STATISTICAL ANALYSIS PLAN

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2 Abbreviations and Definitions

2DR Two-drug regimen
ACTG AIDS Clinical Trial Group
AE Adverse Event
AR Adverse Reaction
ART Antiretroviral Therapy
CA Competent Authority
CI Chief Investigator
CRF Case Report Form
CRO Contract Research Organisation
CTA Clinical Trial Authorisation
DMC Data Monitoring Committee
DTG Dolutegravir
EC European Commission
EMEA European Medicines Agency
EU European Union
EUCTD European Clinical Trials Directive
EudraVIGILANCE European database for Pharmacovigilance
GCP Good Clinical Practice
GMP Good Manufacturing Practice
HIV Human Immunodeficiency Virus
ICF Informed Consent Form
ICH International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC Independent Data Monitoring Committee
IMP Investigational Medicinal Product
IMPD Investigational Medicinal Product Dossier
ISF Investigator Site File
ISRCTN Number International Standard Randomised Controlled Trials
3TC Lamivudine
MA Marketing Authorisation
MHRA Medicines and Healthcare products Regulatory Agency
MS Member State
NHS R&D National Health Service Research & Development
NIMP Non-Investigational Medicinal Product
PASS Post-authorization Safety Study
PI Principal Investigator
PIC Participant Identification Centre
PIS Participant Information Sheet
QA Quality Assurance
QC Quality Control
QP Qualified Person
RCT Randomised Control Trial
REC Research Ethics Committee
RNA Ribonucleic acid
RPV Rilpivirine
SAE Serious Adverse Event
SAR Serious Adverse Reaction
SDV Source Data Verification
SOP Standard Operating Procedure
SmPC Summary of Product Characteristics
SSI Site Specific Information
SUSAR Suspected Unexpected Serious Adverse Reaction
TMG Trial Management Group
TSC Trial Steering Committee
TMF Trial Master File

3 Introduction

3.1 Preface

The efficacy of two-drug regimen (2DR) therapy with an integrase inhibitor plus a reverse transcriptase inhibitor was assessed in various clinical trials. However, all studies had strict inclusion/exclusion criteria. Thus, gathering real world evidence with less restrictive inclusion criteria to evaluate effectiveness of the 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor would further show the value of such regimen.

3.2 Purpose of the analyses

The purpose of the analysis is to assess in real-world the effectiveness of 2DR, following an Antiretroviral treatment with integrase inhibitors DTG plus a reverse transcriptase inhibitor; in patients either as a first-line treatment in naïve patients, a switching option for those with HIV RNA suppression on current treatment (stable switch), or a second-line treatment for those with VF on prior treatment.

4 Study Objectives and Endpoints

4.1 Study Objectives

4.1.1 Primary objective

To assess the effectiveness of a 2DR (integrase inhibitor plus a reverse transcriptase inhibitor).

4.1.2 Secondary objectives

To collect information on the safety of a 2DR in terms of drug related AEs, SAEs and development of resistance

4.2 Endpoints

4.2.1 Primary endpoint

The primary endpoint is:

a) For naïve and VF populations: the proportion of patients with HIV-RNA levels <50 copies/mL at 24, 48, and 96 weeks, estimated using a Kaplan-Meier Method. Participants with virologic rebound or virologic non-response will be considered as failure. Virologic rebound will be defined as two consecutive measurements of ≥50 copies/mL after suppression (one <50 copies/mL). Virologic Non-response will be defined as two consecutive measurements of ≥50 copies/mL after at least 24 weeks of treatment
b) For stable switch population: the proportion of patients who lose virologic control (2 consecutive HIV RNA levels ≥50 copies/mL or HIV RNA ≥50 copies/mL followed by study treatment discontinuation or missing value) within the first 24, 48 and 96 weeks after switching to a 2-DR, estimated using a Kaplan-Meier Method.

Treatment effectiveness will also be assessed by using the following definition for virologic rebound and virologic non-response:

For naïve and VF populations

a) Virologic Rebound: two consecutive measurements of ≥200 copies/mL after suppression (one <50)
b) Virologic Non-response: two consecutive measurements of ≥200 copies/mL after at least 24 weeks of treatment

For stable switch population

c) Virologic Rebound: 2 consecutive HIV RNA levels ≥200 copies/mL or HIV RNA ≥200c/mL followed by study treatment discontinuation or missing value

4.2.2 Secondary endpoint

In each population (naïve, stable switch, and treatment-experienced with VF):

a) Proportion of patients with HIV RNA ≥200 copies/mL after 24, 48 and 96 weeks of treatment (to analyse in real world and quantify the blips).

b) Proportion of patients with low level viremia (VL ≥50 and <200 copies/mL) at each time point for analysis.

c) Time to virologic suppression in the naïve and the switch with VF populations (viral load < 50 copies/mL at the end of 6months/12months/18 months or as pre-specified. This allows for blips during the follow up period).

