RESEARCH PROTOCOL (Final Draft)

Research project title:

ACTIVE SURVEILLANCE OF DOLUTEGRAVIR BASED ANTIRETROVIRAL REGIMENS IN RWANDA

Institutions involved:

Rwanda Biomedical Center (RBC) National HIV/AIDS Control Program

Rwanda Food and Drug Authority (Rwanda FDA)

USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program

Funder:

USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program

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Table of Contents

ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
BIC	Bictegravir
BMI	Body mass index
CAB	Cabotegravir
CD4	Cluster of differentiation 4, variety of lymphocyte (T4)
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DSD	Differentiated service delivery
DTG	Dolutegravir
FDA	Food and Drugs Authority
GoR	Government of Rwanda
HbA1c	Glycated hemoglobin
HDL	High density Lipoprotein
HIV	Human immunodeficiency virus
HLT	Higher-level term
INSTI	Integrase Strand Transfer Inhibitor
IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
LDL	Low density lipoprotein
MeDRA	Medical dictionary for regulatory activities
MMD	Multi-month dispensing
OBBI	Other blood born infections
OR	Odds ratio
PEPFAR	President's Emergency Plan for AIDS Relief
PI	Principal Investigator
PViMS	Pharmacovigilance Monitoring System
PLHIV	People living with HIV
RBC	Rwanda Biomedical Center
RNEC	Rwanda National Ethics Committee
RPHIA	Rwanda Population-Based HIV Impact Assessment

SOP	Standard operating procedure
TC	Total cholesterol
TDF	Tenofovir Disoproxil Fumarate
UMC	Uppsala Monitoring Center
UR	University of Rwanda
WHO	World Health Organization
MTaPS program	USAID Medicines, Technologies, and Pharmaceutical Services program

Research Team Members' Roles and Responsibilities

Team Member(s)	Role(s)	Responsibilities
National level team		
Dr. Dominic Savio	Principal Investigator, Rwanda Biomedical Center (RBC)	● Develop protocol in collaboration with second Principal Investigator (PI) ● Interact with Rwanda National Ethics Committee (RNEC)/Institutional Review Boards (IRBs) for approval of protocol and any necessary revisions to the protocol ● Review developed standard operating procedures (SOPs) and checklists to ensure they are in line with program implementation at facility level ● Oversee overall programmatic planning and implementation of active monitoring at all sites ● Ensure compliance with the provisions of the protocol at all sites including appropriate data collection and compliance with ethical standards during implementation ● Ensure maintenance of scientific integrity of activity at all sites ● Coordinate collaboration with all stakeholders including funding partners, Government of Rwanda (GoR) stakeholders and President's Emergency Plan For AIDS Relief (PEPFAR) clinical partners at site level ● Coordinate all personnel involved in the activity including co-investigators, investigators, and site level personnel ● Present study findings to relevant stakeholders including GoR, donors and other stakeholders ● Support development and publication of final results
Dr. Innocent Hahirwa	Co-Investigator, University of Rwanda (UR)	● Support development of protocol in collaboration with PI ● Develop SOPs and checklists in collaboration with other members of the team ● Ensure maintenance of scientific integrity of activity at all sites ● Develop manuscript for publication of the final result
Eric Remera	Co-investigator, RBC	● Ensure data quality and completeness ● Conduct data cleaning and analysis in collaboration with relevant experts ● Compile study results

Lazarus Ntirenganya	Co-investigator, Rwanda Food and Drug Authority (FDA)	● Support development of protocol, data collection tools and checklist ● Support implementation of the study ● Support data quality and completeness review ● Conduct data cleaning and analysis in collaboration with relevant experts ● Compile study results
● Comfort Ogar ● Abimana Rwandenzi Eugene ● John Patrick Mwesigye	Co-investigators, USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program	● Support development of protocol, data collection tools and checklist ● Support implementation of the study ● Support data collection ● Support data quality and completeness review ● Support data cleaning and analysis in collaboration with relevant experts ● Support compilation of study results ● Support dissemination of the study results
Cyprien Musafiri	Investigator, Pharma-ceutical supply chain Specialist	● Review protocol design ● Support data collection ● Support supply chain management of DTG based regimens
Augustin Mulindabigwi	Investigator, HIV Surveillance specialist	● Support coordination of the activity at health facility level ● Review all study materials, including SOPs and checklists ● Organize trainings for research team members ● Support supervisory visit of site teams to monitor implementation of protocol
Dr. Isabelle Tuyishime	Investigator, Adult and Pediatric treatment	● Provide day-to-day technical guidance to site teams to ensure compliance with the national treatment guidelines for HIV
Sara Cantaroggi	Investigator, Intern	● Support day-to-day coordination of technical staff from the health facilities on the active surveillance
Beatha Sangwayire	Investigator, HIV prevention	● Support day-to-day technical oversight, particularly regarding the available HIV protocols and guidelines as stipulated by RBC/HIV division. ● Support presentation of study results to the GoR and partners
Site level team		

