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1 List of Abbreviations

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
PLWH	People Living with HIV
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
VF	Virologic Failure

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3 Abstract

Title

'COMBINE-2': Real-world evidence for effectiveness of Two Drug Regimen, Antiretroviral therapy with integrase inhibitors plus a reverse transcriptase inhibitor

Keywords: Real-world, Two-drug regimen, HIV

Rationale and background

The efficacy of two-drug regimen (2DR) therapy with an integrase inhibitor plus a reverse transcriptase inhibitor has been assessed in various pilot studies and clinical trials. In the PADDLE study, high rates of HIV RNA suppression were demonstrated after first- line treatment with Dolutegravir (DTG) plus Lamivudine (3TC). In additional phase 3 clinical trials, the two-drug combination DTG/3TC (GEMINI-1, -2) demonstrated high rates of HIV RNA suppression among ART-naïve people with HIV, with suppression rates non-inferior to standard first line 3 drug regimens (3DRs). DTG/3TC (TANGO and SALSA) and DTG/PRV (SWORD-1 and -2) regimens have also shown non-inferior efficacy compared to 3-DRs among people with HIV switching from a 3-DR with stable suppressed viral load in clinical trial settings.

However, data from clinical trials are based on study populations enrolled using specific inclusion/exclusion criteria and protocol-driven follow up, which may not reflect real-world use.

Thus, gathering real world evidence on the use of integrase inhibitor and reverse transcriptase inhibitor 2DRs would further demonstrate the effectiveness and tolerability of these regimens.

Research questions and objectives

This multi-site observational study assessed the effectiveness of INSTI + RTI 2DRs as:

- a first-line treatment for treatment-naïve patients
- a switching option for those with HIV RNA suppression on current treatment (stable switch)
- a second-line treatment for those with virological failure (VF) on prior treatment.

The data collected for this study reflect routine clinical care that patients received during the study period. The primary objective of this study was to assess effectiveness of 2DRs by evaluating HIV RNA suppression below 50 copies/mL and VF by 24 weeks, 48 weeks, and 96 weeks of treatment.

Study design

This is a multi-site observational study, utilizing retrospective and prospective data collection to assess outcomes up to 96-weeks after eligible 2DR initiation.

Setting

European hospitals in UK (7), Spain (3), France (8), Belgium (3), Italy (5) and Portugal (2).

Subjects and study size, including dropouts

The final analysis population included 776 patients (2 were excluded from this analysis, pending query outcomes); 735 patients were in the stable switch population, 23 were ART-naïve, and 16 were ART-experienced with prior VF.

Variables and data sources

Data were collected from individual patient electronic hospital records.

Variables included: Baseline characteristics; duration of undetectability plasma HIV RNA levels at start of 2DR treatment (stable switch population); viral load measurements; CD4 and CD8 measurements; Antiretroviral treatment history; Reasons for stopping or switching each treatment and related toxicity data; resistance tests; co-morbidities and all co-medications; all available drug related adverse events (AEs) and serious adverse events (SAEs).

Exposure was defined as taking any 2DR consisting of an integrase inhibitor among those meeting other inclusion criteria. It was anticipated that most regimens would consist of DTG+3TC or DTG+RPV. Exposure started on the date of the first prescription to an eligible 2DR. Person-time exposed was defined as the number of days that the subject was known to have been exposed to this dual combination regimen (from date 2-DR was first prescribed to censoring event).

The primary outcome evaluating virologic effectiveness varied depending on treatment group.

For stable switch population the primary endpoint was virologic failure (VF) by 24, 48, and 96 weeks, defined as:

a. Virologic rebound: two consecutive measurements of ≥50 copies/mL or 1 HIV RNA >50 c/mL followed by 2-DR discontinuation or missing value.

For treatment-naïve and prior VF groups the primary endpoints were:

a) Suppression: HIV VL <50 copies/mL at 24, 48, and 96 weeks after 2-DR initiation
b) VF by 24, 48, and 96 weeks, defined as:
    1. Virologic Rebound: after achieving suppression, two consecutive measurements of ≥50 copies/mL or 1 HIV RNA >50 copies /mL followed by 2-DR discontinuation or missing value.
    2. Virologic Non-response: two consecutive measurements of ≥200 copies/mL after at least 24 weeks of treatment

Results

In the final analysis population, there were 735 patients who were switched whilst virologically supressed (stable switch), 23 patients for whom 2DR was their first line of treatment (treatment-naïve), and 16 patients who switched following VF on their prior regimen (prior VF).

As the samples sizes are not enough in the naïve and prior VF populations to produce statistics that are representative of the true values in the targeted populations, purely descriptive summary of outcomes in this group are included in the main report text and relevant data tables are presented in the appendix.

Among the 735 stable switch patients, there were 10 patients (Kaplan Meier [KM] estimate: 1.6% [95% CI: 0.9 – 3.0]) with VF by week 96, using a threshold of VL ≥50 copies/mL.

Among these 10 events:

- 1 patient (0.1% [95% CI: 0.0-1.0] experienced 2 consecutive VLs ≥50 copies/mL
- 3 patients (0.4% [95% CI: 0.1-1.4] experienced a single VL ≥50 copies/mL followed by discontinuation of the index 2DR
- 6 patients (1.1% [95% CI:0.5-2.3] had a single VL ≥50 copies/mL at the week 96 time point, and were classified as VF due to missing information after the study end

Using a threshold of ≥200 copies/mL to define VF, there were 3 patients (KM estimate: 0.5% [95% CI: 0.2 – 1.5]) with VF.

There were 39 discontinuations (KM estimate 5.3% [95% CI: 3.8 – 7.2]) by 96 weeks in the stable switch population.

There were 2 drug related SAEs [0.1% [95% CI: 0.0,0.5]), which occurred in 2 patients and included 1 instance of low mood and 1 instance of anxiety and depression. There were no deaths.

Discussion

This analysis demonstrated low rates of virologic failure, with few adverse events and low discontinuations rates over 96 weeks of follow up, demonstrating that integrase inhibitor plus a reverse transcriptase inhibitor 2 drug regimens are effective and well-tolerated regimens among virologically suppressed individuals in a real-world setting.

4 AMENDMENTS AND UPDATES

Number	Date	Section of study report	Amendment or update	Reason
1	[Date]	[Text]	[Text]	[Text]
2	[Date]	[Text]	[Text]	[Text]
…	[Date]	[Text]	[Text]	[Text]

5 MILESTONES

Initiation Date:	December 2018
Completion Date:	October 2022
Early Termination Date:	N/A
Earlier CSRs	N/A
Date of Report	30-05-2023

Milestone	Planned date	Actual date	Comments
Start of data collection	December 2018	November 2019	

Milestone	Planned date	Actual date	Comments
End of data collection	Oct 2022	April 2023	
Annual study progress reports	Yearly, within 30 days of the anniversary date of EC approvals.	Jan 21 Dec 21 Oct 22	Jan 21 report was a delayed submission (due Jul 20) Dec 21 report was a delayed submission (due Jul 21) Oct 22 report was a delayed submission (due Jul 22)
Final report of study results	Nov-2022 or within 12 months after end of study	N/A	

6 RATIONALE AND BACKGROUND

6.1 Background

Two oral 2-drug regimens (2DRs) have been evaluated through clinical trials and approved for use in the EU as complete treatment regimens for HIV: JULUCA (DTG/RPV) received EU marketing authorization in May 2018 and DOVATO (DTG/3TC) received EU marketing authorization in July 2019. Dolutegravir (DTG) is a 2nd generation integrase strand transfer inhibitor (INSTI); rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and lamivudine (3TC) is a nucleoside reverse transcriptase inhibitor (NRTIs). The efficacy of 2DR therapy with an integrase inhibitor plus a reverse transcriptase inhibitor has been assessed in multiple pilot studies and clinical trials.

In the PADDLE study, high rates of HIV RNA suppression were demonstrated after first- line treatment with Dolutegravir (DTG) plus Lamivudine (3TC). In additional phase 3 clinical trials, the two-drug combination DTG/3TC (GEMINI-1, -2) demonstrated high rates of HIV RNA suppression among ART-naïve people with HIV, with suppression rates non-inferior to standard first line 3 drug regimens (3DRs). DTG/3TC (TANGO and SALSA) and DTG/PRV (SWORD-1 and -2) regimens have also shown non-inferior efficacy compared to 3-DRs among people with HIV switching from a 3-DR with stable suppressed viral load in clinical trial settings.

6.2 Rationale

Data from clinical trials are based on study populations enrolled using specific inclusion/exclusion criteria and assess outcomes based on protocol-driven follow up, which may not reflect real-world use.

Thus, gathering real world evidence on the use of INSTI + RTI 2DRs outside of a clinical trial setting would further demonstrate the effectiveness and tolerability of these regimens.

Research question and objectives

This study assessed effectiveness of 2DRs consisting of an integrase inhibitor plus a reverse transcriptase inhibitor, either as a first-line treatment in treatment-naïve individuals, a switching option for those with HIV RNA suppression on current treatment (stable switch), or a second-line treatment for those with prior virological failure.

6.3 Primary Objective:

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

6.4 Secondary Objective:

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

7 RESEARCH METHODS

7.1 Study design

This was a multi-site observational study across Europe. Individuals who had initiated a 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor prior to or during the study period were eligible for inclusion. It was anticipated that the majority of study participants would be taking either DTG and RPV, or DTG and 3TC.

The study did not require any changes to the routine standard of care that PLWH received at each clinical site, and decisions on ARV treatment were made by the healthcare providers, taking into account treatment history, patient characteristics and local guideline or recommendations. Data were collected every 6 months from participating sites for a period of 96 weeks for each patient. Follow up started on the day of the first exposure to the 2DR (date when 2DR was prescribed). Follow-up was censored at week 96, or at the earliest of the following events: date of last study contact, date of 2DR treatment discontinuation (except if the participant was switched to another 2DR), or the date of lost to follow-up.

7.2 Study Population and Setting

Potential NEAT-ID investigational sites across Europe were contacted for feasibility and to ascertain if they already had PWH taking dual combinations of an integrase inhibitor plus a reverse transcriptase inhibitor. Sites with at least 5 patients already taking this treatment (outside clinical trials) since January 2014 or who planned to initiate at least 5 patients in near future were selected to participate in this study.

NEAT ID Network team performed site visits to assess protocol issues, consent, data quality and Study Management quality performance.

7.2.1 Inclusion Criteria

The study population consisted of individuals diagnosed with HIV who were male or female aged 18 years or over, and who started 2DR with an integrase inhibitor plus a reverse transcriptase inhibitor from 2014 onwards as:

a) a first-line treatment among treatment-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.

Stable switch patients were defined as per the local site definition of a supressed patient.

7.2.2 Patient Identification and Consent

The aim was to include approximately 750 patients across European sites once all relevant approvals were in place for the protocol. Selected investigational sites were contacted and asked to identify potential patients on 2DR either retrospectively and/or potential prospective patients. Consent procedures were undertaken as required by country specific regulations and local procedures for the collection of retrospective and/or prospective data. Individuals

included in the analysis population did not need to attend any additional visits or undergo any procedures above their routine standard of care.

7.2.3 Exposure definitions

Individuals with any exposure to a 2DR consisting of an integrase inhibitor, such as DTG, and a reverse transcriptase inhibitor, such as 3TC or RPV, among those meeting other inclusion criteria, were included in the analysis. Exposure started the first day ART of an eligible 2DR was prescribed. Person-time exposed was defined as the number of days that the subject was exposed to this dual combination regimen (from date 2-DR was first prescribed to censoring event).

7.2.4 Outcome definitions

7.2.4.1 Primary Outcomes

For naïve and prior VF populations:

a) Suppression: HIV VL <50 copies/mL at 24, 48, and 96 weeks after 2-DR initiation
b) Virologic failure by 24, 48, and 96 weeks, defined as:
   1. Virologic Rebound: after achieving suppression, two consecutive measurements of ≥50 copies/mL or 1 HIV RNA ≥50 copies /mL followed by 2-DR discontinuation or missing value.
   2. Virologic Non-response: two consecutive measurements of ≥200 copies/mL after at least 24 weeks of treatment

For stable switch population:

a) Virologic failure by 24, 48, and 96 weeks, defined as:
   1. Virologic Rebound: two consecutive measurements of ≥50 copies/mL or 1 HIV RNA ≥50 c/mL followed by 2-DR discontinuation or missing value.

