NON-INTERVENTIONAL STUDY PROTOCOL

Study Title:	**An observational cohort study to evaluate the impact of the tenofovir-based single tablet regimens on adherence, quality of life and cost-effectiveness in HIV-1 infected patients.**
Sponsor:	**Gilead Sciences, Lda. Portugal**
Indication:	HIV-1 Infection
Commercial Gilead Drug Name (prescribed Drug)	Atripla® (ATR), Eviplera® (EPA) and Stribild® (STB)
Protocol ID:	GX-PT-177-0143
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Protocol Version/Date:	Version 4, 19th August 2015

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PROTOCOL SYNOPSIS

GILEAD SCIENCES LDA., PORTUGAL

Study Title:	**An observational cohort study to evaluate the impact of the tenofovir-based single tablet regimens on adherence, quality of life and cost-effectiveness in HIV-1 infected patients**
Study Centers Planned:	Approximately 10-12 centers in Portugal
Rationale	Atripla® (ATR) was the first single tablet regimen (STR) approved for the treatment of HIV-infected patients. It is a fixed-dose combination of efavirenz, emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) that is indicated for the treatment of HIV-1 infection in adults ≥ 18 years with virologic suppression to HIV-1 RNA levels of < 50 copies/mL on their current combination antiretroviral therapy (ART) for more than three months and who have not experienced virological failure on any prior antiretroviral therapy. Since ATR's approval in Europe on December 13th, 2007, two additional tenofovir-based STRs have already been approved by the European Commission: Eviplera® (EPA), on November 28th, 2011 and Stribild® (STB) on May 24th, 2013. Besides being STRs, these new drugs have different therapeutic indications. EPA (rilpivirine/FTC/TDF) is indicated for the treatment of adults infected with HIV-1 without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, TDF or FTC, and with a viral load ≤ 100,000 copies/mL. STB (elvitegravir/cobicistat/FTC/TDF) is indicated for the treatment of adults infected with HIV-1 without known mutations associated with resistance to any of its three antiretroviral agents, regardless of baseline viral load. Taking these new developments in consideration it became important to broaden the study objectives in order to encompass these two recent STRs and evaluate its impact on adherence, quality of life and cost-effectiveness in HIV-1 infected patients.

Objectives:	**Primary objective**
	To prospectively evaluate the impact of tenofovir-based single tablet regimens (STR) on adherence in HIV-1 infected subjects. Adherence will be assessed using the CEAT-VIH, which is an instrument for the assessment of adherence rates to cART in HIV-infected subjects.
	
	Secondary objectives
	• To prospectively evaluate the impact of the tenofovir-based STR on health related quality of life in HIV-1 infected patients. Health quality of life will be assessed using:
	  ➢ SF-6D, which is a validated utility score derived from SF-36.
	  ➢ Modified HAART Intrusiveness Scale (m-HIS), which is a validated questionnaire to measure the adequacy of the cART regimen regarding its compatibility with patients life style.
	• To evaluate concordance of the main adherence measure (CEAT-VIH) with:
	  ➢ Visual analogue scale (VAS) adherence questionnaire (prospectively).
	  ➢ Proportion of days covered (PDC) using the pharmacy's refill electronic database (retrospectively and prospectively).

- To evaluate the impact of tenofovir-based STR on selective adherence (defined as taking some but not all drugs) and non-adherence (defined as not taking any of the drugs in the regimen). These estimates will be obtained using pharmacy refills (retrospectively and prospectively).
- To evaluate the clinical and economic consequences of selective adherence and non-adherence (retrospectively and prospectively).
- To evaluate the impact of switching to tenofovir-based STR on effectiveness, safety and tolerability (retrospectively and prospectively).
- To compare persistence among patients on tenofovir-based STR with that observed in patients on other cART (retrospectively and prospectively).
- To estimate the impact of tenofovir-based STR on the probability of hospitalization (retrospectively and prospectively).
- To estimate the cost differential between cohorts, including:
  - The cART cost (retrospectively and prospectively).
  - Monthly (inpatient and outpatient) non-cART costs (prospectively)
  - Monthly total (SRT plus non-cART) costs (prospectively).