Site research coordinator	Site coordinator	● Coordination of active monitoring activities at the site ● Follow up on progress of patient enrollment and follow up ● Manage administrative issues related to implementation at the site level, such as ensuring availability of all needed tools ● Provide periodic progress report to the Rwanda FDA and RBC as specified in the SOP for data management ● Support site data management and analysis through periodic data spot checks to ensure completeness of collected data as specified in the SOP on data quality
Doctor (could be designated as site coordinator)	Active monitoring site clinical officer	● Provide detailed information about the active monitoring activity to patients including the obtaining of patient informed consent. ● Evaluation of patients for enrollment at initiation ● Enrollment of patient into the cohort; evaluation for possible adverse drug events at follow up ● Documentation of the suspected adverse drug events in the relevant data collection tools ● Clinical management of patients for possible adverse reactions
Nurse	Active monitoring site nurse	● Notify patient about the active monitoring activity ● Identify potential patients for enrollment ● Keep records of patients' follow-up visit dates ● Remind patients to come for follow-up visits ● Track patients who are lost to follow up ● Counsel patients on possible ARV ADRs during administration ● Provide periodic progress reports on patients enrolled and successfully followed up to site coordinator as specified in the SOP for data management
Clinical pharmacist (could be designated site coordinator)	Active monitoring site pharmacist	● Provide further information on the active monitoring to patients ● Interview patients on possible AEs during follow-up visits ● Support site clinician to document reported AEs during follow-up visits ● Support site data management and analysis through periodic data spot checks to ensure completeness of collected data as specified in the SOP for data management

Site data manager	Site data entry	● Manage electronic data collection ● Ensure completeness of data captured for each patient ● Provide feedback to clinical team on data completeness ● Transmit data to the Rwanda FDA and RBC ● Provide periodic progress reports to site coordinator on various indicators as specified in the SOP for data management

Protocol Summary

Title	Active surveillance of Dolutegravir (DTG) based antiretroviral regimens in Rwanda
Type of Study	Safety monitoring for Dolutegravir-based regimens in Rwandan patients including pregnant women
Study Population	People living with human immunodeficiency virus (HIV) under treatment with Dolutegravir-based regimens
Study area	Selected sentinel sites across Rwanda
Duration of Subject Participation	Participants will be followed up for 1 year, except for pregnancy cases occurring 3 months after enrollment, where follow-up may be longer than one year to determine pregnancy outcome
Treatment regimens to be monitored	● Tenofovir (TDF)/Lamivudine (3TC)/Dolutegravir (DTG) 300/300/50mg ● Abacavir/Lamivudine (ABC/3TC) 600/300mg + Dolutegravir 50mg ● Abacavir/Lamivudine 120/60mg + Dolutegravir 50mg
Main Objective	To determine the safety profile of DTG-based regimens including TDF/3TC/DTG and ABC/3TC+DTG among HIV patients in Rwanda
Specific Objectives	1. To characterize adverse event (AE) and adverse drug reaction (ADR) profiles among patients using DTG-based regimens 2. To determine the incidence rate for AEs, in patients using DTG-based regimens 3. To assess causality between observed AEs and the use of DTG-based regimens 4. To determine the effect of DTG-based regimens on weight gain as well as the blood glucose and lipid profiles 5. To identify risk factors for AE/ADR development and determine their effect on AE/ADR incidence and severity among patients using DTG-based regimens 6. To propose possible interventions to prevent AEs and ADRs associated with the use of DTG-based regimens where applicable

1. Background

1.1. Introduction

Over the past four decades there have been tremendous advances in antiretroviral therapy (ART) resulting in longer life expectancy and improved quality of life for people living with HIV (PLHIV) (1-3). A more personalized approach to the selection of treatment regimens, based on tolerability and risk of adverse drug reactions, was made possible by an increase in options of drugs constituting antiretroviral regimens (1-5). In general, antiretroviral therapies used in clinical practice are responsible for durable virologic suppression and cluster of differentiation 4 (CD4+) cell repletion resulting in reduced morbidity, hospitalization rates and mortality for HIV/acquired immunodeficiency syndrome (AIDS) patients (4-6). However, the high level of adverse drug reactions associated with all antiretroviral therapies remains the major cause for switching or discontinuing therapy and for non-adherence to treatment (4, 6-8).

Until 2016, the first-line ART recommended by WHO consisted of Tenofovir, Lamivudine (or Emtricitabine), and Efavirenz (9). In the event of first-line treatment failure, a regimen comprised of Zidovudine, Lamivudine, and a protease inhibitor was recommended for second line treatment (9). Currently, WHO recommends a first line regimen that includes the strand integrase inhibitor, Dolutegravir (DTG) with Tenofovir and Lamivudine for the treatment of naïve patients and those on first-line ART with a recent viral load measurement below 1000 copies/mL (10). DTG in combination with Zidovudine and Lamivudine, is also recommended as a second line regimen in case of virologic failure with Tenofovir, Lamivudine, and Efavirenz (11).