.

Treatment effectiveness was also assessed using the following definition for virologic rebound and virologic non-response (see secondary objective a):

For naïve and prior VF populations:

a) Virologic Rebound: two consecutive measurements of ≥200 copies/mL after suppression (one VL <50 copies/mL) or 1 HIV RNA ≥200c/mL followed by 2-DR discontinuation or missing value.

b) Virologic Non-response: two consecutive measurements of ≥200 copies/mL after at least 24 weeks of treatment

For stable switch population:

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

The time windows around each visit for data collection were defined as follows:

Visit	Window (Through End-of-Study Week)	Window (Days)
12	6-18	43-126
24	18-30	127-210
48	42-54	295-378
72	66-78	463-546
96	90-102	631-714

7.2.4.2 Secondary Outcomes

In each population (naïve, stable switch, and prior virological failure):

a) Proportion of patients with high level viremia (VL ≥200 copies/mL) at 24, 48 and 96 weeks of treatment with index 2DR
b) Proportion of patients with low level viremia (VL ≥50 and <200 copies/mL) at 24, 48, and 96 weeks of treatment with index 2DR
c) Time to virologic suppression in the naïve and the prior VF populations
d) Time to VF in the stable switch population
e) Resistance profile in case of VF while on 2-DR
f) Proportion of patients discontinuing baseline 2-DR during follow up who:
   1. Stable switch while virologically suppressed
   2. Switch after VF
   3. Switching for tolerability, toxicity, and other reasons
g) Frequency of drug related AEs and SAEs
h) Evolution of CD4+, CD8+ T cells counts, and CD4/CD8 ratio at 24, 48, and 96 weeks of treatment
i) Factors associated with plasma HIV-RNA > 50 copies/mL after 96 weeks if number of failures allowed analysis

7.2.5 Confounders and effect modifiers

This is a non-comparative study so evaluation of confounders and modifiers of the relative associations between two or more of the patient groups is not expected.

7.3 Data Sources

Data were collected from all participating European sites. Following all relevant approvals, selected sites were contacted and asked to identify patients currently on 2DR and collect data either retrospectively and/or identify prospective patients to start this treatment. Pseudo anonymised data was collected by electronic transfer of datasets from each site.

The following data was collected <u>if available</u> for each participant and updated information included in the 6 monthly data transfer / collection:

1. Baseline characteristics – age, gender, ethnicity, CD4 and CD8 count at time of first starting 2DR treatment, CD4 nadir, CDC disease stage.
2. Duration of undetectability plasma HIV RNA levels at start of 2DR treatment, where available
3. HIV RNA data – all available HIV RNA results since first starting antiretroviral treatment, with dates. Data on last viral load above 50 copies/mL.

4. Immunological data: all available CD4 and CD8 results since first starting 2DR treatment.
5. Antiretroviral treatment history – all antiretrovirals taken since first-line treatment (if not naïve) started, with dates. Reasons for stopping or switching each treatment and related toxicity data.
6. Resistance tests – results of all HIV resistance tests performed before and during treatment with 2DR.
7. Co-morbidities and all co-medications
8. All available drug related AEs and SAEs since starting DTG+RPV or DTG+3TC.

7.4 Study size

The overall target sample size for this study was 750 people with HIV.

Based on power calculations (details below), at least 90 naïve, 320 stable switch, and 90 patients with prior VF were planned to be included. However, if the number of patients in naïve and VF cohorts was insufficient to fulfil the power calculations, these cohort data were to be included only for purely descriptive purposes (see Appendix).

Actual study enrolment was 776 patients, including 23 ART-naïve, 735 stable switch, and 16 second line with prior VF at the time of 2-DR initiation. Two individuals were excluded after enrolment due to data issues.

Power calculations performed prior to study initiation are below:

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 2- DR was considered acceptable if the percentage of patients in success (HIV RNA <50 copies/mL) at week 48 was significantly above 80%. Assuming a 90% response rate, by including 90 individuals, we planned to have a 95 % probability to discard a combination for which effectiveness is smaller than 80 % and we selected with a power of >80 % the strategy for which the effectiveness 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 was 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 planned to have a 95% probability to discard a combination for which the rate of failure is greater than 8% and we selected 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 prior virological failure, 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 was 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 planned to have a 95 % probability to discard a combination for which effectiveness is smaller than 80 % and we selected with a power of >80 % the strategy for which the effectiveness is above or equal to 90%.

7.5 Data Management

7.5.1 Data Collection

7.5.1.1 Source Data

Source data were contained in source documents (original records or certified copies) maintained at site. No additional data was collected for this study, data was collected as part of routine standard of care data only.

7.5.1.2 Source Documents

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) were maintained at site in accordance with usual standard of care

The subject's number and date of entry into the study, along with a study identifier, were recorded in the subject's study records.

7.5.1.3 Data Collection Methods

In order to maintain confidentiality, participants were identified only by study identifier.

Participant data were collected via extraction from electronic source data by appropriately trained and authorised member(s) of the study team who were identified and authorised in writing by the Principal Investigator (PI). A delegation of responsibility log was updated accordingly.

Sites provided / uploaded data every 6 months to the data management team who stored the data on a secure network drive with access to authorised personnel of the data management team only, maintained on a log of authorised personnel by the sponsor representative.

Participant involvement in this study ended after week 96 data collection.

7.5.2 Data transformation (Data handling conventions)

Data was handled in accordance with data handling guidelines provided to sites.

The Study Monitor and Data Manager reviewed data on an on-going basis and raised any discrepancies with site staff as required.

Identified only by subject number, the data were pseudo-anonymised at all times and transferred securely. All transfers were fully documented.

7.5.3 Resourcing needs

Biostatistical and methodological issues were addressed by the epidemiologist responsible for the study in consultation with a senior level epidemiologist at ViiV with expertise in observational data. A senior level statistician contributed to the development of the protocol and provided expertise and skills as needed during the conduct and analysis of the study.

The analysis was independently conducted by 2 senior level GSK analysts skilled in population-based analyses, using SAS."

The study was overseen and managed by NEAT-ID. NEAT-ID assigned a Project Manager to the study who oversaw the day-to-day activities of the trial and managed the multidisciplinary project team.

ViiV as sponsor retain all responsibilities in relation to regulatory reporting.

7.6 Data analyses

The statistical analysis plan described the primary and secondary analysis and the format of the final tables, figures and listings to be generated. Data was analysed using SAS, SPSS or STATA.

7.6.1 Essential analyses

Outcomes were stratified according to prior treatment status (first-line treatment for treatment-naïve patients, stable switching with HIV RNA suppression, or switching after VF). The 95% two-sided confidence interval (CI) of the observed proportion of patients reaching the effectiveness endpoint was calculated.

In the treatment naïve and prior VF groups, the primary endpoint was the proportion of patients with HIV RNA suppression below 50 copies/mL at 24, 48, and 96 weeks of treatment, estimated using Kaplan-Meier methods.

In the stable switch population, the primary endpoint was the proportion of patients with VF by weeks 24, 48 and 96 (defined as 2 consecutive plasma HIV RNA ≥50 copies/mL, or Plasma HIV RNA≥50 c/mL followed by study treatment discontinuation or missing value). The 95% CI of the observed proportion of patients reaching the effectiveness endpoint was calculated with the Kaplan-Meier method, censoring at week 96 or last follow-up date if missing HIV RNA viral load values at week 96.

Grade 3 and 4 adverse events, ART related adverse events (all grades), treatment-modifying adverse events (all grades); AIDS defining event, death, study treatments discontinuation, as well as serious adverse events (SAE) were described, between 0-24, 24-48, and 48-96 weeks.

Changes from baseline in continuous endpoints in each population (naïve, stable switch, prior VF) between baseline and week 24, 48 and 96 were compared by using Wilcoxon's paired test (last observation carried forward (LOCF) or other imputation method were defined in the statistical analysis plan). We used percentage and 95 % two-sided confidence interval to describe the qualitative endpoints, their change over time was tested with a McNemar test with a 5%Type I error. Linear mixed models were also be used to estimate and compare the evolution of CD4, CD8 count and CD4/CD8 ratio over time. Discontinuations were identified by entries into the EDC from source data.

The number of included patients and the flowchart of the study was presented. The baseline patients' eligibility and characteristics of the study population was described. Quantitative variables were described by their means, standard deviations, medians, Interquartile range (IQR), minimums and maximums. For qualitative variables, figures and percentages per class were presented or method was given. All protocol deviations and their reasons were described.

A planned interim analysis was conducted on 283 individuals in the stable-switch population [Mussini et al, EACS 2021] and analysis of the historic resistance data available after 276 stable switch patients had been included [Mussini et al; BHIVA 2022].

7.6.2 Exploratory analyses

CCI

[redacted]

7.6.3 Amendments to the statistical analysis plan

The overall numbers in the naïve (n=23) and prior VF (n=16) groups were not sufficiently powered for planned outcome analyses. Therefore, only summary descriptions of these groups are included (see Appendix for detailed tables).

7.7 Quality control and quality assurance

Electronic data sets provided an unmonitored subset of existing source data that was subject to data validation. Site selection and training of site staff ensured suitably qualified personnel were involved at every stage of the data gathering process. Data were analysed by a statistician skilled in population database analysis using SAS, SPSS or STATA.

NEAT-ID commissioned an audit performed by the independent QA personnel and in accordance with the GCP and the applicable NEAT-ID Standard Operating Procedures which was conducted in October and November 2021.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Ethical approval and subject consent

Before the start of data collection, this protocol and any accompanying material to be provided to the patients (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) were submitted to Ethics Committee (EC) in the relevant countries. The investigators were not permitted and did not begin any study activities until approval from the EC had been documented and provided as a letter to the investigator.

Any subsequent amendments requiring review by EC were not implemented until the EC granted a favourable opinion for the study which was disseminated to the investigator and sites (NOTE: amendments may also have needed to be reviewed and accepted by the regulatory agencies and/or local EC departments before they can be implemented in practice at sites)

Annual progress reports were submitted to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial was declared ended.

NEAT ID team notified the EC of the end of the study.

8.2 Subject confidentiality

All investigators and study site staff were required to comply with the requirements of the current Data Protection Regulations with regards to the collection, storage, processing and disclosure of personal information and to uphold the Regulation’s core principles.