d) Time to VF in the stable switch population

e) Resistance profile in case of virological failure

f) Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0.

g) Factors associated with plasma HIV-RNA ≥50 copies/mL after 96 weeks if number of failures allows analysis

h) Frequency of drug related AEs and SAEs

i) Proportion of patients with:

   1. Stable switch while virologically suppressed

   2. Switch after Failure

   3. Switching for tolerability, toxicity and other reasons

5 Study Methods

5.1 General Study Design and Plan

COMBINE-2 (2DR) is a multicentre, observational study, across Europe in patients who have started and/or who plan to initiate 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor. We anticipate that the majority of these patients will be taking either DTG plus RPV, or DTG plus 3TC. The study does not require any changes to the routine standard of care that patients receive, and decisions on ARV treatment are made by the healthcare providers taking into account the treatment history, patient characteristics and local guideline or recommendations. Data will be collected every 6 months from participating centres for a period of 96 weeks for each potential participant. Centres with at least 5 patients already taking this treatment (outside clinical trials) since January 2014 or who plan to initiate at least 5 patients in near future will be selected to participate in this study.

Consent procedures will be undertaken as required by country specific regulations and local procedures for the collection of retrospective and/or prospective data.

5.2 Inclusion Criteria and General Study Population

The study population will consist of HIV-infected adults aged 18 years or over and who have started 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor from 2014 onwards as:

a) a first-line treatment among naïve patients, or

b) a switching option for those with HIV RNA suppression on current treatment (stable switches), or

c) a second-line treatment for those with virological failure (VF) on prior treatment.

6 Sample Size

It is anticipated that data from 500 participants are thought adequate to meet the study objectives: 90 naïve, 320 stable switch patients and 90 second line treatment due to VF patients.

a) In ARV naïve population, the expected success rate of a standard 3-drug regimen can be estimated at 90% at week 48 (based on SNGLE, SPRING-2 and FlAMINGO trials results) with a non-inferiority margin of 10% (see FDA guidelines). Therefore the 2DR will be considered acceptable if the percentage of patients in success (HIV RNA <50 copies/mL) at week 48 is significantly above 80%. Assuming a 90% response rate, by including 90 individuals, we will have a 95% probability to discard a combination for which efficacy is smaller than 80% and we will select with a power of >80 % the strategy for which the efficacy is above or equal to 90%.

b) In patients switching with HIV RNA suppression (Stable switch population), the expected VF rate of a standard 3-drug regimen can be estimated at 4% at week 48 (based on NEAT22/SSAT60 trial result, IAS2017) with a non-inferiority margin of 4%. Therefore, the 2-DR will be considered acceptable if the percentage of patients in VF at week 48 is significantly lower than 8%. Assuming a 4% VF, by including 320 individuals, we will have a 95% probability to discard a combination for which the rate of failure is greater than 8% and we will select with a power of >90% the strategy for which the rate of failure is less to 8%.

c) In a population of patients with a second line treatment due to VF on prior treatment, the expected success rate of a standard 3-drug regimen can be estimated at 90% at week 48 (based on the 24-week result (82%) of DTG-containing regimen in the DAWNING trial) with a non-inferiority margin of 10% (see FDA guidelines). Therefore the 2-DR will be considered acceptable if the percentage of patients in success (FDA snapshot method) at week 48 is significantly above 80%. Assuming a 90% response rate, by including 90 individuals, we will have a 95 % probability to discard a combination for which efficacy is smaller than 80% and we will select with a power of >80% the strategy for which the efficacy is above or equal to 90%.

The sample size and power calculation will be made using the statistical software package nQuery Advanced, Exact test for single proportion module (Version 8.4.1.0).

7 General Considerations

7.1 Timing of analyses

The primary efficacy analysis will be performed within the 6 months which follow the last patient last visit week 96.

7.2 Timing of outcome assessments

Visit	Window (Through End-of-Study Week)	Window (Days)
24	18-30	127-210
48	42-54	295-378
72	66-78	463-546
96	90-102	631-714

The outcomes will be determined by the last available measurement while the patient is on treatment and continued on study within the time window.

7.3 Analysis Populations

7.3.1 Full Analysis Population

All enrolled participants who will receive at least one time a 2DR will be included in the Full Analysis Population. The primary endpoint and all secondary endpoints will be analysed on this Full Analysis population, called as an intention-to-treat (ITT) analysis. Participants who will never receive 2DR will be excluded from the full analysis population.

7.3.2 Safety Population

All subjects included in the ITT population who received at least one dose of 2DR treatment.

7.4 Confounders and Effect Modifier

We will examine factors associated with plasma HIV RNA ≥50 copies/mL at after week 96. Univariable and multivariable Cox regression models will be used. Some demographic or HIV characteristics will be assessed: age, gender, ethnicity, CD4 and CD4/CD8 ratio at time of first starting 2DR treatment, CD4 nadir, CDC disease stage, duration of undetectability plasma HIV RNA levels at start of 2DR treatment for stable switch population, plasma HIV RNA levels at start of 2 DR for naïve and VF population.