DTG belongs to the class of Integrase Strand Transfer Inhibitors (INSTIs); they block the integration of the viral genome into the host genome (1-3). It is an un-boosted integrase inhibitor with a plasma half-life of approximately 14 hours, which supports once-daily administration with no need for pharmacokinetic boosting (12). Raltegravir and Elvitegravir constitute the first INSTIs to be approved by USFDA in 2007 and 2012 respectively (13, 14). Due to emerging resistance to these two molecules, including a cross-resistance to each other, second generation INSTIs were developed, including Dolutegravir, Bictegravir (BIC) and Cabotegravir (CAB) (1, 15). DTG and BIC were approved by USFDA in 2013 and 2018, respectively, and CAB was approved for sale in the United States of America in 2019 while still in phase 3 clinical development (16-18).

Currently, second-generation INSTIs are commonly used in first line combination therapy due to their high potency, good tolerability, low toxicity, and high genetic barrier to resistance (1-3). Neurological effects, gastrointestinal symptoms, and weight gain are the main components of the toxicity profile of this class of drugs (2,17-19).

Since its introduction into clinical practice, DTG has demonstrated its efficacy and safety in HIV-1 positive patients (20). Compared with Efavirenz-based regimens, DTG-based regimens were found to be associated with fewer regimen changes and a reduction in the development of major drug resistance mutations (21, 22). In patients starting second-line therapy with at least one active nucleoside reverse transcriptase inhibitor, better treatment outcomes were observed for dolutegravir therapies compared with boosted protease inhibitor-based regimens (23).

Despite the demonstrated benefits of DTG, various studies have shown that a number of adverse events (AEs) are associated with the use of this molecule (24, 25). In actual clinical practice, some of these AEs, particularly neurological effects, may be under-reported because they were not reported with the first drugs of this class (Raltegravir & Elvitegravir). Patients and providers may ignore the possible association of such effects with DTG use. This may lead to the under-reporting of these effects as they are not anticipated (26). Neurological AEs commonly reported with dolutegravir include sleeping disturbances, insomnia, mood alterations, anxiety, and psychosis. Gastrointestinal disorders are also reported to be associated with the use of this drug (26). Both gastrointestinal and neurological adverse events were reported in registration studies, but their prevalence is thought to be much higher in actual clinical practice. This was associated with a higher rate of treatment discontinuation than expected (27, 28). In addition, it was found that the use of dolutegravir-based antiretroviral therapy by pregnant women from the time of conception was associated with an increased prevalence of neural-tube defects (29).

In addition, a possible association between the use of DTG-based regimens and hyperglycemia, as well as elevated levels of glycated hemoglobin (HbA1c) in both experienced and treatment naïve ART users have been reported (30, 31). However, more evidence is needed to confirm these associations. Other metabolic disorders that were reported for DTG-based regimens include weight gain (excess body fat) and high blood cholesterol levels, which may increase the risk for cardiovascular diseases (32-34). A number of studies recommend monitoring blood levels of triglycerides and different types of cholesterol, including total cholesterol, high density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol for people using DTG-based regimens (32, 33). In contrast, other studies have reported an improved lipid metabolism with DTG-based regimens compared to other regimens (35-37). This demonstrates the need for more studies to understand the association between DTG-based regimens and different metabolic disorders.

Since the current WHO guidelines for antiretroviral treatment recommend the inclusion of Dolutegravir in both first-line and second-line regimens (10), more studies involving large cohorts at national or international levels are needed to have a complete profile of adverse events and tolerability of this drug (38). In addition, WHO currently recommends that countries implement active monitoring of the safety of new ARVs as they introduce DTG and other new ARVs (39).

In the framework of this study, WHO-Uppsala Monitoring Center (UMC) and European Union definitions are adopted respectively for AE and ADR. WHO-UMC defines an AE as "any untoward medical occurrence that takes place during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment" (40). According to the European Union's definition, an adverse drug reaction (ADR) is "a response to a medicinal product which is noxious and unintended" (41).

1.2. HIV/AIDS Prevalence and Management in Rwanda

In Rwanda, the first case of HIV/AIDS was identified in the early 1980s. There are currently more than 200,000 people living with HIV (PLHIV) in the country (42-44). According to the Rwanda Population-Based HIV Impact Assessment (RPHIA), which measures the status of the country's national HIV response, the annual incidence rate is 0.08% (around 5,400 new cases per year) (44). RPHIA reports an average HIV prevalence of 3% in adults aged between 15 and 65 with a higher prevalence (3.7%) among females (44). It is important to highlight that this group includes women of reproductive age with a risk of pregnancy while on ART. Further, approximately 84% of HIV patients know their status of being HIV infected while around 98% of HIV positive patients are on antiretroviral therapy (44).

With regard to HIV management in Rwanda, there are currently more than 500 treatment sites being used to manage HIV patients countrywide. There is a well-established system for follow up of three categories of patients, namely stable A, stable B and unstable. Stable patients are those receiving ART for at least 1 year with no adverse drug reactions requiring regular monitoring and with evidence of treatment success. The stable A category includes adult patients on ART for 12 months, with 2 consecutive results of a successful viral load suppression but also willing to be part of this category. The stable B category includes adolescents and children meeting the same criteria as for stable A. Pregnant women and patients with other comorbidities including tuberculosis, Hepatitis and different non-communicable diseases are put under "unstable" category. For stable A, a drug refill is done every three months with a clinical follow up visit every six months, while for stable B patients, a three-month drug refill is done with a clinical visit every three months. For non-stable patients, there is a prescription refilling every month and a clinical visit every three months (45, 46).