Personal information was collected, kept secure, and maintained in line with the following requirements:

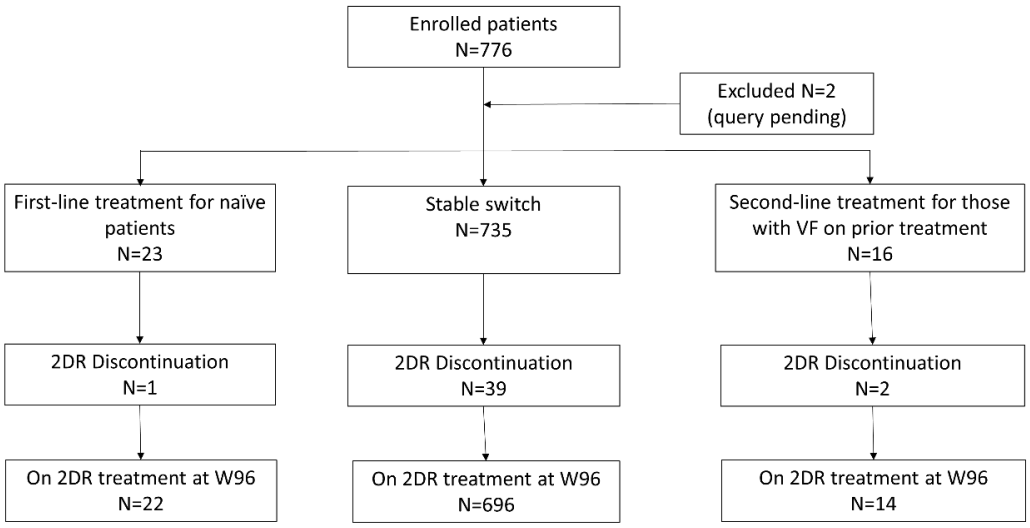
- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders/storage media.
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

9 RESULTS

9.1 Participants

A total of 776 adult patients with HIV were enrolled in the study; 2 patients were excluded from this analysis due to pending queries, for a final analysis population of 774. There were 23 patients included who were treatment-naïve when the 2-drug regimen was initiated, 735 who were suppressed when switched to a 2DR (stable switch) and 16 patients who had experienced prior VF on their first line therapy before initiating on 2DR. (**Figure 1**)

Figure 1: Study Flowchart



9.2 Descriptive data including baseline characteristics.

Table 1: Baseline characteristics of the patients

Characteristics	Treatment-naïve N=23	Stable switch N=735	Prior Virological failure N=16
Age, years, median (IQR)	N=23	N=735	N=16
	37 (34-53)	54 (47-59)	57 (51-61)
Gender – *n* (%)			
Male	19 (82.6)	556 (75.7)	13 (81.3)
Female	3 (13)	176 (24)	3 (18.8)
Transgender	1 (4.3)	2 (0.3)	0 (0.0)
Ethnicity– *n* (%)			
White	16 (69.6)	492 (66.9)	12 (75.0)
Black	1 (4.3)	140 (19)	3 (18.8)
Asian	0 (0.0)	8 (1.1)	1 (6.3)
Other	6 (26.1)	95 (12.9)	0 (0.0)
Duration of antiretroviral treatment (years), median (IQR)		N=735 10.2 (4.7-18.8)	N=16 18.1 (13.2-24.3)

Plasma VL log_{10} (cp/ml), median (IQR)	N=23 4.1 (3-4.9)	N=725 1.3 (1.3-1.6)	N=16 2.7 (1.9-3.4)
CD4 count nadir (cells/mm^3), median (IQR)	N=23 395 (271-553)	N=722 250.5 (134-365)	N=16 106.5 (48-264.5)
CD4 count (cells/mm^3), median (IQR)	N=17 411 (340-553)	N=509 684 (534-920)	N=13 674 (523-807)
CD8 count (cells/mm^3), median (IQR)	N=10 875 (677-1941)	N=486 799 (585-1046)	N=13 1015 (744-1179)
CD4/CD8 ratio, median (IQR)	N=10 0.6 (0.4-0.9)	N=486 0.9 (0.6-1.2)	N=13 0.7 (0.4-0.9)
Baseline regimen– *n* (%)			
DTG + RPV	2 (8.7)	186 (25.3)	10 (62.5)
DTG + 3TC	21 (91.3)	534 (72.7)	5 (31.3)
Other*	0 (0.0)	15 (2.0)	1 (6.3)
Comorbidities – n (%)			
Hypertension	1 (4.3)	177 (24.1)	2 (12.5)
Hyperlipidemia	0 (0)	190 (25.9)	7 (43.8)
Renal disorder	0 (0)	102 (13.9)	2 (12.5)
Liver disorder	0 (0)	60 (8.2)	4 (25)
Diabetes	0 (0)	46 (6.3)	1 (6.3)
Resistance mutations – n (%)	3/17 (17.6)	227/454 (50.0)	9/13 (69.2)
NRTI	2/17 (11.8)	105/454 (23.1)	6/13 (46.2)
NNRTI	1/17 (5.9)	91/454 (20.0)	7/13 (53.8)
PI	1/17 (5.9)	147/454 (32.4)	7/13 (53.8)
INI	0 /17(0.0)	9/454 (2.0)	1/13 (7.7)
*Other: Raltegravir/etravirine (n=11 including 1 in the prior VF group); Raltegravir/Nevirapine (n=1); Raltegravir/Rilpivirine (n=1); Dolutegravir/Tenofovir disoproxil (n=1); Dolutegravir/Efavirenz (n=1); Dolutegravir/Etravirine (n=1)			

Characteristics at the time of 2DR initiation (baseline) are presented in **Table 1**.

- The median age of the treatment-naïve group was 37 years (IQR, 34-53), it was 54 years (IQR, 47-59) in the stable switch group, and 57 years (IQR, 51-61) in prior VF group.
- Overall, 588 (76.0%) patients were male, 182 (23.5%) were female, and 3 patients (0.4%) were transgender, with similar proportions across treatment groups. Ethnicity was predominantly reported as white 520/774 (67.2%), regardless of treatment group.
- The median length of ART prior to 2DR initiation for the stable switch patients was 10.2 years (IQR: 4.7 – 18.8) and for the prior virological failure patients, it was 18.1 years (IQR: 13.2 – 24.3).

- Most patients were prescribed a 2-DR containing either DTG + RPV (196/774 patients [25.3%]) or DTG + 3TC (560/774 patients [72.4%]); there were 16 patients (2.1%) patients on another 2 DR combination (see the footnote for Table 1).
  - Among ART-naïve patients, 21 (91.3%) patients were prescribed DTG+3TC and 2 (8.7%) were prescribed DTG+RPV.

- Among the stable switch patients, 534 (72.7%) were prescribed DTG+3TC, 186 (25.3%) were prescribed DTG+RPV, and 15 (2.0%) were prescribed another combination of an INSTI and an RTI.
- Among the 16 patients with prior VF, 5 (31.3%) were prescibed DTG+3TC, 10 (62.5%) were prescribed DTG+RPV, and 1 person took a regimen of raltegravir + etravirine.

Drug resistance mutations (DRMs) were evaluated prior to treatment initiation in 17 (73.9%) ART-naïve patients. For treatment-experienced individuals, 454 (61.8%) of the suppressed switch population and 13 (81.3%) of the prior virologic failure population had at least 1 documented resistance test at some point prior to initiating a 2DR. (**Table 1**)

- Transmitted drug resistance mutations to any class of ARVs were documented in 3 (17.6% of those tested) naïve patients. Among the suppressed switch population, 227 (50% of tested) had any history of DRMs at baseline and 9 (69.2% of tested) prior VF patients had any DRMs.
- NRTI resistance was most common in the naïve (11.8%). History of PI-associated DRMs (32.4%) was most common in the suppressed switch group, while NNRTI and PIs (53.8%) DRMs were most common in the prior VF group. INI-associated DRMs were uncommon across treatment groups.

Table 2: Frequency of last regimen prior to switch for 2DR

n (%)	Treatment-naïve N=23	Stable switch N=735	Prior VF N=16	Total N=774
None were specified	23	5 (0.7)	0 (0)	5 (0.6)
ABC+3TC+DTG		134 (18.2)	2 (12.5)	136 (17.6)
TAF+FTC+DTG		50 (6.8)	0 (0)	50 (6.5)
TDF+FTC+DTG		42 (5.7)	0 (0)	42 (5.4)
TDF+FTC+EFV		36 (4.9)	1 (6.3)	37 (4.8)
TAF+FTC+EVG+COBI		31 (4.2)	0 (0)	31 (4)
TDF+FTC+RPV		28 (3.8)	0 (0)	28 (3.6)
TDF+FTC+RAL		23 (3.1)	0 (0)	23 (3)
TAF+FTC+DRV+COBI		14 (1.9)	1 (6.3)	15 (1.9)
TDF+FTC+DRV+RTV		15 (2)	0 (0)	15 (1.9)
3TC+DRV+COBI		12 (1.6)	0 (0)	12 (1.6)
DRV+RTV		12 (1.6)	0 (0)	12 (1.6)
ABC+3TC+NVP		10 (1.4)	1 (6.3)	11 (1.4)
ABC+3TC+RAL		11 (1.5)	0 (0)	11 (1.4)
TDF+FTC+ATV+RTV		9 (1.2)	2 (12.5)	11 (1.4)
RAL+DRV+RTV		9 (1.2)	1 (6.3)	10 (1.3)
3TC+ATV+COBI		8 (1.1)	1 (6.3)	9 (1.2)
DRV+COBI		9 (1.2)	0 (0)	9 (1.2)
DTG		9 (1.2)	0 (0)	9 (1.2)
DTG+DRV+COBI		8 (1.1)	1 (6.3)	9 (1.2)
TAF+FTC+BIC		9 (1.2)	0 (0)	9 (1.2)
3TC+DRV+RTV		8 (1.1)	0 (0)	8 (1)
ABC+3TC+DRV+RTV		7 (1)	1 (6.3)	8 (1)
TAF+FTC+RPV		8 (1.1)	0 (0)	8 (1)
TDF+FTC+NVP		8 (1.1)	0 (0)	8 (1)
ABC+3TC+DRV+COBI		7 (1)	0 (0)	7 (0.9)
ABC+3TC+EFV		7 (1)	0 (0)	7 (0.9)
TAF+FTC+RAL		7 (1)	0 (0)	7 (0.9)
TDF+FTC+ETR		7 (1)	0 (0)	7 (0.9)
TDF+FTC+EVG+COBI		7 (1)	0 (0)	7 (0.9)
ABC+3TC+RPV		6 (0.8)	0 (0)	6 (0.8)
RAL+ATV+RTV		6 (0.8)	0 (0)	6 (0.8)
TDF+FTC+DRV+COBI		6 (0.8)	0 (0)	6 (0.8)

ABC+3TC		4 (0.5)	1 (6.3)	5 (0.6)
ABC+3TC+ATV+COBI		5 (0.7)	0 (0)	5 (0.6)
RPV+DRV+COBI		5 (0.7)	0 (0)	5 (0.6)
TAF+FTC		5 (0.7)	0 (0)	5 (0.6)
TAF+FTC+NVP		5 (0.7)	0 (0)	5 (0.6)
3TC+LPV+RTV		4 (0.5)	0 (0)	4 (0.5)
AZT+3TC+ABC		4 (0.5)	0 (0)	4 (0.5)
DTG+DRV+RTV		4 (0.5)	0 (0)	4 (0.5)
ETR+DRV+RTV		4 (0.5)	0 (0)	4 (0.5)
3TC+ATV+RTV		3 (0.4)	0 (0)	3 (0.4)
RAL+ETR+3TC		3 (0.4)	0 (0)	3 (0.4)
TDF+3TC+DTG		3 (0.4)	0 (0)	3 (0.4)
3TC+AZT+DRV+RTV		2 (0.3)	0 (0)	2 (0.3)
3TC+RTV		2 (0.3)	0 (0)	2 (0.3)
ABC+3TC+ATV		2 (0.3)	0 (0)	2 (0.3)
ABC+3TC+ATV+RTV		2 (0.3)	0 (0)	2 (0.3)
ABC+3TC+MVC		2 (0.3)	0 (0)	2 (0.3)
ABC+DTG+3TC		2 (0.3)	0 (0)	2 (0.3)
ATV+RTV		2 (0.3)	0 (0)	2 (0.3)
DTG+3TC+DRV+RTV		2 (0.3)	0 (0)	2 (0.3)
DTG+3TC+RPV		2 (0.3)	0 (0)	2 (0.3)
DTG+ATV		2 (0.3)	0 (0)	2 (0.3)
DTG+ATV+COBI		2 (0.3)	0 (0)	2 (0.3)
DTG+RPV+MVC		2 (0.3)	0 (0)	2 (0.3)
LPV+RTV		1 (0.1)	1 (6.3)	2 (0.3)
MVC+DRV+COBI		2 (0.3)	0 (0)	2 (0.3)
NVP+DRV+COBI		2 (0.3)	0 (0)	2 (0.3)
RAL		2 (0.3)	0 (0)	2 (0.3)
RAL+ATV+COBI		2 (0.3)	0 (0)	2 (0.3)
RAL+DRV+COBI		2 (0.3)	0 (0)	2 (0.3)
RPV+DRV+RTV		2 (0.3)	0 (0)	2 (0.3)
TDF+FTC		2 (0.3)	0 (0)	2 (0.3)
TDF+FTC+ATV+COBI		2 (0.3)	0 (0)	2 (0.3)
3TC+AZT+EFV		1 (0.1)	0 (0)	1 (0.1)
3TC+AZT+NVP		1 (0.1)	0 (0)	1 (0.1)
3TC+DTG+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
3TC+FPV		0 (0)	1 (6.3)	1 (0.1)
3TC+NVP		1 (0.1)	0 (0)	1 (0.1)
3TC+NVP+AZT		1 (0.1)	0 (0)	1 (0.1)
ABC+3TC+ETR		1 (0.1)	0 (0)	1 (0.1)
ABC+3TC+ETR+DTG		1 (0.1)	0 (0)	1 (0.1)
ABC+3TC+FPV+RTV		1 (0.1)	0 (0)	1 (0.1)
ABC+3TC+LPV+RTV		1 (0.1)	0 (0)	1 (0.1)
ABC+3TC+SQV+RTV		1 (0.1)	0 (0)	1 (0.1)
ABC+ATV		1 (0.1)	0 (0)	1 (0.1)
ABC+ETR+RAL		1 (0.1)	0 (0)	1 (0.1)
ABC+FTC+DTG		1 (0.1)	0 (0)	1 (0.1)
ABC+RAL+DRV+RTV		0 (0)	1 (6.3)	1 (0.1)
ABC+RAL+ETR		1 (0.1)	0 (0)	1 (0.1)
ABC+RPV+DTG		1 (0.1)	0 (0)	1 (0.1)
ATV+COBI		1 (0.1)	0 (0)	1 (0.1)
AZT+3TC+DTG		0 (0)	1 (6.3)	1 (0.1)
AZT+3TC+EFV		1 (0.1)	0 (0)	1 (0.1)
AZT+3TC+NVP		1 (0.1)	0 (0)	1 (0.1)
DDI+3TC+RAL		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+ATV+RTV		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+DRV+COBI		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+EFV		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+LPV+RTV		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+MVC		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+NVP		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+RAL		1 (0.1)	0 (0)	1 (0.1)
DTG+3TC+RTV		1 (0.1)	0 (0)	1 (0.1)
DTG+DRV		1 (0.1)	0 (0)	1 (0.1)