We will assess whether continuous variables will be better modelled as continuous variables or as terciles based on the lowest value of Akaike's information criterion (AIC) for the corresponding univariable Cox regression models, and grouped together the closest values in order to obtain two classes for certain variables. Variables with univariable P values below 0.15 will be then entered in multivariable Cox regression models.

7.5 Missing Data

For the factors associated analysis, as some parameters with missing data could influence the response rate, and because it is better to impute missing data than to ignore them, we will create 10 datasets in which missing data will be replaced. Analyses will be run on each of the 10 data sets, and the results will be combined with Rubin's rules.

For the primary endpoint analysis, all treatment or follow-up discontinuations for reasons other than virological non-response (naïve and VF populations) or virological failure (stable switch population) will be censored at the date of discontinuation. All virological non-response and viral rebound (naïve or VF populations) or virological failure (stable switch population) events occurring in participants who previously stopped the study treatment will not be considered as events in the analysis.

For the immunological analysis (CD4, CD8, and CD4/CD8 ratio), we will use mixed model to account for all ITT population in the analysis.

8 SUMMARY OF STUDY DATA

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

8.1 Subject Disposition

The number of patients enrolled, and the flowchart of the study will be presented by study population. The period of the initiation of the 2DR treatment and the number of patients who never take the 2DR treatment will also be presented and the reason will be given and those who remained on the 2DR treatment up to week 96 will be presented. The number of patients who discontinued the study will be presented and the reason of discontinuation will be given. All these information will be shown in the study Flowchart (refer to Figure 1 in the appendix).

8.2 Demographic and Baseline Variables

The baseline will be the date at the first starting 2DR treatment.

The following variables will be considered as demographic or baseline variables: age, gender, ethnicity, CD4, CD8 and CD4/CD8 ratio at time of first starting 2DR treatment, CD4 nadir, CDC disease stage, duration of undetectability plasma HIV RNA levels at start of 2DR treatment (switch population), plasma HIV RNA levels at start of 2 DR (naïve and VF population), type of 2DR treatment (DTG+3TC, DTG+RPV, Other).

All summary tables will be structured with a column for each Population in the order (Naïve population, VF population, and Stable switch population). These summary tables will be annotated with the total population size for each group, including any missing observations (refer to Table 1 in the appendix).

8.3 Exposure variables

Any exposure to integrase inhibitors such as DTG and reverse transcriptase inhibitors such as 3TC or RPV is of interest. Exposure starts the first day ART of an integrase inhibitor plus a reverse transcriptase inhibitor are known to have taken. Person time exposed is defined as the number of days that the subject is known to have been exposed to this dual combination regimen.

8.4 Premature stop

Participants who lost to follow-up, or discontinue the 2DR treatment will be considered as premature stop. Participants with missing data at the last visit of the study protocol will be considered as lost to follow-up. Any change to the integrase inhibitor in the 2-DR will be considered as a discontinuation, while changes to the second drug (NRTI or NNRTI) will not be considered as a discontinuation. The frequency of premature stop will be described, and reasons will be given.

8.5 Concurrent Illnesses and Medical Conditions

The number and percentage of participants with comorbidities at baseline will be given. The summary statistics will be produced in accordance with section 8. The most frequent comorbidities will be displayed (refer to Table 2 in the appendix).

8.6 Prior and Concurrent Medications

All medications ongoing (anti-hypertensive agents, anti-diabetic agents and lipid lowering agents) at baseline and week 96 will be described. The last observation carried forward approach will be used to fill in missing data at week 96. The summary statistics will be produced in accordance with section 8 (refer to Table 3 in the appendix).

9 Efficacy Analyses

9.1 Primary Efficacy Analysis

The primary outcome analysis will be performed with the ITT population. Separate analyses will be done with each population (naïve population, VF population, stable switch population).

- For naïve and VF populations, the proportion of participants with HIV RNA <50 copies/mL will be estimated using the Kaplan-Meier estimator. The associated two-sided 95% confidence intervals will be calculated with Kalbfleisch and Prentice's formula. Events will be defined as absence of viral rebound after one VL<50 copies/mL and absence of virological non-response. Participants who will discontinue the 2DR treatment before week 24 will be censored at the date of discontinuation. Time to event will be defined as the time between the date of first start of 2DR and the date of first HIV RNA<50 copies/mL. Follow-up will be censored at week 96, or the date of last study contact, or date of 2DR treatment discontinuation, or the date of lost to follow-up,

whichever will occur first. Kaplan-Meier curves will be plotted for the primary endpoint in each population and will include a curve for each study population, a legend with the number of patients in each study population and the corresponding number of virological success, the number of patients at risk at weeks 0, 24, 48, 72 and 96, and the estimate proportion with associated 95% confidence interval at week 96.