The pharmacological management of HIV/AIDS in Rwanda involves different ART regimens, including DTG-based therapies. DTG was first introduced in Rwanda in 2018, through circular No 20/5895/RBC/2018. Dolutegravir-based regimens currently used in Rwanda include Tenofovir/Lamivudine/Dolutegravir (varying strengths) and Abacavir/Lamivudine + Dolutegravir (varying strengths). It is important to highlight that DTG can be used for both first-line and second-line treatments. According to circular No 20/8683/RBC/2019 of 20th December 2019, DTG-based regimens are recommended as the preferred first-line HIV treatment in Rwanda if the weight of the patient is not less than 20 kgs. According to RBC/HIV

data, currently in Rwanda about 140,000 patients are managed with DTG-based regimens. This number is expected to increase up to more than 170,000 by December 2021, due to a progressive shift from Efavirenz-based regimens to DTG-based regimens and a projected number of new patients who will initiate their antiretroviral treatment with DTG-based regimens.

It is therefore essential to know the safety profile of antiretroviral drugs among such a large number of patients. This is particularly important for newly introduced drugs such as those containing DTG, knowing that safety data from different phases of the drug development process, including clinical phases, may not reflect some peculiarities (genetic and environmental factors) of the Rwandan population.

1.3. Use of the Study Findings

Findings from this study will provide information on the safety profile of DTG-based regimens specific to Rwandan patients, which will help the Ministry of Health and the National HIV program to establish strategies to control and manage AEs and ADRs associated with the use of these regimens. The results from this study may also inform review of HIV treatment guidelines in Rwanda. The guidelines will be used by healthcare providers to improve the quality of care provided to HIV patients.

2. Study Objectives

2.1. Main Objective

The aim of this study is to determine the safety profile of DTG-based regimens including Tenofovir/Lamivudine/Dolutegravir (TDF/3TC/DTG) and Abacavir/Lamivudine + Dolutegravir (ABC/3TC+DTG) among HIV patients in Rwanda.

2.2. Specific Objectives

To achieve the study goal, it is necessary to:

1. Characterize the AE and ADR profile among patients using DTG-based regimens
2. Determine the incidence rate for AEs and ADRs in patients using DTG-based regimens
3. Assess causality between observed AEs and the use of DTG-based regimens
4. Determine the effect of DTG-based regimens on weight gain as well as the blood glucose and lipid profiles of enrolled patients
5. Identify risk factors for AE/ADR development and determine their effect on AE/ADR incidence and severity among patients using DTG-based regimens
7. Propose possible interventions to prevent AEs and ADRs associated with the use of DGT-based regimens where applicable

3. METHODS

3.1. Study Design

This will be a prospective, inceptional, descriptive, observational study involving HIV patients being managed with DTG-based regimens in selected sentinel sites. Patients will be observed for the development of AEs over a one-year period. The observation period will be extended in cases of pregnancies occurring three months after enrollment to ensure adequate follow up to document the outcome of the pregnancy. The medical history prior to commencement of DTG-based regimens will be collected for all patients enrolled in each cohort.

To better understand the association between DTG-based regimens and different metabolic functions, a sub-cohort of patients (males and females belonging to different age groups and including both treatment-naïve and experienced patients) will be monitored for the development of signs suggestive of certain metabolic problems, including hyperglycemia and hyperlipidemia. For this portion of the study, blood samples will be collected from all 300 patients at defined intervals during the study (at baseline and after every six months) to monitor glucose and lipid profiles.

3.2. Study Population and Recruitment Methods

This study will involve a cohort of HIV patients treated with DTG-based regimens in selected sentinel sites across the country. This will include treatment naïve patients starting their treatment with a DTG-based regimen and those who may be initiated on this regimen after the failure of other regimens. To be able to detect an AE occurring at the rate of 1:1000, at least 3,000 people will need to be enrolled in this study. This number gives a 95% probability of identifying such an AE at 80% statistical power (47, 48). Among the study participants, 300 people will be randomly selected for the monitoring of glucose and lipid profiles in addition to the general follow-up.

3.2.1. Inclusion Criteria

- All HIV patients regardless of age and gender who commence antiretroviral treatment with any DTG-based regimen, including treatment naïve patients and those switching from other ART regimens
- Pregnant women in the first, second, and third trimesters of pregnancy
- Patients with other co-morbidities who are initiating treatment with any of the monitored DTG-based regimens.