DTG+EFV		1 (0.1)	0 (0)	1 (0.1)
DTG+FTC		1 (0.1)	0 (0)	1 (0.1)
DTG+RPV+DRV		1 (0.1)	0 (0)	1 (0.1)
DTG+RPV+DRV+COBI		1 (0.1)	0 (0)	1 (0.1)
EFV		1 (0.1)	0 (0)	1 (0.1)
EFV+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
ETR+ATV+RTV		1 (0.1)	0 (0)	1 (0.1)
ETR+DRV+COBI		1 (0.1)	0 (0)	1 (0.1)
ETR+FTC+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
ETR+LPV+RTV+MVC		1 (0.1)	0 (0)	1 (0.1)
ETR+RAL		1 (0.1)	0 (0)	1 (0.1)
FPV+RTV		1 (0.1)	0 (0)	1 (0.1)
FTC+ATV+RTV		1 (0.1)	0 (0)	1 (0.1)
FTC+RPV+DTG		1 (0.1)	0 (0)	1 (0.1)
MVC+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
MVC+RAL		1 (0.1)	0 (0)	1 (0.1)
NVP+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
NVP+DTG+RPV		1 (0.1)	0 (0)	1 (0.1)
NVP+LPV+RTV		1 (0.1)	0 (0)	1 (0.1)
RAL+3TC+ATV		1 (0.1)	0 (0)	1 (0.1)
RAL+3TC+DRV+COBI		1 (0.1)	0 (0)	1 (0.1)
RAL+3TC+MVC		1 (0.1)	0 (0)	1 (0.1)
RAL+ABC		1 (0.1)	0 (0)	1 (0.1)
RAL+ATV		1 (0.1)	0 (0)	1 (0.1)
RAL+ETR+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
RAL+ETR+MVC		1 (0.1)	0 (0)	1 (0.1)
RAL+FTC+ATV		1 (0.1)	0 (0)	1 (0.1)
RAL+MVC		1 (0.1)	0 (0)	1 (0.1)
RAL+NVP		1 (0.1)	0 (0)	1 (0.1)
RAL+NVP+MVC		1 (0.1)	0 (0)	1 (0.1)
RPV+TDF		1 (0.1)	0 (0)	1 (0.1)
TAF+FTC+ATV+COBI		1 (0.1)	0 (0)	1 (0.1)
TAF+FTC+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
TAF+FTC+EFV		1 (0.1)	0 (0)	1 (0.1)
TDF +FTC+DRV+COBI		1 (0.1)	0 (0)	1 (0.1)
TDF +FTC+DTG		1 (0.1)	0 (0)	1 (0.1)
TDF +FTC+RPV+DTG		1 (0.1)	0 (0)	1 (0.1)
TDF+3TC+DRV+COBI		1 (0.1)	0 (0)	1 (0.1)
TDF+3TC+NVP		1 (0.1)	0 (0)	1 (0.1)
TDF+ABC+SQV+RTV		1 (0.1)	0 (0)	1 (0.1)
TDF+ETR+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+ATV		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+DTG+DRV+RTV		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+DTG+RPV		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+EFV+ABC		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+RAL+LPV+RTV		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+RAL+MVC		1 (0.1)	0 (0)	1 (0.1)
TDF+FTC+SQV+RTV		1 (0.1)	0 (0)	1 (0.1)
TDF+RPV+RAL		1 (0.1)	0 (0)	1 (0.1)

In total there were 145 prior ART regimens specified (5 not specified) in the stable switch and prior virological failure arms. (**Table 2**)

- The most common regimen before the 2-DR regimen was abacavir (ABC)+3TC+DTG, with 136 (17.6%) patients on this ART regimen immediately prior to 2DR initiation. The next most common regimen was tenofovir alafenamide (TAF)+ emtricitabine (FTC)+DTG (50 [6.5%] patients) and tenofovir disoproxil (TDF)+ emtricitabine (FTC)+DTG (42 [5.4%] patients).

9.3 Results of effectiveness analyses

The number of patients recruited in the treatment-naive and prior VF arms of the analysis did not reach the required 90 patients to sufficiently power calculations on virological failure.

Basic summaries of outcomes in these populations are provided in the main results. Listing of the evolution of plasma viral load of these participants are found in Appendix 14.3.

Detailed outcomes are provided for the stable switch group in the main body of this report.

9.3.1 Primary effectiveness analysis

9.3.1.1 Suppressed switch population

Table 3 shows the primary outcome for the stable switch group using the Kaplan Meier model to estimate VF using thresholds of viral load ≥50 copies per ml and viral load ≥200 copies per ml at week 96.

Kaplan-Meier estimate of virologic failure (VL≥50 copies/mL) by Week 96:

- 2 consecutives of VL≥50 copies/mL
  or
- 1VL≥50 copies/mL followed by 2DR treatment discontinuation or with no follow-up values thereafter
  or
- a VL ≥50 at week 96

Kaplan-Meier estimate of virologic failure **(VL≥200 copies/mL)** by Week 96:

- 2 consecutives of VL≥200 copies/mL
  or
- a VL≥200 copies/mL followed by 2DR treatment discontinuation or with no follow-up values thereafter or
- a VL ≥200 at week 96

Table 3: Proportion of stable switch participants with virologic failure at week 96

	Stable switch population Total N=735	
	Nb events	% (95% CI)
Kaplan-Meier estimate of loss of viral control **(VL≥50 copies/mL)** at Week 96[Y]	**10**	**1.6 (0.9 – 3.0)**
Two consecutive VL≥50 copies/mL	1	0.1 (0.0 – 1.0)
a VL≥50 copies/mL followed by 2DR treatment discontinuation	3	0.4 (0.1 – 1.4)
a VL ≥50 copies/mL and no follow-up values thereafter	0	0.0 (0.0 – 0.5)
a VL ≥50 copies/mL at week 96	6	1.1 (0.5 – 2.3)
Kaplan-Meier estimate of loss of viral control **(VL≥200 copies/mL)** at Week 96[¥]	3	0.5 (0.2 – 1.5)
Other events		
Kaplan-Meier estimate of discontinuation of 2DR at Week 96	35	4.8 (3.5 – 6.6)

[Y] VF is defined as 2 consecutives of VL≥50 copies/mL or a VL≥50 copies/mL followed by 2DR treatment discontinuation or with no follow-up values thereafter or a VL ≥50 at week 96.

[¥]VF is defined as 2 consecutives of VL≥200 copies/mL or a VL≥200 copies/mL followed by 2DR treatment discontinuation or with no follow-up values thereafter or a VL ≥200 at week 96

There were 10 patients (KM estimate: 1.6% [95% CI: 0.9 – 3.0]) with VF defined using a threshold of ≥50 copies/ml at week 96. (**Table 3**)

- The majority (n=6, KM estimate: 1.1% [95% CI: 0.5 – 2.3]) of these failure events were among individuals with a single elevated VL ≥50 copies/mL at week 96. Due to end of follow up for the individual patient, data on VLs and regimen changes after 96 weeks are missing.
- 1 patient (0.1% [95% CI: 0.0-1.0]) experienced 2 consecutive VLs ≥50 copies/mL
- 3 patients (0.4% [95% CI: 0.1-1.4]) experienced a single VL ≥50 copies/mL followed by discontinuation of the index 2DR

There were 3 patients (KM estimate: 0.5% [95% CI: 0.2 – 1.5]) with VF based on VF definitions using VL ≥200 copies/ml.

Table 4: List of participants with virologic failure by week 96

Label	Baseline treatment	VL.0	VL.24	VL.48	VL.72	VL.96	NRTI mutation at baseline	NNRTI mutation at baseline	PI mutation at baseline	Treatment modification	Reason for stopping	Loss of viral control sub definition
1	DTG+3TC	20		10257 ctr: 2226						DRV/c+FTC+TAF at Week 70	VIROLOGICAL FAILURE	2 VL≥50 copies/mL
2	DTG+RPV	20	20	129				K103N		BIC+FTC+TAF at Week 56	VIROLOGIC FAILURE	VL≥50 copies/mL & discontinuation
3	DTG+RPV	20	27		80					DOR+3TC+TDF at W72 BIC+FTC+TAF at W76 DRV/c+FTC+TAF at W83	VIROLOGIC FAILURE	VL≥50 copies/mL & discontinuation
4	DTG+3TC	20	55							DTG+FTC+TDF at Week 24	PARTIAL VIROLOGIC FAILURE	VL≥50 copies/mL & discontinuation
5	DTG+3TC	20	20	20	20	68			A71V			VL≥50 copies/mL at week 96
6	DTG+3TC	49	61	49		52						VL≥50 copies/mL at week 96
7	DTG+RPV	20		20		95	K65R M184VI	K103HNST V90I Y188C	H69K I13V I15V K20I L89IMRT M36I			VL≥50 copies/mL at week 96
8	DTG+RPV	20	20	20		75						VL≥50 copies/mL at week 96
9	DTG+3TC	20				1530						VL≥50 copies/mL at week 96
10	DTG+RPV	20	20	20		354						VL≥50 copies/mL at week 96

Red text denotes viral load value ≥50 copies/mL occurring as part of a virologic failure event

VL.0: viral load measured at baseline; **VL.24:** viral load measured between baseline and 24 weeks; **VL.48:** viral load measured between 24 and 48 weeks; **VL.72:** viral load measured between 48 and 72 weeks; **VL.96:** viral load measured between 72 and 96 weeks

Baseline drug resistance mutations identified any time prior to initiation of baseline 2DR

Table 4 shows the detailed listing of the 10 patients counted in Table 3 who were included in the Kaplan-Maier estimate of virologic failure (VL≥50 copies) by Week 96. It includes the details of treatment discontinuation: when it occurred, the reason the site gave and to which treatment the patient was changed. It also shows mutations at baseline for these patients and which sub-definition of loss of viral control the participant met.