- For stable switch population, the proportion of participants who loss viral control will be estimated using the Kaplan-Meier estimator. The associated two-sided 95% confidence intervals will be calculated with Kalbfleisch and Prentice's formula. Events will be defined as 2 consecutives of VL≥50 copies/mL or a VL≥50 copies/mL followed by 2DR treatment discontinuation or lost to follow-up. Participants who will discontinue the 2DR treatment with HIV RNA <50 copies/mL 24 will be censored at the date of discontinuation. Time to event will be defined as the time between the date of first start of 2DR and the date of loss of viral control (date of first VL≥50 copies/mL). Follow-up will be censored at week 96, or the date of last study contact (if VL<50 copies/mL), or date of 2DR treatment discontinuation (if VL<50 copies/mL), or the date of lost to follow-up (if VL<50 copies/mL), whichever will occur first. Kaplan-Meier curves will be plotted for the primary endpoint and will include a legend with the number of patients and the corresponding number of participants with loss of viral control, the number of patients at risk at weeks 0, 24, 48, 72 and 96, and the estimate proportion with associated 95% confidence interval at week 96.

Similar analyses will be carried out by modifying the efficacy threshold (by replacing 50 copies/mL by 200 copies/mL).

A table will summarize the events according to the study populations (refer to Table 4a and 4b in the appendix).

9.2 Secondary Efficacy Analyses

All secondary efficacy outcome analyses will be performed with the ITT population. All p-values will be two-sided with a significant level set at 0.05.

a) Proportion of patients with HIV RNA ≥200 copies/mL after 24, 48 and 96 weeks of treatment. (to analyse in real world and quantify the blips).

Separate analyses will be done with each population (naïve population, VF population, stable switch population).

The proportion of patients with HIV RNA ≥200 copies/mL after 24, 48 and 96 weeks of treatment will be estimated using the Kaplan-Meier estimator for each study population. The associated two-sided 95% confidence intervals will be calculated with Kalbfleisch and Prentice's formula. Event will be defined by a VL ≥200 copies/mL at week 24 or after in the naïve and VF populations, and a first occurrence of VL ≥200 during the 96 weeks of follow-up in the stable switch population. Time to event will be defined as the time between the date of first start of 2DR and the date of event. Follow-up will be censored at week 96, or the date of last study contact, or date of 2DR treatment discontinuation, or the date of lost to follow-up, whichever will occur first. Kaplan-Meier curves will be plotted according to the study population and will include a curve for each study population, a legend with the number of patients in each study population and the corresponding number of patients VL ≥200 copies/mL, the number of patients at risk at weeks 0, 24, 48, 72 and 96, and the estimate proportion with associated 95% confidence interval at week 96.

Data will be summarized as in Table 5 in the appendix.

Incidence of viral blips in each population will be estimated by the total number of viral blips during the study period divided by the person-years. The associated two-sided 95% confidence intervals will be calculated with Poisson regression model. A viral blip will be defined as a VL≥50 copies/mL at a given visit followed by a second measurement (control) <50 copies/mL in participants with already suppressed viremia (one VL<50 copies/mL).

Data will be summarized as in Table 7 in the appendix.

b) Proportion of patients with low level viremia (VL ≥50 and <200 copies/mL) at each time point for analysis.

Separate analyses will be done with each population (naïve population, VF population, stable switch population).

The proportion of participants with low level viremia (VL ≥50 and <200 copies/mL) at each time point in each population will be estimated by dividing the number of participants with VL ≥50 and <200 copies/mL by the total number of participants in the ITT population at each time point. The associated two-sided 95% exact (Clopper–Pearson) confidence intervals will be calculated. These data will be summarized as in Table 6 in the appendix.

An additional analysis will be performed using the Poisson regression model. The follow-up will be categorized in period (0-24 weeks, 24-48 weeks, 48-72 weeks and 72-96 weeks). We will calculate the incidence of low-level viremia in each period by dividing the total number of events occurred in the period by the number of person-year of the period. The associated two-sided 95% confidence intervals will be calculated (refer to Table 8 in the appendix).

c) Time to virologic suppression in the naïve and the switch with VF populations (viral load < 50 copies/mL at the end of 6months/12months/18 months or as pre-specified. This allows for blips during the follow up period).

The median time to virologic suppression in the naïve and the VF populations will be estimated using the Kaplan-Meier estimates. Event will be defined as the first occurrence of VL<50 copies/mL during the study period. Time to event will be defined as the time between the date of first start of 2DR and the date of event. Follow-up will be censored at week 96, or the date of last study contact, or date of 2DR treatment discontinuation, or the date of lost to follow-up, whichever will occur first. The associated two-sided 95% confidence intervals will be calculated. The proportion of participants with VL <50 copies/mL at weeks 24, 48, 72 and 96 will also be estimated with the associated 95% confidence intervals.

Kaplan Meier curve will be plotted and will include a curve for each population, a legend with the number of patients in each population and the corresponding number of virological success, the number of patients at risk at weeks 0, 24, 48, 72 and 96, and the estimate proportion with associated 95% confidence interval at week 96 for each population.