Study Design:

This is a multicenter, observational study with a control cohort, with retrospective and prospective follow up periods. The cohort under investigation (**STR Cohort**) will consist of patients who switched or initiated a tenofovir-based STR (**ATR, EPA or STB)**. The **Control Cohort** will comprise subjects who initiated cART with any multi tablet recommended regimen according to EACS Guidelines in force at the time of treatment initiation and **who never switched** to any STR up to the date of study inclusion. The study duration from enrolment of the first subject to completion of the 2 years of prospective follow up of the last subject is approximately 5 years..

Number of Subjects Planned:

A total of 860 adult subjects infected with HIV-1 are expected to be included in this study (400 in the STRs Cohort and 460 in the Control Cohort). Subjects who meet eligibility criteria and give their written consent to participate will be enrolled and, at all circumstances during the prospective observation period, the Investigator's treatment decisions and management of the disease will be based on the local HIV/AIDS treatment guidelines and routine medical practice. Each site is expected to enrol the same number of patients in both cohorts.

Within the STR Cohort, the sites should include all the patients that initiated **EPA or STB** up to 30th June 2015. By including all patients on **EPA** or **STB** and considering the current status of recruitment of ATR patients**,** it is expected to achieve a ratio of 1:1 between ATR and EPA/ STB patients at the study level.

Observation Period:

Observation period of the **STR Cohort:**

Baseline date for retrospective follow up: date of introduction of the first ARV regimen - The first ARV regimen should have started after 1st January 2008 and no later than 30th June 2015. (STR should have started up to 30th June 2015).

Enrolment date: the initiation of follow up for the prospective portion of the study.

End of follow up date for each subject: two years after the enrolment date.

Observation period of the **Control Cohort:**

Baseline date for retrospective follow up: date of introduction of the first ARV regimen. The first ARV regimen should have started

after 1st January 2008 and no later than 30th June 2015.
Enrolment date: initiation of follow up for the prospective portion of the study.
End of follow up for each subject: two years after the enrolment date (if at the 24th month of follow up, 24-month data has not been collected, the follow up will continue until the next visit, up to a maximum of 27 months after the enrolment date).

Target Population: Adult HIV-1 infected subjects who initiated cART between 1st January 2008 and 30th June 2015 according to EACS Guidelines in force at the time.

Diagnosis and Main Eligibility Criteria:

Inclusion criteria

1. Subjects who give written informed consent.
2. HIV-1 infected subjects, aged 18 years or older at time of introduction of first cART.
3. Availability of complete antiretroviral therapy clinical history and pharmacy refills (pharmacy's electronic database).
4. Subjects who initiated therapy with a regimen containing one boosted protease inhibitor (PI/r) plus two Nucleoside Reverse Transcriptase Inhibitors (2NRTI) or one Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) plus 2NRTI or one integrase inhibitor (INSTI) boosted or not plus 2NRTI, according to the EACS Guidelines in force at the time.

- **Specific inclusion criteria for the STRs Cohort:**

a) **Subjects who started tenofovir-based STR** up to 30th June 2015 (not necessarily on STR at the time of enrolment). Note: subjects who switched from one STR to another STR can also be enrolled.

b) Treatment with STRs according to Summary of Product Characteristics.

- **Specific inclusion criteria of Control Cohort:**

c) Subjects who have **never had a pharmacy refill of a** tenofovir**-based STR up to the time of inclusion in the study.**

Exclusion criteria

1. Subject who had participated in an interventional study during the retrospective period. Those who, during the follow-up period, entered in an interventional study will be considered in the statistical analysis up to the moment of inclusion in the interventional study.

Study variables: Demographics, subject characteristics (cART at initiation, at the moment of enrolment, and at Months 12 and 24), cART, adherence to cART (CEAT-HIV questionnaire, VAS questionnaire, pharmacy refills), Quality of Life (SF-6D index based on SF-36 questionnaire, HAART Intrusiveness Scale: m-HIS questionnaire), laboratory parameters, resistance profile, opportunistic infections, cancers and other diseases, adverse events, appointments, inpatient care, non-cART drugs and complementary diagnostic tests.

Medicinal Product: Tenofovir-based STRs (ATR, EPA and STB) should be used according to the approved local label. All cART will be prescribed by the investigator according to the local standard of care of HIV infected

subjects. Subjects will obtain commercially available cART as they would in routine clinical practice.