- Overall, 5/186 (2.7%) of individuals on DTG+RPV and 5/534 (0.9%) of individuals on DTG+3TC experienced virologic failure.
- Among the 5 VFs on DTG+3TC, 1 person experienced 2 consecutive VLs ≥50 copies/mL, 1 person experienced 1 VL ≥50 copies/mL followed by discontinuation, and 3 people experienced 1 VL ≥50 copies/mL and the 96-week time point. None of the patients who experienced VF on DTG+3TC had a history of DRMs associated with reduced susceptibility to the components of their 2DR (INSTI or NRTI resistance).
- Among the 5 VFs on DTG+RPV, 2 people experienced 1 VL ≥50 copies/mL followed by discontinuation, and 3 people experienced 1 VL ≥50 copies/mL and the 96-week

time point. Two people experiencing VF on DTG+RPV had a history of DRMs associated with reduced susceptibility to one of the classes of their 2DR (NNRTI baseline resistance), although not specifically to RPV.

9.3.1.2 ART-naïve and prior VF populations

Among ART-naïve individuals (n=23) initiating a 2DR (**Appendix 14.3.1 Table 15**) all but one of the 20 people (95.0%) with VL tests at the 24-week time point achieved suppression (1 patient had low level viremia with VL =51 copies/mL). At weeks 48, 72, and 96, all of the individuals with a VL measurement were suppressed (n=19, 6, and 20, respectively). There were no events of VF.

Among individuals with prior VF (n=16) taking a 2-DR (**Appendix 14.3.1 Table 16**), all 16 had a VL measured at 24 weeks, and all but 2 had achieved suppression. One of these individuals (taking DTG+3TC) remained viremic at weeks 48 before switching to another regimen (VF event). The other individual (taking RAL+ETR) who was not suppressed at 24 weeks did suppress by 48 weeks, but later experienced virologic rebound (VF event). There was a 3rd VF event among 1 person taking DTG+RPV who initially suppressed but experienced a VL>50 copies/mL at 96 weeks.

9.3.2 Secondary endpoints

9.3.2.1 Time to virologic failure

Time to virologic failure in the stable switch population (2 consecutive VL ≥50 copies/mL or a VL≥50 copies/mL followed by 2DR discontinuation or missing info) is not presented as the number of events is not large enough to allow this estimate.

9.3.2.2 Frequency of any VL ≥ 50 copies/mL

This includes both virologic failure events and viral blips, where there was a single VL≥50 copies followed by regaining suppression (VL <50 copies/mL).

Table 5: Incidence of any viral load VL≥50 copies/mL during the 96-week of follow-up

		Weeks	Weeks	Weeks	Weeks	Overall
		0-24	24-48	48-72	72-96	0-96 weeks
Stable switch population	N of participants	735	712	668	574	**735**
	Number of VL≥50 copies/mL	7	9	4	7	**27**
	Person-years of follow-up	364	356	334	287	**1340**
	Incidence rate per 100 p-y	1.9	2.5	1.2	2.4	**2.0**
	95% confidence interval of IR	0.8-4.0	1.2-4.8	0.3-3.1	1.0-5.0	**1.3 – 2.9**

Table 6: List of participants with any VL≥50 copies/mL during the follow-up (N=26)

Label	Baseline treatment	VL.0	VL.24	VL.48	VL.72	VL.96	NRTI mutation at baseline	NNRTI mutation at baseline	PI mutation at baseline	INI mutation at baseline	Treatment modification	Reason for stopping
1	DTG+3TC	20	148 Ctr : 20			20						
2	DTG+3TC	20		10257 Ctr : 2226							DRV/c+FTC+TAF at Week 70	VIROLOGICAL FAILURE
3	DTG+3TC	20	85	20		20	F77FL					
4	DTG+3TC	20	20	20	20	68			A71V			
5	DTG+3TC	40	48		91 Ctr : 40							
6	DTG+3TC	40	40		8	168			L33I			
7	DTG+RPV	20	77	20		20	L210W M41L T215S					
8	DTG+3TC	20	20	55	28							
9	DTG+3TC	49	61	49		52						
10	DTG+RPV	20		20		95	K65R M184VI	K103HNST V90I Y188C	H69K I13V I15V K20I L89IMRT M36I			
11	DTG+RPV	20	79	20	20		M184I	K103N		L74I		
12	DTG+3TC	20		56		20			H69K L89M M36I			
13	DTG+RPV	20	0	129				K103N			BIC+FTC+TAF at Week 56	VIROLOGIC FAILURE
14	DTG+RPV	20	20	20		75						
15	DTG+RPV	20	27		80						DOR+3TC+TDF at W72 BIC+FTC+TAF at W76 DRV/c+FTC+TAF at W83	VIROLOGIC FAILURE
16	DTG+RPV	20	742	20		20			K20I			
17	DTG+RPV	20	20	58	20		M184V	G190A K101E K103N P225H				
18	DTG+3TC	20				1530						
19	DTG+RPV	20	20	20		354						
20	DTG+RPV	20	20	52		33						
21	DTG+3TC	20	55								DTG+FTC+TDF at Week 24	PARTIAL VIROLOGIC FAILURE
22	DTG+3TC	20	20	20	55	20						
23	DTG+RPV	20	49	49	53	49						
24	DTG+3TC	21		63		49						
25	DTG+3TC	20		52 Ctr : 0		0						
26	DTG+3TC	89	33	54		20						

Red text denotes viral load value ≥50 copies/mL.

VL.0: viral load measured at baseline; **VL.24:** viral load measured between baseline and 24 weeks; **VL.48:** viral load measured between 24 and 48 weeks; **VL.72:** viral load measured between 48 and 72 weeks; **VL.96:** viral load measured between 72 and 96 weeks

Baseline drug resistance mutations identified any time prior to initiation of baseline 2DR

Table 5 presents the frequency and rate of any VL ≥50 copies/mL. Among 735 suppressed switch patients, there were 27 VL's measured in 26 patients through 96 weeks of follow up that were ≥50 copies/mL. The incidence rate for any VL ≥50 copies/mL was 2.0 per 100 person-years (95% CI: 1.3 – 2.9);10 of these events were classified as VF. (**Table 4**)

Details of the 26 individuals experiencing any VL ≥50 copies/mL are presented in **Table 6**. The remaining 17 VLs ≥50 copies/mL were single VL elevations (viral blips), followed by re-

suppression to VL<50 copies/mL. The 27 VLs >50 copies/mL can be further classified as low-level viremia (50≤ VL <200 copies/mL) and high-level viremia (VL ≥200 copies/mL).

Table 7: 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
Stable switch population	N of participants	735	712	668	574	**735**
	Number of low-level viremias	6	8	4	5	**23**
	Person-years of follow-up	364	356	334	287	**1340**
	Incidence rate per 100 p-y	1.6	2.2	1.2	1.7	**1.7**
	95% confidence interval of IR	0.6-3.6	1.0-4.4	0.3-3.1	0.6-4.1	**1.1-2.6**

In total, through 96 weeks, there were 23 incidences of low-level viremia where the patients' viral loads were ≥50 but <200 copies/mL, occurring over 1340 person-years of follow-up. This was an incidence rate of 1.7 incidence per 100 person-years (95% CI: 1.1 – 2.6). (**Table 7**)

Table 8: Incidence of high-level viremia (VL ≥200) during the 96-weeks of follow-up

		Weeks	Weeks	Weeks	Weeks	Overall
		0-24	24-48	48-72	72-96	0-96 weeks
Stable switch population	N of participants	735	712	668	574	**735**
	Number of high-level viremias	1	1	0	2	**4**
	Person-years of follow-up	364	356	334	287	**1340**
	Incidence rate per 100 p-y	0.3	0.3	0.0	0.7	**0.3**
	95% confidence interval of IR	0-1.5	0-1.6	0-1.1	0.1-2.5	**0.1-0.8**

There were 4 participants who had incident high-level viremia (VL ≥200 copies/ml), occurring over 1340 person-years of follow-up. This was an incidence rate of 0.3 incidence per 100 person-years (95% CI: 0.1 – 0.8). (**Table 8**)

Among ART-naïve patients (n=23; **Appendix 14.3.1 Table 15**), there was one event of low-level viremia (VL=51 copies/mL) that occurred at the week 24 time point. There were no other VLs≥50 copies/mL measured during the 96-week follow up period.

Among patients with prior VF (n=16; **Appendix 14.3.1 Table 16**), there were 7 VLs >50 copies/mL experienced by 3 individuals, including a total of 5 high-level viremia VLs and 2 low-level viremia VLs. All 3 individuals experiencing VLs >50 copies/mL were classified as having a VF event.

9.3.2.3 Discontinuation

Table 9: Proportions of participants with discontinuations of their 2DRs

	Stable switch population Total N=735	
	N	% (95% CI)
Total discontinuation	**39**	**5.3 (3.8 – 7.2)**
Switch while virologically suppressed	2	0.3 (0 – 1.0)
Switch for failure	4	0.5 (0.1 – 1.4)
Switch for tolerability	17	2.3 (1.3 – 3.7)
Switch for toxicity	5	0.7 (0.2 – 1.6)
Switch for other reasons	11	1.5 (0.7 – 2.7)

39/735 patients (5.3%, [95% CI: 3.8 – 7.2]) stable switch participants discontinued their 2DR regimen during the 96-week period of follow up. Of these, 17/39 patients (43.6%) were discontinued due to tolerability issues and 5/39 (12.8%) patients for toxicity and 11/39 patients (28.2%) were switched for other reasons. (**Table 9**)

- 4/735 patients (0.5%, 95% CI: 0.1 – 1.4) were discontinued explicitly for treatment failure (10.3% of the patients who were discontinued). These 4 patients all met the protocol definition of VF.

A detailed list of reasons for stopping for all treatment groups can be found in the **Appendix 14.1 Table 13**.

- Among ART-naïve patients (n=23; see Table 15 in Appendix), one patient discontinued their 2DR (DTG+3TC) at week 58 due to an adverse event.
- Among patients with prior VF (n=16; see Table 16 in Appendix), there were 2 discontinuations, 1 at week 48 after experiencing failure to suppress (VF event) and the other at week 87 due to concomitant disease.

9.3.2.4 Change in Immunologic measures from baseline to week 96

Table 10: Change from baseline in CD4 count, CD8 count and CD4/CD8 ratio at week 96

	Stable switch population N=735
CD4 count/mm^3	
Number of participants	509
Baseline mean (95% CI)	733 (705-762)
Mean (95% CI) change at week 96, P-value	+5 (-13 to 24), p=0.5936
CD8 count/mm^3	
Number of participants	486
Baseline mean (95% CI)	861 (826-895)
Mean (95% CI) change at week 96, P-value	-38 (-64 to -13), **p=0.0035**
CD4/CD8 ratio	
Number of participants	486
Baseline mean (95% CI)	1.00 (0.95–1.06)
Mean (95% CI) change at week 96, P-value	+0.05 (0.02 to 0.07), **p=0.0003**
Analyses were done using mixed model with random intercept and spatial power covariance structure, due to unequal time intervals between visits.	

Table 11: Evolution of CD4 count, CD8 count and CD4/CD8 ratio over time

	Week	**N**	**Mean**	**std**	**Median**	**Q1**	**Q3**	**Minimum**	**Maximum**
CD4 Count	**0**	509	733	316	684	534	920	51	1976
	24	353	770	343	712	534	956	84	2618
	48	358	744	334	709	520	921	96	2557
	96	460	740	310	694	528	898	27	2110
CD8 Count	**0**	486	861	408	798	585	1046	86	3128
	24	343	879	408	796	587	1118	105	2626
	48	347	845	373	794	586	1027	177	2398
	96	450	827	386	786	558	1033	46	3059
Ratio CD4/CD8	**0**	486	1.00	0.59	0.88	0.61	1.24	0.07	4.30
	24	343	1.03	0.63	0.89	0.66	1.28	0.10	5.50
	48	347	1.01	0.55	0.89	0.64	1.24	0.15	3.75
	96	450	1.05	0.58	0.95	0.65	1.29	0.16	4.65

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The change to the CD8 count over the 96 week follow up period in the 486/735 patients who were included in this analysis was found to be significant (p=0.0035), with a mean decrease of -38 (95% CI: -64 to -13). The CD4:CD8 ratio change over the study period also showed a statistically significant change of +0.05 (0.02 to 0.07, p=0.0003). The change in CD4 count was not statistically significant. (**Table 10**)

Details of changes in CD4, CD8, and CD4:CD8 over 96 weeks of following up among the the ART-naïve and previous VF patients are presented in **Appendix 14.3.2 Table 17 and Table 18**.