Data will be summarized as in Table 9 in the appendix.

d) Time to VF in the stable switch population

The median time to virologic failure in the stable switch population will be estimated using the Kaplan-Meier estimates. Virologic failure will be defined as two consecutives of VL≥50 copies/mL or a VL≥50 followed by 2DR treatment discontinuation or lost to follow-up during the study period. Time to event will be defined as the time between the date of first start of 2DR and the date of virologic failure. Follow-up will be censored at week 96, or the date of last study contact, or date of 2DR treatment discontinuation, or the date of lost to follow-up, whichever will occur first. Kaplan Meier curves will be plotted and will include a legend with the number of patients and the corresponding number of VF, the number of patients at risk at weeks 0, 24, 48, 72 and 96, and the estimate proportion with associated 95% confidence interval at week 96.

Data will be summarized as in Table 9 in the appendix.

e) Resistance profile in case of virological failure

Separate analyses will be done with each population (naïve population, VF population, stable switch population).

The proportion of participants with genotypic resistance viruses among those with virological failure will be estimated by dividing the number of participants with genotypic resistance viruses by the total number of participants with virological failure. The associated two-sided 95% exact (Clopper–Pearson) confidence intervals will be calculated.

Virological failure will be defined as 2 consecutives VL ≥50 copies per mL after week 24 in the naïve and VF populations, and 2 consecutives VL ≥50 copies/mL during the study period or a VL≥50 copies/mL followed by 2DR treatment discontinuation or follow-up in the stable switch population. Participants with virological failure and their genotypic resistance results will be listed as in the Table 10 in the appendix.

f) Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0.

Separate analyses will be done with each population (naïve population, VF population, stable switch population).

The evolution of the CD4, CD8 and CD4/CD8 ratio between baseline and week 96 according to the study population will be described by boxplots for each population at baseline, W24, W48, W72 and W96. The changes from baseline to week 96 in CD4 T cell count, CD8 T cell count and CD4/CD8 ratio will be compared within each study population by using mixed models for repeated measures with random effects and unstructured covariance matrix. The models will include time as categorical variable. Data will be summarized as in Table 11 in the appendix.

g) Factors associated with plasma HIV-RNA ≥50 copies/mL after 96 weeks if number of failures allows analysis

Separate analyses will be done with each population (naïve population, VF population, stable switch population).

Univariable and Multivariable Cox regression models will be used to assess factors associated with plasma HIV RNA ≥50 copies/mL at after week 96. Participants who will discontinue 2DR treatment, lost to follow-up before week 96 or with missing value at week 96, will be censored at the date of discontinuation, date of follow-up or date of last available HIV RNA data, respectively. The following variables will be assessed: age, gender, ethnicity, CD4 and

CD4/CD8 ratio at time of first starting 2DR treatment, CD4 nadir, CDC disease stage, duration of undetectability plasma HIV RNA levels at start of 2DR treatment (stable switch population only), plasma HIV RNA levels at start of 2 DR (naïve and VF population only).

We will assess whether continuous variables will be better modelled as continuous variables or as terciles based on the lowest value of Akaike's information criterion (AIC) for the corresponding univariate Cox regression models, and grouped together the closest values in order to obtain two classes for certain variables. Variables with univariable P values below 0.15 will be then entered in multivariable Cox regression models.

As some parameters with missing data can influence the response rate, and because it is better to impute missing data than to ignore them, we will create 10 datasets in which missing data will be replaced. Analyses will be run on each of the 10 data sets, and the results will be combined with Rubin's rules.

Data will be summarized as presented in Table 12a, 12b and 12c in the appendix.

10 Safety Analyses

10.1 Serious adverse events and drug-related adverse events

h) Frequency of drug related AEs and SAEs

Separate analyses will be done with each population (naïve population, VF population, stable switch population).

Any serious adverse events (SAE), drug-related AEs and death will be described. Incidences will be estimated by the total number of each event occurred during the study period by the total number of person-years. The two-sided 95% confidence intervals will be calculated using Poisson regression analysis. The Poisson regression models will include the number of events, and the duration of exposure in year. Analyses will be performed for each study population.

A table will summarize the frequency of serious adverse events and drug-related AEs. This table will include the name of event, number and percentage of patients with events, number of events, and incidence rate (IR) per 100 person-years in each study population with the associated 95% confidence intervals (refer to Table 13 in the appendix).

10.2 Discontinuation of the 2DR treatment

i) Proportion of patients with: (1) Stable switch while virologically suppressed; (2) Switch after Failure; (3) Switching for tolerability, toxicity and other reasons

The premature stops of the study follow-up or the study treatment will be reported in a table. This table will include a column for the patient codes, a column for treatment duration in weeks and a column for the reasons of discontinuation. The analysis will be performed for each study. The proportion of participants who stopped the 2DR treatment before week 96 will be estimated using the Kaplan-Meier estimates in each study population. The two-sided 95% confidence intervals will be calculated with Kalbfleisch and Prentice's formula. The proportion of participants with stable switch while virologically suppressed, switch after failure, switching for tolerability, toxicity and other reasons will be estimated using the Kaplan-Meier estimates. The associated 95% confidence intervals will also be calculated.