3.2.2. Exclusion Criteria for Enrollment

- All patients irrespective of age and sex that commenced treatment with any DTG-based regimen prior to being enrolled into the active monitoring exercise
- Patients who do not wish to be part of the active monitoring study
- Patients for whom adequate medical history cannot be obtained

3.2.3. Exclusion Criteria During Follow Up

The study will exclude the following patients from further follow-up, although their previously collected data will be analyzed separately unless they state otherwise

- All participants who voluntarily withdraw from the study
- Those who are lost to follow up and cannot be traced
- Those who switch to non-DTG-based regimens for any reason, including toxicity
- Patients with confirmed treatment non-compliance not due to drug toxicity

3.3. Data Collection Sites

Sentinel sites across the country meeting the selection criteria outlined in section 3.4 will be invited to participate in patient enrollment and follow-up. The enrollment will take place over a period of six months.

3.4. Site Selection Criteria

The following criteria will be considered to select the patient enrollment sites:

- The facility manages not less than 500 HIV-infected patients who are likely to be placed on DTG-based regimens during the enrollment period
- The facility is supported by a PEPFAR clinical partner and has experience or ability to follow up with patients routinely (including through phone calls or home visits if necessary) with health care providers who are willing to participate in the monitoring process and who may have prior experience in active monitoring
- The facility has existing electronic data collection and management tools (i.e., uses electronic patient management systems)

3.5. Variables

3.5.1. Dependent Variables

The dependent variables in the present study are AEs and ADRs among our study population. Independent Variables

The independent variables in this study include age, sex, and weight (body mass index, BMI). Other independent variables include comorbidities, concomitant medications, and pregnancy status.

3.6. Data Collection Methods

Enrolled patients will be followed up for up to one year after enrollment (with possible extension as specified above for pregnant women). Day 0 is the day the patient is started on the DTG-based regimen and enrolled in the active monitoring activity. Any patients not enrolled in the active monitoring on the day their DTG-based regimen started, will be excluded from the study.

To avoid any additional burden to participants or the health system, patients' active monitoring follow-up visits will be in accordance with the national guidelines for regular HIV patient follow up visits (47). According to these guidelines, a follow up visit should be done on a monthly basis for the first three months after commencement of HIV treatment with DTG-based regimen, then every three months for up to one year of total follow-up (45, 46).

The sub-cohort of 300 patients for blood glucose and lipid profile monitoring will be required to perform six biomarker tests at 3 intervals during the one-year monitoring period. The first test (baseline) will be performed during the DTG-based regimen treatment initiation visit on day 0. The second test will be performed after six months of treatment, and the third test will be performed at the end of the follow-up period (after 12 months). The six tests that will be performed for the sub-cohort are listed below:

- Glycated hemoglobin (HbA1c)
- Glycaemia
- Total cholesterol
- HDL-cholesterol
- LDL-cholesterol
- Triglycerides

Prior to data collection, all staff involved in the research will be trained on the protocol and study processes by a team of experts from RBC, Rwanda FDA, and MTaPS. A team of trained healthcare providers at each selected site will be responsible for enrolling patients in the study at initiation of treatment, and for following up at scheduled visits to record ADRs/AEs. A combination of in-person clinic visits, phone calls and home visits (if necessary) will be used for patient follow up to improve the study completion rate. This is particularly important in the context of multi-month dispensing (MMD) and differentiated service delivery (DSD), and in the context of the current COVID-19 global pandemic (47).

All AEs experienced by the patient will be recorded, including abnormal laboratory results and "no event." Health care providers who attend to patients at their follow-up visits will also

monitor and record specific AEs that have been reported for DTG in other studies, including insomnia, neuropsychiatric effects, cardiovascular events, and Immune Reconstitution Inflammatory Syndrome, etc. (49).

AEs to be monitored and documented include:

- Insomnia
- Neuropsychiatric events
- Cardiovascular events
- Immune Reconstitution Inflammatory Syndrome (IRIS)
- Hyperglycemia
- Hyperlipidemia
- Weight gain
- Stillbirths
- Miscarriages
- Low birth weight (< 2.5 kg) deliveries
- Preterm deliveries (< 37 gestation weeks)
- Abnormalities in newborns, including neural tube defects
- Any other AE reported during the follow up

Information on abnormal laboratory results and the absence of AE will also be collected for all enrolled patients where available.

3.7. Data Collection Tools

Data will be collected electronically using a web-based data collection tool: Pharmacovigilance Monitoring System (PViMS). The data elements to be collected at treatment initiation and follow up visits are specified in Annex 1 and are all available in existing databases. These data elements were identified using the generic templates provided by the WHO and our experience with implementation of similar programs (45, 50). Standard operating procedures (SOPs) and guidelines will be developed to guide data collection, including SOPs for participant enrollment and follow-up and for AE reporting.

3.8. Plan for Data Management and Analysis

All data collected through this active monitoring study will be managed and analyzed electronically by Rwanda FDA and RBC. Rwanda FDA currently use the Pharmacovigilance Monitoring System (PViMS) for routine data collection, data analysis and AE reporting. This tool has integrated relevant standard coding systems such as the medical dictionary for regulatory activities (MedDRA) and will be used to collect longitudinal patient-level data. MTaPS will provide technical support for data management and analysis.

A team of experts from Rwanda FDA will assess reported events for causality, to determine the extent to which a reported event is related to the medicine(s) taken by the patient using the causality assessment support tool included in PViMS. This will enable events to be classified as ADRs or 'background noise' based on the assessed causal relationship.

