral standard of care. The DSMB recommended that all eligible participants should be offered long-acting injectable cabotegravir + rilpivirine. The study is ongoing and more results are eagerly awaited in due course.

CAPACITY BUILDING THROUGH IMPALA

It is essential to embed both individual and institutional capacity building within clinical trials so that there is a lasting positive legacy regardless of the scientific results of the trial. Within the coordinating centre team three staff members are undertaking doctoral studies alongside their day to day trial work. Dominic Bukenya is conducting the social sciences work and will graduate from LSHTM in due course. Dr Jonathan Kitonsa is looking at cardiometabolic aspects of LA ART and Dr Claire Norcross will undertake next generation sequencing and look at drug resistance, both will graduate from Brighton and Sussex Medical School.

COMMUNITY ENGAGEMENT EVENT FOR WORLD AIDS DAY

This year, Uganda commemorated World AIDS Day on 1st December 2024, in Buyende District under the theme *"Accelerating Interventions to End AIDS by 2030."* The event brought together a diverse group of participants, including stakeholders from national and subnational levels, the international community, and various organizations involved in the HIV/AIDS response.

A key highlight of the celebrations was showcasing and exhibiting new innovations in HIV/AIDS prevention, testing, care, and treatment. Among the exhibitors was the IMPALA study team, which proudly presented its work on long-acting injectable antiretrovirals.

The event's chief guest, H.E. Yoweri Kaguta Museveni, President of the Republic of Uganda, engaged with the exhibitors and commended their efforts in the fight against HIV/AIDS. In his official address, the President emphasized the urgency of accelerating interventions, highlighting the advantages of bi-monthly injectable antiretrovirals over daily oral pills, alongside other interventions showcased at the event. He expressed his gratitude for the groundbreaking work of scientists and pledged his continued support for efforts to achieve an AIDS-free generation.

Dr. Ubaldo Bahemuka & Dr. Jonathan showcasing the IMPALA study to H.E Yoweri Kaguta Museveni, the President of Uganda.

LOOKING AHEAD TO 2025

The final M12 visit is scheduled to take place in April 2025 and we plan to share the results with investigators shortly afterward during a confidential results meetings. The results will remain confidential pending presentation at a conference – hopefully the International AIDS Society Conference which will take place in Rwanda in July. We also anticipate publication of the primary manuscript in 2025. Your efforts in ensuring that participants attend their visits on time, and that the HIV VL is tested with originally set window, are very much appreciated.

For now, the whole team at the Trial Coordinating Centre wishes you and your families a healthy and happy Christmas. May the festive period bring opportunity to rest and restore. Wishing you a successful and joyful year head. See you in 2025!

MRC/UVRI and LSHTM Uganda Research Unit

CONTACTS

TCC communications: impala@lists.lshtm.ac.uk

Safety: impala_safety@lists.lshtm.ac.uk

HELPFUL LINKS

https://www.lshtm.ac.uk/research/centres-projects-groups/impala