The Kaplan-Meier curves will also be plotted and will include a curve for each study population, a legend with the number of patients in each population and the corresponding number of discontinuation, the number of patients at risk at weeks 0, 24, 48, 72 and 96, and the estimate proportion with associated 95% confidence interval at week 96 for each study population.

Data will be summarized as in Table 14 in the appendix.

11 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

12 Technical Details

Analyses will be performed with the SAS®, SPSS® or Stata® software package (last available version for Windows or later). Meetings will be held to discuss and reproduce the primary analysis summary statistics tables. The reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing tables as well as any other pieces of code as desired.

13 Appendix

Figure 1: Study flowchart

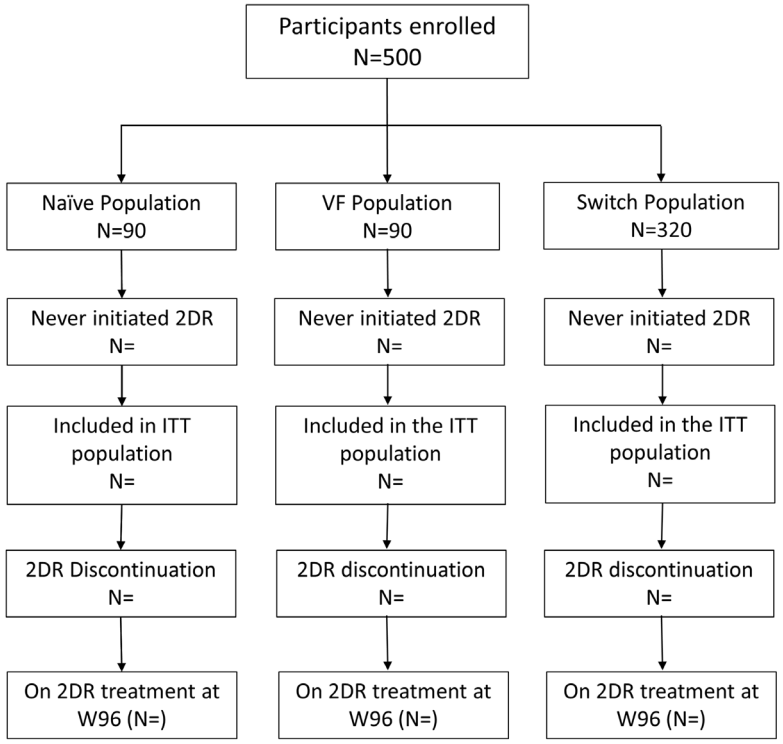

Table 1: Baseline characteristics of the patients

Characteristics	Naïve population N=	VF population N=	Stable switch population N=
Age, years, median (IQR)			
Male – ***n*** (%)			
Ethnicity– ***n*** (%)			
- White			
- Black			
- Asian			
- Other			
CDC disease stage – ***n*** (%)			
- A			
- B			
- C			
Duration of antiretroviral treatment (years), median (IQR)			
Duration of suppression of HIV viremia (pVL<50 copies/mL) (years), median (IQR)	NA	NA	
Plasma VL log_{10} (cp/ml), median (IQR)			
CD4 count nadir (cells/mm^3), median (IQR)			
CD4 count (cells/mm^3), median (IQR)			

CD4/CD8 ratio, median (IQR)

Baseline regimen– *n* (%)

- DTG + 3TC
- DTG + RPV
- Other (Specify)

Table 2: Proportion of participants with comorbidities at baseline and the list of most frequent comorbidities

		Naïve population Total N=		**VF population Total N=**		**Stable switch population Total N=**	
	Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Comorbidities -Presence	Any Comorbidities						
	No Comorbidities						
	Unknown						
Comorbidities	Hypertension						
	Diabetes						
	Liver disorder						
	Cardiovasular disorder						
	Obesity						

Table 3: Proportion of participants with concomitant medication at baseline and 96

		Naïve population Total N=		**VF population Total N=**		**Stable switch population Total N=**	
	TimePoint	**n**	**%**	**n**	**%**	**n**	**%**
Anti-hypertensive agents	Baseline						
	Week 96						
Anti-diabetic agents	Baseline						
	Week 96						
Lipid lowering agents	Baseline						
	Week 96						

Table 4a: Proportion of participants with Virological success (Threshold at 50 c/mL)

	Naïve population Total N=		**VF population Total N=**		**Stable switch population Total N=**	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
virological success					NA	NA
loss of viral control	NA	NA	NA	NA		
Consored events are described below						
virological rebond						
virological non-response						
discontinuation of 2DR						
death						
lost to follow-up						