Rwanda FDA, with support from MTaPS, will analyze the collected data periodically (monthly at the initial stage and quarterly thereafter) to provide descriptive frequency tables for demographics, medicine use, and adverse events. The incidence of AEs (and associated confidence intervals) will be calculated for the overall population and by age group, sex, risk groups, and pregnancy status using the number of patient-years contributed by each participant. The team will undertake monthly data quality checks and perform a mid-term statistical data analysis to present various adverse drug reaction profiles, including incidence rates, predictors of adverse reactions and relative risks. The frequency of AEs will be assessed and reported as percentages and will be grouped by MedDRA higher-level term (HLT) according to age group and sex. Chi-square test or Fischer's exact test (where appropriate) will be used to detect any differences in the proportion of AEs between patient groups. Univariate analyses using crude odds ratios (ORs) will be used to describe the risk factors for AE reporting. Multivariate analysis using logistic regression and 95% confidence intervals (CIs) will be performed to investigate the combined effect of patient characteristics in relation to the occurrence of an AE. Variables significant at $p<0.2$ in univariate analyses will be included in the logistic regression model. Statistical significance will be set at $p<0.05$.

A similar analysis will be performed for the sub-cohort that will be monitored for the development of metabolic disorders through laboratory testing of specific biomarkers.

4. Study Strengths & Limitations

Having a functional pharmacovigilance monitoring system (PViMS) at Rwanda FDA will simplify the collection of accurate data for this study. Furthermore, DTG-based regimens are largely used in Rwanda and there is existing systematic monitoring for patients on treatment. This will support the use of safety data to reflect the actual clinical safety in the Rwandan context, and thus help to establish a reliable safety profile for these regimens.

With regard to the study limitations, the lack of healthcare providers with capacity for high-quality AE detection constitutes a major limitation to our study. No comparison group will be used in our study, which is also a limitation. The study will also not detect rare and delayed AEs occurring after one year. Since the study will not involve all treatment sites, possible biases in selection of study sites and participants might also constitute a limitation of our study.

5. Ethical Considerations

This is an observational, non-interventional study that will not interfere at all with patient treatment. No extra visits beyond the routinely scheduled ARV pick-up for patients will be required for the study participants. For participants who will be included in the sub-cohort for blood glucose and lipid monitoring, 3 additional laboratory tests will be required, with blood samples collected for these tests during their usual scheduled visits and by the same staff involved in routine patient management. We will seek ethical approval for the study from the appropriate Ethics committee or Institutional Review Board (IRB). All participants will be required to sign an informed consent form prior to enrollment in the study. Participants will have the right to withdraw from the study at any point or refuse to participate.

Participation in the study will bring no additional risk to the participant beyond the risk that they would face during their routine schedule visit, as this is an observational study. The cost for the extra laboratory tests required for blood glucose and lipid monitoring will be covered by the research funds. The greatest risk to participants would be loss of confidentiality due to unintended disclosure of patient's medical information. To mitigate this, all information collected in the framework of this study will be kept strictly confidential using access restricted measures. Access to systems containing patient data, including participant personal information, will be controlled by password protected access that will be given to only people involved in this study. Where necessary, these people will be trained in the strict maintenance of security and confidentiality. No published data will contain any information that could identify any participant.

Participants will not gain any direct benefits from their participation in the study. However, information obtained from this study will be of benefit to patients managed with Dolutegravir-based regimens in the future. The information collected through this study may provide the basis to improve the use of these medications and limit their possible toxicity.

6. References

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Annex 1: Data Elements to be Collected for Active Safety Monitoring

Data Elements	Specific Data to be Collected	Collection Timing
Patient demographics (all patients)	Hospital number	Initiation and follow up
	Unique ID	Initiation and follow up
	Name	Initiation and follow up
	Age/Date of Birth	Initiation and follow up
	Sex	Initiation and follow up
	Weight	Initiation and follow up
	Height	Initiation (and follow up for patients <19 years)
	BMI	Initiation and follow up
	Blood Pressure	Initiation and follow up
	Clinical status/WHO stage	Initiation
For women of childbearing age (in addition to above)	Date of last menstrual period (LMP)	Initiation and follow up
	Pregnancy status/trimester	Initiation and follow up
	Outcome of previous pregnancies/gravidity/parity	Follow up
Medical history pre DTG initiation	Use of alcohol, tobacco, and other substances	Initiation
	Medical event(s) of significance in the last month	Initiation
	Hepatitis B	Initiation
	Hepatitis C	Initiation
	Malnutrition	Initiation
	Current/pre-existing medical condition(s) of significance other than HIV/TB	Initiation
	Abnormal laboratory tests in the last three months (with date and results)	Initiation and follow up
Medicines	Medicines taken in last one month, including dosage, frequency, and start and stop dates (including ARVs other than DTG based regimen and folates)	Initiation
	Medicines currently being taken (excluding DTG based regimen) with dosage, frequency, and start date	Initiation and follow up
	Medicines newly prescribed (including DTG based regimen and medicines to treat adverse effects) at each visit with dosage and frequency including the reason for use of DTG based regimen (e.g., Treatment initiation, transition from another regimen, second line)	Initiation and follow up
Adverse events	New medical events (including abnormal lab results and “no event”) since the start of	Follow up