- Among naïve patients (n=23), median CD4 increased from a median of 411 cells/mm3 (IQR: 340-553) at 2DR initiation to a median of 741 cells/mm^3 (610-1033)

at 96 weeks. Median CD8 also increased between baseline (875 cells/mm^3 [677-1941]) and 96 weeks (1548 cells/mm3 [930- 2162]). CD4:CD8 increased over time, peaking at 48 weeks (median 1.02 [0.70- 1.38]).

- Among patients with previous VF, median CD4 increased from a median of 674 cells/mm3 (IQR: 523-807) at 2DR initiation to a median of 804 cells/mm^3 (505-1151) at 96 weeks. Median CD8 decreased between baseline (1015 cells/mm^3 [744, 1179]) and 96 weeks (932 cells/mm3 [760-1260]). CD4:CD8 increased over time, from baseline (0.72 [0.36- 0.90]) to 96 weeks (0.95 [0.5-1.52])

9.3.2.5 Resistance mutations following failure events

No patients were tested for resistance following a failure event in any of the 3 treatment groups.

9.4 Adverse events/adverse reactions

Table 12: Incidence of drug related non-serious adverse events and drug-related serious adverse events

	Overall switch population N=735			DTG+3TC N=534			DTG+RPV N=186		
	Person-years: 1340			Person-years: 973			Person-years: 338		
	N of events	N of pts (%)	Incidence rate per 100 p-y (95% CI)	N of events	N of pts (%)	Incidence rate per 100 p-y (95% CI)	N of events	N of pts (%)	Incidence rate per 100 p-y (95% CI)
Non-Serious Drug related AEs	**47**	**39 (5.3)**	**3.5 (2.6 – 4.7)**	**29**	**26 (4.9)**	**3.0 (2.0 – 4.3)**	**18**	**13 (7.0)**	**5.3 (3.2-8.4)**
WEIGHT GAIN	8			7			1		
DIARRHEA	3			3			0		
SLEEP DISORDERS	3			2			1		
PRURITUS	2			1			1		
RASH	2			2			0		
ACUTE URINARY RETENTION	1			0			1		
ALOPECIA	1			1			0		
ANEMIA	1			1			0		
ANXIETY AND DEPRESSION	1			0			1		
BILATERAL FLANK PAIN	1			0			1		
CNS AE	1			1			0		
CRAMPS	1			0			1		
CYTOLISIS	1			0			1		
DEPRESSION	1			1			0		
DESTRUCTIVE BEHAVIOUR	1			0			1		
EDEMA OF THE LOWER LIMBS	1			1			0		
FATIGUE	1			1			0		
FLATULENCY	1			1			0		
HYPERCREATININAEMIA	1			0			1		
INSOMNIA	1			1			0		
KIDNEY FUNCTION DECLINE EGFR 58ML/MIN	1			1			0		
LEFT LEG NUMBNESS	1			0			1		
LIQUID STOOL	1			0			1		
LOOSE STOOLS	1			1			0		
LOW MOOD	1			1			0		
MOODSWINGS	1			0			1		

NOCTURNAL AND DIURNAL COUGH	1			1			0		
PANTOPRAZOLO	1			0			1		
PSYCHOLOGICAL PROBLEMS AND INSOMNIA	1			0			1		
RIGHT HAND PARESTHESIA	1			0			1		
SWEATING	1			0			1		
TINITUS	1			1			0		
WORSENING OF GASTRO OESOPHAGIAL REFLUX	1			0			1		
WORSENING OF PARKINSON DISEASE	1			1			0		
Drug related SAE	**2**	**2 (0.3)**	**0.1 (0.0 – 0.5)**	**1**	**1 (0.2)**	**0.1 (0 - 0.6)**	**1**	**1 (0.5)**	**0.3 (0 - 1.6)**
LOW MOOD	1			1			0		
ANXIETY AND DEPRESSION	1			0			1		
Death	**0**	**0 (0.0)**	**0 (0 – 0.3)**	**0**	**0 (0.0)**	**0 (0 - 0.4)**	**0**	**0 (0.0)**	**0 (0 - 1.1)**

There were 47 non-serious drug-related adverse events in 39/735 (5.3%) patients. The most common AE was weight gain which occurred in 8 patients. Diarrhoea, sleep disorders and pruritus and rash all occurred in a low number of patients (3, 3, 2, and 2 patients, respectively). All other AEs occurred in single patients only. **(Table 12)**

- There were 2 drug related serious adverse events which occurred in 2 patients, 1 instance of low mood and 1 instance of anxiety and depression.

10 DISCUSSION

10.1 Interpretations of Results

This analysis demonstrated high levels of virologic control and low discontinuations rates over 96 weeks of follow up, demonstrating that INSTI+RTI 2DRs are effective and persistent regimens among virologically suppressed individuals in a real-world setting.

ART-naïve and ART-experienced patients switching to a 2DR after VF experienced high rates of suppression and low rates of VF, particularly among the naïve users, although numbers in both groups were too small to fully analyse these groups.

Among the suppressed switch population, there were 10 participants who reached the protocol definitions for VF. Based on study definitions, however, failures include 6 individuals with a single viral load measurement >50 copies/mL at week 96 and no additional follow up labs, with 4 of these patients having a viral load still less than 100 c/ml at the week 96 time point. These six individuals may have regained suppression had observation continued.

Only 4 participants during the study period discontinued 2-DR due to site-defined virological failure; 3 of these patients had one VL≥50 copies/mL during the 96 weeks and were then discontinued 2DR; the remaining patient has loss of viral control after 2 consecutive VL≥50 copies/mL, taken at week 48 and a follow up taken before week 72 and they were then switched to another ART.

Neither the presence of resistance mutations nor the previous ART regimen were significant in the occurrence of viral failure events, although this conclusion is based on a small number of events and 69% of the participants in the stable switch group were initiated with no documented history of resistance testing.

CD4 count mean was 733 at baseline and did not significantly change during the follow up period (+5 (-13 to 24), p=0.5936) however the CD8 and CD4:8 ratio did significantly change with a reduction in CD8 (.38 (-34 to -13). P=0.0035) and thus an increase in the CD4:8 ratio was due to the decrease in CD8 rather than an increase in CD4.

There are also very few drug-related Adverse Events in general, with only 5.3% of patients reporting any. The two drug-related SAEs were related to mental health conditions (low mood, and anxiety and depression).

Maintenance of HIV suppression in this study is consistent results of phase 3-non-inferiority studies comparing DTG+RPV to continuing on current 3-drug regimens (SWORD-1 and SWORD-2) and comparing DTG+3TC to continuing current 3- or 4-drug (SALSA and TANGO). In these studies, INSTI+RTI two-drug regimens where shown to be non-inferior to

standard of care three-drug regimens [Aboud M et al, 2019; Llibre JM et al,2023; van Wyk et al., 2020].

10.2 Limitations.

Limitations of this study are common to non-randomized non-interventional study. Selection bias may be present as the sites may elect to enrol participants that may have a better or worse health status compared to the general HIV positive treated population. Channelling bias may also be present however no formal assessment of whether the treated patients included in this observational study would be more or less likely to be high-risk than those not treated was made at this time.

There is also potential bias in the reporting of safety events which will not be as rigorous in the real world as it would be in a randomised control trial as less severe adverse events will be less likely to be reported by patients or documented by clinical team.

11 OTHER INFORMATION

None

12 CONCLUSIONS

For virologically suppressed individuals in real world settings, rates of virologic failure and viral blips were low, and relatively few discontinuations were experienced. Virological control among those with history of resistance mutations continued to be high. The safety data presented show that 2DR regimens are also well tolerated.

ART-naïve and ART-experienced patients switching to a 2DR after VF experienced high rates of suppression. There were no cases of VF among the naïve treatment group. There were low rates of discontinuation in both groups. The number of individuals in each group that these conclusions are based upon, however, was small and should be interpreted with caution.

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14 APPENDICES

14.1 Table13: Detail for the reason for stopping the study treatment in the stable switch population

	Label	Reason for stopping.1	Reason for stopping.2	Reason for stopping. 3	Baseline treatment	New treatment 1 and date of initiation	New treatment 2 and date of initiation	New treatment 3 and date of initiation	Date of dual therapy initiation	Week 96 date
Switch while virologically suppressed n=2	1	SIMPLIFICATION			DTG+3TC	CAB+RPVLA | 25-FEB-2022			16-SEP-2020	29-JUN-2022
	2	SWITCH TO INJECTABLE THERAPY			DTG+3TC	CAB+RPVLA | 25-NOV-2020			13-JUN-2019	11-FEB-2021
Switch for failure n=4	3	VIROLOGICAL FAILURE			DTG+3TC	DRV/c+FTC+TAF | 03-AUG-2021			28-MAR-2020	29-JAN-2022
	4	VIROLOGIC FAILURE			DTG+RPV	BIC+FTC+TAF | 25-FEB-2020			25-JAN-2019	04-FEB-2021
	5	VIROLOGICAL FAILURE			DTG+RPV	DRV/c+FTC+TAF | 31-MAR-2021			04-SEP-2019	07-JUL-2021
	6	PARTIAL VIROLOGIC FAILURE			DTG+3TC	DTG+FTC+TDF | 04-FEB-2020			11-SEP-2019	07-JUL-2021
Switch for tolerability n=17	7	LOW MOOD			DTG+3TC	DRV/c | 07-JAN-2020			23-NOV-2019	02-DEC-2021
	8	ADVERSE EVENT	UNKNOWN	VIRTUAL CLINIC ADVISE	DTG+RPV	DRV/r | 02-MAY-2017	DTG+DRV/r | 03-DEC-2018	DTG+FTC+TAF | 15-JAN-2019	07-MAR-2017	05-MAR-2019
	9	SLEEP TROUBLE	UNKNOWN		DTG+3TC	RAL+FTC+TDF | 11-MAR-2019	NVP+FTC+TDF | 12-MAR-2019		07-JAN-2019	28-OCT-2020
	10	ADR	ADR		DTG+RPV	DRV/c+FTC+TAF | 18-MAR-2020	BIC+FTC+TAF | 12-MAR-2021		20-SEP-2019	23-JUL-2021
	11	ITCHINESS IN THE SKIN + LOOSE BOWEL			DTG+RPV	BIC+FTC+TAF | 22-FEB-2021			21-JAN-2020	29-DEC-2021
	12	LOW MOOD			DTG+3TC	DOR+3TC+TDF | 11-NOV-2021			22-JUL-2020	01-JUN-2022
	13	WEIGHT GAIN ON DTG			DTG+3TC	DOR+3TC+TDF | 15-JAN-2021			09-JUL-2019	11-MAY-2021
	14	WEIGHT GAIN			DTG+3TC	DOR+3TC+TDF | 18-DEC-2020			19-MAR-2019	19-FEB-2021
	15	WEIGHT GAIN			DTG+3TC	RAL+FTC+TDF | 22-SEP-2020			29-JAN-2019	01-DEC-2020
	16	DEPRESSION			DTG+3TC	DRV/c | 11-SEP-2020			10-SEP-2019	15-JUL-2021
	17	CNS EFFECTS			DTG+3TC	DOR+3TC+TDF | 18-NOV-2020			19-NOV-2019	27-JUL-2021
	18	RENAL CONCERNS EGFR LOW	CHRONIC RENAL FAILURE		DTG+RPV	EFV+3TC+ABC | 16-NOV-2019	RAL+3TC+ABC | 17-NOV-2020		12-JUN-2019	14-APR-2021
	19	SLEEP ISSUES			DTG+3TC	DRV/r+FTC+TDF | 02-NOV-2020			17-JAN-2020	08-OCT-2021
	20	POSSIBLE SIDE EFFECT OF MEED CHANGES			DTG+3TC	RPV+FTC+TAF | 05-OCT-2020			20-JAN-2020	22-NOV-2021
	21	SLEEP DISORDERS	SLEEP DISORDERS	INSOMNIA	DTG+RPV	DOR+3TC+TDF | 05-NOV-2021	BIC+FTC+TAF | 15-JAN-2022	DRV/c+FTC+TAF | 31-MAR-2022	24-AUG-2020	21-APR-2022
	22	RASH			DTG+3TC	RPV+FTC+TAF | 01-JUL-2019			15-MAY-2018	14-APR-2020
	23	FATIQUE			DTG+3TC	DRV/c | 07-DEC-2018			01-DEC-2018	23-SEP-2020
Switch for	24	GASTROINTESTINAL TOXICITY			DTG+3TC	RPV+FTC+TAF | 17-JUL-2020			20-JUN-2020	23-MAY-2022