Loss of viral control will be defined as 2 consecutives of VL≥50 copies/mL or a VL≥50 copies/mL followed by 2DR treatment discontinuation or lost to follow-up in the stable switch population
Virological rebound will be defined as 2 consecutives of VL≥50 copies/mL or a VL≥50 copies/mL followed by 2DR treatment discontinuation or lost to follow-up in the naive and VF population after a VL<50 copies/mL
Virological non-response will be defined as never reaching a VL<50 copies/mL in the naive and VF populations
Kaplan-Meier estimates will be used to estimate the proportion of participants who achieved virological success and those who lost viral control

Table 4b: Proportion of participants with Virological success (Threshold at 200 c/mL)

	Naïve population Total N=		**VF population Total N=**		**Stable switch population Total N=**	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
virological success					NA	NA
loss of viral control	NA	NA	NA			
Consored events are described below						
virological rebond						
virological non-response						
discontinuation of 2DR						
death						
lost to follow-up						

Loss of viral control will be defined as 2 consecutives of VL≥200 copies/mL or a VL≥200 copies/mL followed by 2DR treatment discontinuation or lost to follow-up in the stable switch population
Virological rebound will be defined as 2 consecutives of VL≥200 copies/mL or a VL≥200 copies/mL followed by 2DR treatment discontinuation or lost to follow-up in the naive and VF population after a VL<200 copies/mL
Virological non-response will be defined as never reaching a VL<200 copies/mL in the naive and VF populations
Kaplan-Meier estimates will be used to estimate the proportion of participants who achieved virological success and those who lost viral control

Table 5: Proportion of participants with HIV RNA ≥200 copies/mL after 24, 48 and 96 weeks of treatment

	Naïve population Total N=		**VF population Total N=**		**Stable switch population Total N=**	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Week 24						
Week 48						
Week 96						

Kaplan-Meier estimates will be used to estimate the proportion of participants with HIV RNA ≥200 copies/mL at week 24, 48 and 96. Event will be defined by a VL ≥200 copies/mL at week 24 or after in the naïve and VF populations, and a first occurrence of VL ≥200 during the 96 weeks of follow-up in the stable switch population.

Table 6: Proportion of participants with low level viremia (VL ≥50 and <200 copies/mL) at each time point

	Naïve population			**VF population**			**Stable switch population**		
	Total N	Nb event	% (95% CI)	Total N	Nb event	% (95% CI)	Total N	Nb event	% (95% CI)
Week 24									
Week 48									
Week 96									

The proportion will be estimated by dividing the number of participants with VL ≥50 and <200 copies/mL by the total number of participants in the ITT population at each time point. Participants with missing values at the time point will be excluded.

Table 7: Incidence of viral blips during the 96-weeks of follow-up. A viral blip will be defined as a VL≥50 copies/mL at a given visit followed by a second measurement (control) <50 copies/mL in participants with already suppressed viremia (one VL<50 copies/mL)

	Naive population	**VF population**	**Stable switch population**
N of participants			
Number of events			
Person-years of follow-up			
Incidence rate per 100 p-y			
95% confidence interval of IR			
IRR			

Table 8: Incidence of low level viremia (VL ≥50 and <200 copies/mL) during the 96-weeks of follow-up.

		Weeks	Weeks	Weeks	Weeks	Overall
		0-24	24-48	48-72	72-96	0-96 weeks
Naive population	N of participants					
	Number of events					
	Person-years of follow-up					
	Incidence rate per 100 p-y					
	95% confidence interval of IR					
	IRR					
VF poulation	N of participants					
	Number of events					
	Person-years of follow-up					
	Incidence rate per 100 p-y					
	95% confidence interval of IR					
	IRR					
Stable switch population	N of participants					
	Number of events					
	Person-years of follow-up					
	Incidence rate per 100 p-y					
	95% confidence interval of IR					
	IRR					

Table 9: Time to virologic suppression in the naïve and the switch with VF populations (viral load < 50 copies/mL) and time to virological failure in the stable switch population (2 consecutive VL ≥50 copies/mL or a VL≥50 copies/mL followed by 2DR discontinuation)

	Naïve population N=	**VF population N=**	**Stable switch population N=**
Virological suppression			
Number of viral suppression by week 96			NA
Kaplan-Meier estimate of viral suppression by week 96 – % (95% CI)			NA
Median time to viral suppression (95% CI) - weeks			NA
Virological failure			
Number of virological failure by week 96	NA	NA	
Kaplan-Meier estimate of virological failure by week 96 – % (95% CI)	NA	NA	
Median time to virological failure (95% CI) - weeks	NA	NA	

Table 10: List of participants with virological failure and their genotypic resistance results.