	DTG-based regimen with start and stop dates, seriousness, severity, and outcome	
	Change in existing medical condition(s) since the start of DTG-based regimen with start and stop dates and outcome	Follow up
	The appearance of AEs of interest, including weight gain, hyperglycemia, hyperlipidemia, effects on pregnancy (miscarriage, stillbirth, spontaneous abortion, low birth weight, preterm delivery) with start and stop dates, seriousness, severity, and outcome	Follow up
Anticipated risk factors for weight gain	Smoking status	Initiation and follow up
	Alcohol consumption	Initiation and follow up
	Physical activity	Initiation and follow up
Additional Laboratory tests for sub-cohort of 300 participants	Glycaemia	Initiation and every 6 months
	Glycated Hemoglobin (HBA1c)	Initiation and every 6 months
	Blood cholesterol (LDL, HDL & TC)	Initiation at and every 6 months
	Triglycerides	Initiation and every 6 months

ANNEX 2: INFORMED CONSENT FORM

1. Study information

Research project title: ACTIVE SURVEILLANCE OF DOLUTEGRAVIR BASED ANTIRETROVIRAL REGIMENS IN RWANDA

Principal Investigator: Dr. Dominique Savio HABIMANA (PI), Rwanda Biomedical Center (RBC), HIV division.

Co-Investigators: Mr. Lazare NTIRENGANYA, Rwanda Food and Drugs Authority (Rwanda FDA)

Mr. Eric Remera, Rwanda Biomedical Center (RBC)

Dr. Innocent Hahirwa, University of Rwanda (UoR)

This work is done in the framework of safety monitoring for Dolutegravir-based regimens in Rwandan patients.

2. Invitation for participation

You are invited to participate in this research study by accepting to be enrolled in the study and be followed up for safety monitoring of your treatment regimen. You have the right to know that consent is purely voluntary, and that your permission to participate in research may be withdrawn at any time. This document contains important information that you should know before enrolling in the study. Please take your time to review this form. Feel free to discuss it with your family, friends, or doctor before you make your decision.

3. Why is this study being done?

The purpose of this study is to determine the safety profile of DTG-based regimens, including Tenofovir/Lamivudine/Dolutegravir and Abacavir/Lamivudine + Dolutegravir among HIV patients in Rwanda.

Dolutegravir is one of the newly introduced antiretroviral drugs being used for both first-line and second-line HIV treatment in Rwanda. Despite the demonstrated benefits of Dolutegravir, various studies have shown that a number of adverse events are associated with the use of this molecule, but more data are still needed to determine its safety profile in real practice. Findings from this study will provide information on the safety profile of Dolutegravir-based regimens specific to Rwandan patients, which will help the Ministry of Health and the National HIV program to come up with strategies to control and manage adverse events and adverse drug events associated with the use of these regimens. The results from this study may also inform

special guidelines with regards to HIV treatment in Rwanda. These guidelines will be used by healthcare providers to improve the quality of care provided to HIV patients.

4. What are the procedures involved in this Study?

If you agree to participate in this study, you will be required to sign this consent form. After signing the consent form, you will be enrolled in the study and followed up for safety monitoring during a one-year period. Information about your medical history will be accessed from your medical records and other specific information will be collected during your routine visits to the treatment site. In addition to the usual laboratory tests performed for routine HIV management, we may need to perform extra tests to measure your blood sugar and lipid levels. Participation in the study involves also reporting or notifying your medical team of all medication adverse events/effects. All this information will be used for research purposes only.

5. What are the risks of the Study?

Participation in the study will not bring any additional risk to you as this is an observational study, thus there will be no additional intervention to your routine treatment. The greatest risk would be the release of medical information from your medical record, but this will be avoided by keeping you anonymous and your records well protected.

6. What about confidentiality?

All information collected in this study will be kept strictly confidential. Your personal data used in this research study will be stored with a confidential code and your name will not be included with any data that can be shared with other investigators. The medical information produced as a part of this study will not become part of your medical record.

The information obtained from this study may be published in scientific journals and, while we will always acknowledge the people's participation, no individual information will ever be published in any format.

7. What are the benefits involved?

There will be no direct benefit to you from participating in this study, but the information obtained from this study may be of benefit to patients managed with Dolutegravir-based regimens in the future. In fact, this information may help to improve the use of these regimens and limit their toxicity.

8. What are personal costs?

There will not be any cost for your participation in this study. Your routine visits for follow up will be used for data collection. In case an additional visit may be required for study reasons, the related cost will be covered by the research budget. If you are part of the cohort for blood glucose and lipid monitoring, additional laboratory tests will be covered by the research funds.