toxicity n=5	25	PHYSICIAN DECISION FOR MORE EFFECTIVE TREATMENT FOR ENCEPHALOPATHY HIV	HEMATOTOXICITY		DTG+3TC	3TC+ABC+AZT | 25-OCT-2019	DRV/c+FTC+TAF | 16-MAY-2020		04-MAY-2019	06-MAR-2021
	26	TOXICITY, UNSPECIFIED			DTG+RPV	NVP+3TC+AZT | 21-JUN-2019			03-MAY-2019	11-MAR-2021
	27	TOXICITY, PREDOMINANTLY FROM NERVOUS SYSTEM			DTG+RPV	DOR+3TC+TDF | 13-JAN-2020			04-MAY-2019	14-DEC-2020
	28	TOXICITY, PREDOMINANTLY FROM NERVOUS SYSTEM			DTG+RPV	DTG+FTC+TDF | 14-MAR-2018			27-SEP-2017	31-JUL-2019
Switch for other reason n=11	29	DRUG INTERACTION			DTG+RPV	DRV/r | 19-APR-2018			18-APR-2018	19-FEB-2020
	30	NOT SPECIFIED			DTG+3TC	DOR+3TC+TDF | 27-AUG-2020			13-FEB-2019	16-DEC-2020
	31	UNKNOWN			RAL+ETR	RAL+ETR+DRV/r | 21-DEC-2015			24-APR-2014	12-MAY-2016
	32	THERAPEUTIC INTENSIFICATION			DTG+RPV	DTG+RPV+TDF | 29-DEC-2016			27-JUL-2016	22-JUN-2018
	33	PHYSICIAN'S DECISION			DTG+3TC	EVG/c+FTC+TAF | 15-AUG-2019			11-MAR-2019	11-JAN-2021
	34	PHYSICIAN'S DECISION	PHYSICIAN'S DECISION		DTG+3TC	EFV+FTC+TDF | 22-APR-2021	CAB+RPVLA | 13-DEC-2021		27-MAY-2020	28-JAN-2022
	35	UNKNOWN	SIMPLIFICATION		DTG+3TC	DTG+3TC+ABC | 30-JUN-2020	BIC+FTC+TAF | 16-MAR-2022		05-MAR-2020	09-MAR-2022
	36	RELATED TO PREGNANCY	SWITCH TO EASY TREATMENT	PHYSICIAN'S DECISION	DTG+3TC	DRV/r+FTC+TDF | 10-JUL-2020	DRV/c+FTC+TAF | 18-NOV-2020	BIC+FTC+TAF | 24-JUN-2021	21-NOV-2019	17-SEP-2021
	37	SIDE EFFECTS NOT SPECIFIED			DTG+3TC	BIC+FTC+TAF | 28-FEB-2020			01-JAN-2020	27-SEP-2021
	38	UNKNOWN	INTOLERANCE	UNKNOWN	DTG+3TC	DTG+3TC+ABC | 01-APR-2018	EVG/c+FTC+TAF | 21-MAR-2019	BIC+FTC+TAF | 12-OCT-2020	28-NOV-2016	19-NOV-2018
	39	UNKNOWN	VIROLOGICAL FAILURE		DTG+RPV	DTG+FTC+TAF | 21-AUG-2017	RPV+FTC+TAF | 12-MAR-2018		02-NOV-2015	05-OCT-2017

14.2 Table 14: List of participants with resistance mutation prior to baseline

	NRTI mutation	NNRTI mutation	PI mutation	INI mutation
First-line treatment for treatment-naïve patients N=3	E40D			
		V179ILMT		
	L210W T215S		A71V E35D I54V L89M N88D	
Stable switch N=227	A62V			
	A62V		I15V L63C M36I M36MI R41K	
		K103N	I13V I62V L10I M36L	
	M184I M184V		A71V I93L K20R M46L	
			I13V L10V M36I	
			I13V I62V I64V L10I	
	M184V M41L T215Y		A71V I84V K20R L10I L90M M36I M36L N88D	
			I62V I93L L10I L63LIPT M36I R41K	
			L10IV	
		E138A		
	F77FL			
		V179I	L10V L89M M36I	
			A71V	
	E44D M41L V75L	A98G V108I		
	L74V	V108I V179I Y181C	L10I M36I	
		G190AG Y181YC	L63P M36I	
		V106I		
	D67DG L210WL			
	D67N E44D K219Q K70KR L210WL M184V M41L T215Y	K103R		
	K65R M184V	K103N V106M Y188CY		F121Y
		K103N		
		V179D		
	K219KQ K70KR M184V			
		K103N		
		G190A		
	L210FL			
	L210WL M184V M41L T215Y			
	M41L T215D			
		K103N		
		E138A		
		E138A		
		K103N		
	K65R	G190A K101Q K103N	L63P	
			A71AV L33I	
			L10FL	
	D67N E44D K219E L210W M184V M41L T215Y	K101P K103N	L63Q M36I	
			L33I	
		V179DV	K20KR L63P	

			L63P	
	L210W M41L T215S			
	L210W M41L T215S		M36I	
	D67N K70R T215Y		L63P M36I	
			L10I	
			H69K I13V L89M M36I	
		A98S	E35D F99L H69K I13V K14R K20L K70R L89I M36I R41K T91S V82I	
			A71V A77I G16E I62V I93L L10I L36P M36I	
		V179DV	A71V E35D I62V I72T I93L L63H R57K	
		E138A		
				E157Q
	M184V	H221Y K101E V179E		L74I
		E138G	L10F	
	D67N E44D L210W M184VI M41L T215YF		E35D I13V I54A L10I L63P L90M M36I M46I Q58E V77I V82AFT	
			L63P	
	D67N M184VI T215ILNSV T215YF		D60E L10FV L63P	
	L210W T215ILNSV		A71VT I54V L10I L63P L90M M46I V82S	L74I
	K65R M184VI	K103HNST V90I Y188C	H69K I13V I15V K20I L89IMRT M36I	
			A71VT H69INQRY L63P	
		E138A	V77I V82I	
	K70R M184VI		A71VT G73ST I54V I62V K20MR K20R K43E L10FV L63P M36I V83AFT	
	L210W M184VI M41L T215YF			
	M184I	K103N		L74I
	D67N K219QE K70R M184VI M41L T215YF		D60E I13V L63P R41K	
	D67N K219QE K70R M184VI T215ILNSV		I62V L63P V77I	
	E44D L210W M184VI M184VL M41L T215YF T69D		E35D H69K I13V K20I L63P	
			L89ML M36I	
			E35D H69K I13V I15V K20I L89IMRT M36I R41K V82I	
	D67N E44D K70R M184I M41I M41L T215Y V75A		I62V L10I L33V	
			I15IV K20I L10I	
		M230I		
	M184VI			
				V72I
			I15V I62V	
			D60E L10V	
	M184VI	K103HNST		
		K103N		
		K103KN Y181C		
	L210WL D67DN E44ED M41L			

	T215Y T69DANT			
	M41ML T215NTYS T215YF	K103HNST		
	D67N L210W M184V M184VI M41L T215Y T215YF	K103HNST		
	D67N K219Q K70R T215Y			
	D67N L210W M184VI M41L T215ACDEGH T215YF		D30N E35D I15V L10FRV L63P M36I N88D Q58E	
	T215ILNSV T69S		I15V M36I	
		V179ILMT	G16E H69K L89IMRT M36I	
	M184V T215FIS	H221Y V179I Y181C	G16E H69K L89M M36I	
	L210ML D67DG T215S		L63P M36I	
			H69K L63P L89M M36I	
	D67N E44D K219N L210W M184V M41L T215Y	G190E K103R	A71V F53L I84V L10F L63P M46I V82T	
			H69K L89M M36I	
	M184V			
			H69K L89M M36I	
	L210W M184V M41L T215Y	K103N		
		E138A		
			H69K K20I L10FRV L10I M36I	
			G73S H69K K20I L89IMRT M36I V77I	
	D67N K219Q K70R		H69K I15V K20T L10F L89I L89V M36I M46L	L74I
		H221Y	D60E H69K K20M L10I L89I M36I	
	D67N K219E K219Q K70R L63P M184V T215I	K103N K103R	I13V V77I	
	K70E M184IV		L63P R41K V77I	
	D67N K219H K219Q K70R M184I M184V M41L T215N T215S T215Y	K103N V108I	H69Y L33V L63P R41K	
	D67N E44D K70R L210W L74I L74V M184V M41L T215Y T69A T69D T69N	A98S	M36I V77I	
	D67N K219Q K70R M184V T215F	A98G	I62V L63P R41K V77I	
	T69N		I62V L63P V77I	V72I
		K101R V179I		
	K65R M184V	K103N		
	E44D L210W M184V M41L T215C		IS52V L63P V77I	
	D67N L210W M184V M41L T215Y			
		K103N		
	D67N L210W M41L T215Y		A71T I54IV I84V L63P L90M M46I N88ND V82VA	
	L74V M184V			
			G16E H69K K20I KVI L10I L89M L89V M36I	
	M41L T215L			
	D67N L210W M184V M41L T215Y		A71V G48V L63P L90M V77I V82A	
	D67N L210W M184V M41L T215Y	G190A	L63P	
	D67N L210W M41L T215Y		H69K M36I N83D	
	T215E			
		E138A K103N		
			K20I	

			K20I L89V	
			G16E I62V L10I M36I	
			L63P	
			L33F	
	D67N E44D K219N L210W M184V M41L T215Y	G190A		
			K20I	
		K103N	L33F	
	D67N L210W M41L T215Y	K101EQ K103N		
			L89M M36I V82I	
			K20I	
	M184V	G190A K101E K103N P225H		
		E138A		
			H69K I13V K20I L89M M36I	
	M41LM T215D	V106IV		
	K219Q K70R M184V			
		K103N		
	D67N E44D L210W M184V M41L T215Y T69D		A71T G48V I54V I62V I85V K20R L10I L19I L63P L90M M36I T74S V82A	
			K20I M36I	
	D67N K219Q K70R M184V	K103N	A71V L63P L90M M46I	
	T215D			
			M63I	
	D67N E44D K219E K70R L210W M41L T215F V75M	K103T V108I	A71V G73S I47V I84A K20I M36I M46I T74S	
			M46L	
		E138A		
		Y188L		
		A98S	L63P V77I	
			H69K I13V L10I L89M M36I	
	D67N L210W M41L T215Y		A71T L10F M36I M46L	
	K65R	Y181C	A71T L10V	
			K20I	
			K20R L10I M36I	
				A128T T97A
	M184V			
	M184V		H69K I13V K20I L89M M36I	
		G190A V106I		
			K20I M36I	
	K219Q K70R		H69K L89M M36I	
			H69K K20KR L33V L63P L89M M36IM	
			I13V L19I L89M M36I	
	D67N E40D K219E K70R M184V M41L M41ML T215F		I54IL K20T L10F L10Y L33LF L89I L89V M46I N88S V82I	
			K20I L10I L63T L89M M36I V82I	
			D60E G16E H69Y L10V L63H L89M M36I	
		V108IV	K20M L89ML	
	M184V M41L T215F		M36I	