Patient group	Pt	Baseline ART regimen	ART regimen at failure	Time of VF	Suspected VF /Confirmed VF (c/ml)	RAM* at baseline	RAM* at failure	Modification of treatment
Naïve population	1							
	2							
	3							
VF population	1							
	2							
	3							
Stable switch population	1							
	2							
	3							

Table 11: Change from baseline in CD4 count, CD8 count and CD4/CD8 ratio at week 96

	Naïve population N=	**VF population N=**	**Stable switch population N=**
CD4 count/mm^3			
Number of participants			
Baseline mean (95% CI)			
Mean (95% CI) change at week 96, P-value			
CD8 count/mm^3			
Number of participants			
Baseline mean (95% CI)			
Mean (95% CI) change at week 96, P-value			
CD4/CD8 ratio			
Number of participants			
Baseline mean (95% CI)			
Mean (95% CI) change at week 96, P-value			
Changes from baseline to week 96 in CD4 T cell count, CD8 T cell count and CD4/CD8 ratio will be compared within each study population by using mixed models for repeated measures with random effects and unstructured covariance matrix. The models will include time as categorical variable.			

Table 12a: Factors associated with plasma viral load ≥50 copies/mL at week 96 in the naive population

Characteristics	Number of participants	Number of events	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, years				
Gender				
- **Female**				
- **Male**				
Ethnicity				
- White				
- Black				
- Asian				
- Other				
CDC disease stage				
- A				
- B				
- C				
Duration of antiretroviral treatment (years)				
Plasma VL log_{10} (cp/ml)				
CD4 count nadir (cells/mm^3)				
CD4 count (cells/mm^3)				
CD4/CD8 ratio				
Baseline regimen				
- DTG + 3TC				
- DTG + RPV				
- Other (Specify)				

We will assess whether continuous variables will be better modelled as continuous variables or as terciles based on the lowest value of Akaike's information criterion (AIC) for the corresponding univariable Cox regression models, and grouped together the closest values in order to obtain two classes for certain variables. Variables with univariable P values below 0.15 will be then entered in multivariable Cox regression models. Multiple imputation approach will be used to fill in missing variables. Analyses will be run on each of the 10 data sets, and the results will be combined with Rubin's rules.

Table 12b: Factors associated with plasma viral load ≥50 copies/mL at week 96 in the VF population

Characteristics	Number of participants	Number of events	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, years				
Gender				
- Female				
- Male				
Ethnicity				
- White				
- Black				
- Asian				
- Other				
CDC disease stage				
- A				
- B				
- C				
Duration of antiretroviral treatment (years)				
Plasma VL log_{10} (cp/ml)				
CD4 count nadir (cells/mm^3)				
CD4 count (cells/mm^3)				
CD4/CD8 ratio				
Baseline regimen– *n* (%)				
- DTG + 3TC				
- DTG + RPV				
- Other (Specify)				

We will assess whether continuous variables will be better modelled as continuous variables or as terciles based on the lowest value of Akaike's information criterion (AIC) for the corresponding univariable Cox regression models, and grouped together the closest values in order to obtain two classes for certain variables. Variables with univariable P values below 0.15 will be then entered in multivariable Cox regression models. Multiple imputation approach will be used to fill in missing variables. Analyses will be run on each of the 10 data sets, and the results will be combined with Rubin's rules.

Table 12c: Factors associated with plasma viral load ≥50 copies/mL at week 96 in the stable switch population

Characteristics	Number of participants	Number of events	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, years				
Gender				
- Female				
- Male				
Ethnicity				
- White				
- Black				
- Asian				
- Other				
CDC disease stage				
- A				
- B				
- C				
Duration of antiretroviral treatment (years)				
Duration of suppression of HIV viremia (pVL<50 copies/mL) (years)				
CD4 count nadir (cells/mm^3)				
CD4 count (cells/mm^3)				
CD4/CD8 ratio				
Baseline regimen– *n* (%)				
- DTG + 3TC				
- DTG + RPV				
- Other (Specify)				

We will assess whether continuous variables will be better modelled as continuous variables or as terciles based on the lowest value of Akaike's information criterion (AIC) for the corresponding univariable Cox regression models, and grouped together the closest values in order to obtain two classes for certain variables. Variables with univariable P values below 0.15 will be then entered in multivariable Cox regression models. Multiple imputation approach will be used to fill in missing variables. Analyses will be run on each of the 10 data sets, and the results will be combined with Rubin's rules.

Table 13: Incidence of Serious adverse events and drug-related adverse events

	Naive population N=			**VF population N=**			**Stable switch population N=**		
	Person-year:			Person-year:			Person-year:		
	N of events	N of pts (%)	Incidence rate/100 p-y (95% CI)	N of events	N of pts (%)	Incidence rate/100 p-y (95% CI)	N of events	N of pts (%)	Incidence rate/100 p-y (95% CI)
Drug related AEs									
list of events									
Serious adverse events (SAE)									
list of events									
Death									

Table 14: Proportion of participants with discontinuation of the 2DR

	Naïve population Total N=		VF population Total N=		Stable switch population Total N=	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Total discontinuation						
Switch while virologically suppressed						
Switch for failure						
Switch for tolerability						
Switch for toxicity						
Switch for other reasons						