Endpoints

Primary endpoint

Adherence

Mean score of CEAT-VIH questionnaire in the subgroup of subjects of the STR cohort who are on tenofovir-based at the time the questionnaire is administered, compared to the mean score of the same questionnaire among subjects in the control cohort. Comparison will be performed at enrolment, 12 months and at 24 months, after adjusting for baseline variables and other confounders.

Secondary endpoints

Quality of life

- Mean score of SF-6D in the subgroup of subjects of the STR cohort who are on tenofovir-based STR at the time the SF-36 questionnaire is administered, compared to the mean score of the same index among subjects in the control cohort. Comparison will be performed at enrolment, 12 months and at 24 months, after adjusting for baseline variables and other confounders.
- Mean score of m-HIS questionnaire in the subgroup of subjects of the STR cohort who are on tenofovir-based STR at the time the questionnaire is administered, compared to the mean score of the same questionnaire among subjects in the control cohort. Comparison will be performed at enrolment only, after adjusting for baseline variables and other confounders.

Adherence

- Mean score of VAS questionnaire in the subgroup of subjects of the STRs cohort who are on tenofovir-based STR at the time the questionnaire is administered, compared to the mean score of the same questionnaire among subjects in the control cohort. Comparison will be performed at enrolment, 12 months and at 24 months, after adjusting for baseline variables and other confounders.
- PDC based on confirmed pharmacy refills among patients of the STRs cohort - while on tenofovir-based STR - compared to the PDC among subjects in the control cohort. Comparison will consider a patient regimen as the unit of observation, will only include patients-regimens of at least 90 days and will be performed at enrolment, 12 months and 24 months after adjusting for baseline values and other confounders.
- PDC based on confirmed pharmacy refills among patients on a tenofovir-based STR, compared to the PDC among subjects on a two-pill regimen. Comparison will consider a patient-regimen as the unit of observation, will only include patients-regimens of at least 90 days and will be performed based on the retrospective period and based on the complete (retrospective plus prospective periods, jointly), after adjusting for baseline variables and other confounders.

Effectiveness, safety and tolerability (data collected during retrospective and prospective follow-up)

- Time from tenofovir-based STR initiation to virologic failure (defined as detectable viral load [HIV-1 RNA level ≥50 copies per milliliter] at least 4 weeks apart) after viral suppression has been achieved or unreached viral suppression - using the first lab result available after 24 weeks of tenofovir-based STR initiation).
- Annual median changes in CD4+ T-lymphocyte cell counts (absolute and percentage) in each cohort (retrospectively and prospectively)
- For patients with 2 or more lines of therapy (including at least one STR regimen and one non-STR regimen), comparison of CD4+ T-lymphocyte value assessed prior and each year post-switch to

tenofovir-based STR.

- Differences in persistence by ARV regimen (persistence is the time between the date of regimen initiation and the occurrence of at least one of the following events: missing more than 90 days of antiretroviral medication or having any change in the ARV regimen including switch or addition).
- Time from tenofovir-based STR initiation to treatment discontinuation due to toxicity (defined by the investigator).
- Time to development of resistance in the STRs cohort versus the control cohort.
- Confounder adjusted, incidence of grade 3/4 adverse events per person-year of observation, in the prospective period.
- Confounder adjusted, incidence of increase in the sum of genotypic sensitivity scores (over all drugs) per person-year of observation (retrospective and prospective).

Costs and hospitalization

- Impact of tenofovir-based STR on the probability of hospitalization, after controlling for baseline characteristics and other confounding factors (retrospectively and prospectively).
- Cost differential between the two cohorts (difference in medians and means) at current prices, after adjusting for baseline characteristics and other confounders:
  - Monthly cART cost (retrospectively and prospectively).
  - Monthly non-cART (inpatient and outpatient) costs (prospectively).
  - Monthly total cost (SRT+ non-ART) (prospectively).

Statistical Methods: For qualitative data, absolute and relative frequencies will be presented. Percentages will be based on the total number of subjects with non-missing values unless specified otherwise. Counts for missing values will be also tabulated but missing values will not be considered in the percentages.

For quantitative data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum and number of non-missing cases (95% confidence intervals for parameters of interest) will be presented.

Comparisons intra-patient for two paired quantitative variables will be carried out using linear models or Wilcoxon Sign-Rank test if normality assumption is not accepted.

In order to maximize homogeneity between the two cohorts and reduce the impact of treatment-selection bias a propensity score matching (PSM) approach will be applied in the statistical analysis.