9. Who to contact for research related issues?

This research study has been reviewed and approved by the Rwanda National Ethics Committee (RNEC) for Studies Involving Human Subjects. For research problems or questions regarding subjects, RNEC may be contacted P.O. Box 84 Kigali, Rwanda Tel: +250 788592004

Email: info@rnecrwanda.org

10. Signature

Your signature below indicates that you have been given the opportunity to read this consent form and to ask questions. Your questions have been answered to your satisfaction. You voluntarily agree to participate in this research study. Upon signing below, you will receive a copy of the consent form.

Name of Participant/Family member/Patient Guardian	Signature and Telephone	Date
Name of the Person Obtaining the Consent	Signature of the Person Obtaining the Consent	Date

Annex 3: Study Work Plan

Proposed Study plan																																							
			Time (Months)																																				
			Y2	Y3												Y4												Y5											
			July - Sep 2020	Oct 1 2020 - Sep 30 2021												Oct 1 2021 - Sep 30 2022												Oct 1 2022 - Sep 30 2023											
Activity	**Deliverables**	**Responsible**		Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
Development of protocol and SOPs	Protocol SOPs data elements for collection	MTaPS																																					
Selection of the sentinel sites	List of implementation sites	Rwanda FDA/RBC																																					
Development of training materials	Training materials	MTaPS																																					
Obtain in IRB approval	IRB approval	Rwanda FDA/RBC																																					
Pilot the electronic data collection tools at facilities	Pilots tests results	Rwanda FDA/RBC/MTaPS																																					
Training healthcare providers on protocl and their roles and responsabilities	Training report	MTaPS																																					
Establish TLD active monitoring committee	Committee members identified and notified; terms of reference and meeting schedule	Rwanda FDA/RBC																																					
Enroll patients into the cohort and commence data collection	Patients enrollment progress report	Site teams/Rwanda FDA/RBC																																					
Follow up enrolled patients	Report of patient follow up	Site teams/Rwanda FDA/RBC																																					
Undertake support supervisory visits and onsite mentoring to site teams	Support supervisory and mentoring report	Rwanda FDA/RBC																																					
Data cleaning and quality checks	Cleaned data	Rwanda FDA/RBC																																					
Data Analysis	Data analysis report	Site teams/Rwanda FDA																																					
Interim data review	Data progress collection																																						
Committee review meetings	Meeting resolutions	Rwanda FDA/RBC/MTaPS																																					
Data cleaning and final analysis	Committee meeting reports	Rwanda FDA/RBC/MTaPS																																					
Dissemination progress report, findings and recommendations from the activity to local and wider audience	Data meeting report	Rwanda FDA/RBC/MTaPS																																					
Manuscript development	Manuscript developed	Rwanda FDA/RBC/MTaPS																																					
Journal publication	Article published	MTaPS																																					

BUDGET ESTIMATION

INTERVENTION	Activities	Quantity	Frequency	Unit Cost	Total Cost (Rwf)	Total in $
1. Protocol IRB clearance	RNEC Approval	1	1	1,500,000	1,500,000	1,515.15
	S/Total 1				*1,500,000*	*1,515.15*
2. Training of data collectors (HCPs)	Conference package	40	2	30,000	2,400,000	2,424.24
	Transport of HCPs	30	2	5,000	300,000	303.03
	Per diem	30	3	20,000	1,800,000	1,818.18
	Accomodation of HCPs	30	2	60,000	3,600,000	3,636.36
	S/Total 2				*8,100,000*	*8,181.82*
3. Data collection	Communication fee for HCPs	30	12	20,000	7,200,000	7,272.73
	SOPs printing	20	10	50	10,000	10.10
	Internet conections	30	12	10,000	3,600,000	3,636.36
	S/Total 3				*10,810,000*	*10,919.19*
4. Supervision of data collection	Transport for supervisors	16	4	112,000	7,168,000	7,240.40
	Accomodation	32	4	60,000	7,680,000	7,757.58
	Per diem	32	4	26,500	3,392,000	3,426.26
	S/Total				*18,240,000*	18,424.24
5. Coordination meeting		***32***	***1***	*35,000*	*1,120,000*	1,131.31

7. Stakeholders' meeting		***32***	***1***	*35,000*	*1,120,000*	1,131.31
					2,240,000	2,262.63
8. Data analysis	**Biostatistician**	**1**		**1,500,000**	1,500,000	1,515.15
9. Report writing	**TA**	**1**		**1,000,000**	1,000,000	1,010.10
					2,500,000	2,525.25
	G/Total				*43,390,000*	43,828.28
5.Biomarker	**Glycaemia**	300	3	6148	*5,533,200*	*5,589.09*
	Glycated haemoglobin	300	3	6986	*6,287,400*	*6,350.91*
	LDL-Cholesterol	300	3	5589	*5,030,100*	*5,080.91*
	HDI-Cholesterol,	300	3	5589	*5,030,100*	*5,080.91*
	Triglycerides	300	3	5589	*5,030,100*	*5,080.91*
	Total Cholesterol	300	3	5589	*5,030,100*	*5,080.91*
					26,407,800	*26,674.55*
	BMI measures obesity					
	Waste circumference for Cardiovercular deases					
					-	-
Big Total					***69,797,800***	***70,502.83***

Exchange rate = $ 990