		V106I	E35D I13V L10I L63P V77I	
			E35D I13V L10I M36I	
			E35D L63P V77I	
			G16E K20R M36I	
		V108I V179I	I93L L63P V77I	
			D60E L63P M36I	
			G16E	
		K101Q	I13V K20I M36I	
			E35D I93L	
			L10I L63P M36I	
		E138G V179D	D60E E35D I93L L63P	
			I13V K20I M36I	
			M36I	
		V106W	M36I	
			A71T I93L V77I	
			E35D I13V K49R L63P M36L	
		K101Q V179I	G16E	
		K103N	A71V I93L K20R M36I V77I	
			D60E L63P M36I	
		K101R	I13V M36I	
			L63P M36I	
			L63P	
		A98S	E35D	
			A71T E35D I93L	
		V179W	D60E E35D I93L L63P V77I	
			L63P V77I	
			E35D L63P	
			E35D I13V L63P M36L	
		V179I	I93L L63P	
			L63P	
		E138A	I13V I93L L63P M36I	
			G16E G45R I13V M36I	
			L63P	
			D60E E35D G45R M36I Q58E	
			A71V I93L L63P	
			I93L M36I	
	L210F	V106I	I93L L63P M36I Q58E V77I	
		K103N		
	M41LM			
	A62V D67AT K219E K70R M184V M41L T215I		F53FL G73S I54V I84V L33F L90N	
	K65R M184V	E138A		
	D67N K219Q K70R M184V	G190S		
	D67N K219Q K70R M184V			
	D67N L210W M184V M41L T215Y T69D		I84V L90M N88D	
	M184V			
	L210W M184V M41L T215N	E138A V179D	I54V L24I M46I V82A	
	K70KR			
	D67D M184MV M184V M41L T215Y	V90L		
	M184V M41L T215N		D30N L10F M46V N88D	
	D67N K70R M184V T215ISF	E138A G190A K103N		

	D67N K219Q K70R M184V T69D	Y181C		
	M184V T215I	K103N		
	M184V			
	D67DN K219KQ K70KR			
	M184V		D30N M46I	
	D67N K219E K70R M184V T215I			
	L210W M41L T215V			
	T215Y	K103N		
	D67N M184V M41L T215Y	K103N	Q58E	
	K70R M184V M41L			
	L210W L74V M184V M41L T215Y	F227L K103N V106A	I54V L90M V82A	
	D67G K219Q K70R M184V T215F		K43T	
	K70R M184V M41L			
	K65R K70R M184V	K103N V106A Y181C		
	D67DN D67N L210LW L210W M184V M41L T215NSTY T215Y T69ADNT T69D	A98S K101KQ K103N	A71V I54V K20I L63P L90M M36I T74S V82I V82T	
		V179EV		
Second-line treatment for those with VF on prior treatment N=9	M184V M41L T215NSYC T215Y	V106A	I84V M46I V77I	S230N V72I
	L210W M184V M41L T215Y		M46L	
	D67N K219N L210W M184V M41L T215C T215Y T69D T69E V75M	G190A		
		Y188H	K20R	
		Y188C	I13V L63P M36I	
	D67N K219E L210W M184V M41L T215C V75LS	K103N	F53L I54V L90M	
		V106M Y188C		
	D67N K219E K70R L74I M184V M41L T215Y	K103N V108I	K20T N88S	
	M184V		I54L L33F	

14.3 Listings for Treatment Naïve and Prior Virological Failure patients

As the number of patients recruited in the Treatment naïve and Prior virological failure patients did not reach the 90 required for to power primary endpoint calculations, the data collected is presented as listings here.

14.3.1 Evolution of plasma viral of participants in the treatment-naïve and prior viral failure patient groups

Table 15: Evolution of plasma viral of participants in the First-line treatment for treatment-naïve patients' group

Label	Baseline treatment	Date of dual therapy initiation	Treatment modification	Reason for stopping	VL.0	VL.24	VL.48	VL.72	VL.96	NRTI mutation at baseline	NNRTI mutation at baseline	PI mutation at baseline	INI mutation at baseline
1	DTG+3TC	03-AUG-2017			40	40	40	40	43				
2	DTG+3TC	14-NOV-2016			13680		40	40	40				
3	DTG+3TC	02-MAR-2017			1116	40	40	40	40				
4	DTG+3TC	20-MAY-2019			8128	40							
5	DTG+3TC	15-NOV-2016			74300				49				
6	DTG+3TC	17-JAN-2017			14615	49	49	49	49	E40D			
7	DTG+3TC	05-FEB-2020			622	40	40		20				
8	DTG+3TC	01-JUL-2016			174	28			22				
9	DTG+3TC	07-SEP-2020			6940	20	19		19		V179ILMT		
10	DTG+3TC	27-JUL-2020			62		20		20				
11	DTG+3TC	26-JUN-2020			155	20	20						
12	DTG+RPV	30-SEP-2019			59600	20			20				
13	DTG+3TC	22-JUN-2020			19400	20	20		20				
14	DTG+3TC	02-APR-2020			135000	20	47		20				
15	DTG+3TC	28-AUG-2020	DRV/c+FTC+TAF 13-OCT-2021 at Week 58	PHYSICIAN DECISION DUE TO ADVERSE EVENT	140000	20	20		34				
16	DTG+3TC	12-FEB-2020			6840	20	20		20				
17	DTG+RPV	10-AUG-2015			8820	20	20	20	20	L210W T215S		A71V E35D I54V L89M N88D	

18	DTG+ 3TC	25-JUN-2019			38586	20	20	20					
19	DTG+ 3TC	27-DEC-2016			13445	49	49		49				
20	DTG+ 3TC	21-MAR-2017			119160	49	49		49				
21	DTG+ 3TC	09-FEB-2017			335643	49	49		49				
22	DTG+ 3TC	27-MAR-2017			358691	51	49		49				
23	DTG+ 3TC	12-DEC-2016			13643	49	49		49				

Red text denotes viral load value ≥50 copies/mL after baseline (VL.0)

VL.0: viral load measured at baseline; **VL.24:** viral load measured between baseline and 24 weeks; **VL.48:** viral load measured between 24 and 48 weeks; **VL.72:** viral load measured between 48 and 72 weeks; **VL.96:** viral load measured between 72 and 96 weeks

Baseline drug resistance mutations identified any time prior to initiation of baseline 2DR

Table16: Evolution of plasma viral load in participants in the Second-line treatment for those with prior virological failure group

Label	Last treatment prior to 2DR	Baseline treatment	Date of dual therapy initiation	Treatment modification	Reason for stopping	VL.0	VL.24	VL.48	VL.72	VL.96	NRTI mutation at baseline	NNRTI mutation at baseline	PI mutation at baseline	INI mutation at baseline
1	ABC+3TC+DRV+RTV	DTG+RPV	13-JUN-2018			5370	40	40		40				
2	TDF+FTC+ATV+RTV	DTG+3TC	23-JAN-2020			8913	40			40				
3	ABC+RAL+DRV+RTV	DTG+RPV	27-AUG-2020			67	30	42	40	30	M184V M41L T215NSYC T215Y	V106A	I84V M46I V77I	S230N V72I
4	ABC+3TC+DTG	DTG+3TC	22-JAN-2020			63	20							

5	TAF+FTC+DRV+COBI	DTG+RPV	20-OCT-2019			381	20		20	3380	L210W M184V M41L T215Y		M46L	
6	RAL+DRV+RTV	RAL+ETR	01-SEP-2015			66	268	47	92	145	D67N K219N L210W M184V M41L T215C T215Y T69D T69E V75M	G190A		
7	ABC+3TC	DTG+3TC	12-JUN-2020			63	20	20		20				
8	ABC+3TC+DTG	DTG+3TC	24-JUN-2020	DTG+3TC+ABC 08-JUN-2021 at Week 48	UNKNOWN	143000	592000	404000				Y188H	K20R	
9	AZT+3TC+DTG	DTG+RPV	20-OCT-2016			1040	22	26	20					
10	ABC+3TC+NVP	DTG+3TC	24-JAN-2017			561	40	40		40		Y188C	I13V L63P M36I	
11	DTG+DRV+COBI	DTG+RPV	28-MAY-2019			90	20	20	28		D67N K219E L210W M184V M41L T215C V75L S	K103N	F53L I54V L90M	
12	LPV+RTV	DTG+RPV	03-AUG-2017	DRV/c+RPV 04-APR-2019 at Week 87	CONCOMITANT DISEASE	98	20	0		20				
13	TDF+FTC+EFV	DTG+RPV	27-NOV-2017			734	12	0		20		V106M Y188C		

14	3TC+ATV+COBI	DTG+RPV	30-JUN-2017			553	8	8		0	D67N K219E K70R L74I M184V M41L T215Y	K103N V108I	K20T N88S	
15	3TC+FPV	DTG+RPV	14-SEP-2018			204	0	20		20	M184V		I54L L33F	
16	TDF+FTC+ATV+RTV	DTG+RPV	10-AUG-2015			55010	20		32	49				

Red text denotes viral load value ≥50 copies/mL occurring after baseline (VL.0)

VL.0: viral load measured at baseline; **VL.24:** viral load measured between baseline and 24 weeks; **VL.48:** viral load measured between 24 and 48 weeks; **VL.72:** viral load measured between 48 and 72 weeks; **VL.96:** viral load measured between 72 and 96 weeks

Baseline drug resistance mutations identified any time prior to initiation of baseline 2DR

14.3.2 Change in Immunological factors from baseline to week 96 in Treatment naïve and those with prior virological failure group

Table 17: Evolution of CD4, CD8 and CD4/CD8 ratio of participants in the First-line treatment for treatment-naïve patients' group

	Week	N	Mean	std	Median	Percentile 25	Percentile 75	Minimum	Maximum
CD4 Count	0	17	534	390	**411**	340	553	169	1714
	24	15	640	245	**579**	477	693	346	1251
	48	11	794	522	**634**	465	976	364	2209
	96	13	905	555	**741**	610	1033	402	2566
CD8 Count	0	10	1150	712	**875**	677	1941	303	2312
	24	9	1007	763	**709**	564	812	349	2627
	48	6	1056	718	**688**	661	1804	378	2119
	96	6	1527	765	**1548**	930	2162	619	2357
CD4/CD8 Ratio	0	10	0.66	0.35	**0.60**	0.41	0.88	0.10	1.21
	24	9	0.88	0.45	**0.72**	0.66	1.06	0.13	1.66
	48	6	1.05	0.45	**1.02**	0.70	1.38	0.51	1.68
	96	6	0.79	0.34	**0.79**	0.54	1.06	0.31	1.21

a. Patient Group = First-line treatment for treatment-naïve patients

Table18: Evolution of CD4, CD8, and CD4/CD8 ratio in participants in the Second-line treatment for those with prior virological failure group

[a]	Week	N	Mean	std	Median	Percentile 25	Percentile 75	Minimum	Maximum
CD4 Count	0	13	674	389	**674**	523	807	88	1464
	24	12	804	522	**709**	541	980	10	1862
	48	11	800	464	**801**	576	883	8	1762
	96	11	893	450	**804**	505	1151	385	1903
CD8 Count	0	13	1037	399	**1015**	744	1179	563	1944
	24	12	988	535	**879**	645	1396	105	1846
	48	11	935	515	**879**	640	1171	138	1861
	96	11	973	342	**932**	760	1260	290	1504
CD4/CD8 Ratio	0	13	0.70	0.42	**0.72**	0.36	0.90	0.11	1.60
	24	12	0.85	0.53	**0.75**	0.43	1.31	0.10	1.84
	48	11	0.93	0.58	**0.90**	0.39	1.50	0.06	1.90
	96	11	0.99	0.45	**0.95**	0.52	1.52	0.46	1.60
	a. Patient Group = Second-line treatment for those with VF on prior treatment								

14.4 List of stand-alone documents

Number	Document reference number	Date	Title
1	[Number]	[Date]	[Text]
2	[Number]	[Date]	[Text]
…	[Number]	[Date]	[Text]