Matched comparisons will use conditional logistic regression when the outcome is binary or ordinal.

For further exploration of parameters of interest, multivariate panel data modeling will be conducted, as required

Generalized linear mixed models may be used in the analysis of repeated measures.

Sample size The power to detect a difference in adherence proportion of 0.025, assuming a sample size of 400 in each cohort (400 patients in the STRs cohort, in a proportion of 1:1 for ATR and EPA or STB, and 400 in the Control cohort), a standard deviation of the difference of 0.110 and using a test to compare two proportions with a 0.05 two-sided significance level was calculated at 0.89. In addition, a 15% oversampling on the non-STR cohort should be considered to enable a final sample size, post PSM, of 400 pairs of patients. Hence, 400 subjects will need to be included in the STRs cohort and 460 subjects will need to be included in the non-STR cohort.

The sample size calculation did not take into account the number of

covariates in the statistical modelling analysis.

SPONSOR'S SIGNATURE PAGE

An observational cohort study to evaluate the impact of the tenofovir-based single tablet regimens on adherence, quality of life and cost-effectiveness in HIV-1 infected patients

PROTOCOL NUMBER: GX-PT-177-0143
Protocol version/Date: Version 4, 19th August 2015

Approved by:

Cláudia Delgado/Ass. Dir., Medical Affairs	CMDelgado	31. AGO. 2015
Name/Title	Signature	Date

Steering Committee's signature page

An observational cohort study to evaluate the impact of the tenofovir-based single tablet regimen on adherence, quality of life and cost-effectiveness in HIV-1 infected patients.

Protocol Number: **GX-PT-177-0143**
Protocol version/Date: Version 4, 19th August 2015

Francisco Antunes	Professor Doutor
Name	Degree
Signature	31.08.2015
	Date

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Av. Prof. Egas Moniz, 1649-028, Lisboa, Portugal

Investigator's signature page

An observational cohort study to evaluate the impact of the tenofovir-based single tablet regimen on adherence, quality of life and cost-effectiveness in HIV-1 infected patients.

Protocol Number: **GX-PT-177-0143**
Protocol version/Date: Version 4, 19th August 2015

- I have read this protocol and agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
- I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
- I agree to give access to all relevant data and records to Sponsor (or designee) monitors, auditors, Clinical Quality Assurance representatives, Ethics Committee and regulatory authorities, if required.

Investigator's Name	Degree

Investigator's Signature	Date

Institution's Address:

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
cART	combination antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	Atripla
CEAT-VIH	Cuestionario para la Evaluación de la Adhesión al Tratamiento Antiretroviral
CRO	contract (or clinical) research organization
DRG	diagnosis-related group
EACS	European Aids Clinical Society
eCRF	electronic case report form
EFV	Efavirenz
EPA	Eviplera
EU	European Union
FTC	Emtricitabine
HIV	Human immunodeficiency virus
IEC	Independent Ethics Committee
m-HIS	Modified HAART Intrusiveness Scale
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
PI/r	Ritonavir-boosted protease inhibitor
QoL	Quality of Life
SF-6D	Short form-6D
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SD	Standard deviation
SmPC	Summary of product characteristics
STB	Stribild
STR	Single tablet regimen
SUSAR	Suspected unexpected serious adverse reaction
TDF	Tenofovir
VAS	Visual analogic scale

1. INTRODUCTION

1.1. Background

Approximately 33.3 million people were infected with the human immunodeficiency virus (HIV) worldwide by the end of 2010.[1] According to the "Unidade de Referência e Vigilância Epidemiológica do Departamento de Doenças Infecciosas" report of December 2010, a total of 39.347 cases of HIV/AIDS at any stage of the disease were reported in Portugal, of which 16.360 were cases of AIDS.[2]

Standard-of-care for the treatment of HIV infection involves the use of a combination of antiretroviral (ARV) drugs from multiple classes to suppress viral replication below detectable limits, to increase CD4+ T-lymphocyte cell counts, and to delay disease progression. Combination antiretroviral therapy (cART) has evolved considerably over the past 12 years, leading to a better control of HIV replication, preservation of the immune system and decreased incidence of opportunistic infections, malignancies and deaths.[3]

However, to achieve such a successful treatment rate with cART, adherence is of utmost importance. The association between adherence and therapeutic success has been demonstrated across a range of ARV regimens. Poor adherence may lead to drug failure, viral mutations and development of drug resistance. Research and daily practice have shown that strict adherence is difficult to achieve for many HIV infected patients treated with antiretroviral therapy. Successful cART has been hampered by complicated regimens, high pill burden, drug-drug interactions, and frequent short- and long-term adverse effects.[3] To overcome such an important barrier, a daily pill count reduction was performed by combining selected ARV drugs in a fixed dose combination, known as single tablet regimens (STR). The advantage of STRs is its combination of a total daily ARV regimen in one pill.

Clinical trials have shown the benefit of simplified regimens that provide a lower pill burden, reduced dosing frequency and a favourable safety profile. Patients prefer once-daily single drug regimens resulting in increased quality of life.[3-5]

Higher adherence rates and a better virological response were also observed in a prospective observational study among a cohort of homeless and marginally housed individuals receiving STR compared to individuals receiving non-one-pill-daily regimens.[4]

Moreover, STRs have been demonstrated to be associated with better adherence and adherence has been shown to be associated with lower mortality and slower rates of progression to AIDS.[6-9]

Several guidelines recommend the usage of fixed-dose combinations for the treatment of HIV infection, including Atripla®.[10-13]

1.2. Tenofovir-based single tablet regimens

Atripla® is a fixed-dose combination of efavirenz (EFV), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). All three active substances block the activity of reverse transcriptase (NRTIs after intracellular phosporylation), an enzyme produced by HIV, which is essential for viral replication. Atripla® is indicated for the treatment of HIV-1 infection in adults with virologic suppression to HIV-RNA levels of <50 copies/mL on their current cART for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have

harboured virus strains with mutations conferring significant resistance to any of the three components of Atripla® prior to initiation of their first antiretroviral treatment regimen. Further information is available in the Summary of Product Characteristics (SmPC).[14]
The European Commission granted marketing authorisation in the EU for Atripla® to Bristol-Myers Squibb and Gilead Sciences Limited on December 2007. Atripla® became available in the Portuguese market in October 2008.[14]
Since ATR's approval in Europe on December 13th, 2007, two additional tenofovir-based STRs have already been approved by the European Commission: Eviplera® (EPA), on November 28th, 2011 and Stribild® (STB) on May 24th, 2013. Besides being STRs, these new drugs have different therapeutic indications.
EPA (rilpivirine/FTC/TDF) is indicated for the treatment of adults infected with HIV-1 without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, TDF or FTC, and with a viral load ≤ 100,000 copies/mL.[15]
STB (elvitegravir/cobicistat/FTC/TDF) is indicated for the treatment of adults infected with HIV-1 without known mutations associated with resistance to any of its three antiretroviral agents, regardless of baseline viral load.[16]

1.3. Rationale

To date, few data are available on the cost-effectiveness of adherence interventions[17-20] and no studies have evaluated the cost-effectiveness of STRs as an adherence improving strategy.
We hypothesize that HIV-1 infected patients receiving tenofovir-based STRs will show better adherence rates and better quality of life when compared to patients on other ARV regimens, and that tenofovir-based STRs are cost-effective when compared to those other regimens.

The present study aims to evaluate the impact of the tenofovir-based STRs on adherence rates, health related quality of life and cost-effectiveness in a large cohort of adult HIV-1 infected patients. The present study will also provide effectiveness (real-life efficacy), safety and tolerability data related with the use of these STRs and compare it with matched control subjects receiving other cART. A cohort of HIV-1 infected patients who receive other ARV regimens will constitute the control cohort.

Results from this study are expected to reinforce the benefits of tenofovir-based STRs and, at the same time, constitute a working platform for other STRs both in terms of data collected and of results obtained.
Observational studies using large health care databases can complement findings from randomised clinical trials (RCTs) by assessing treatment effectiveness in patients encountered in daily clinical practice. Results from these designs can expand upon outcomes of RCTs due to the inclusion of larger and more diverse patient populations with common comorbidities and longer follow-up periods. Furthermore, well-designed observational studies can identify clinically important differences among therapeutic options and provide data on long-term drug effectiveness and safety.[21]

2. OBJECTIVES

2.1. Primary Objective

To prospectively evaluate the impact of the tenofovir-based STRs on adherence in HIV-1 infected subjects. Adherence will be assessed using the CEAT-VIH[19-20], which is an instrument for the assessment of adherence rates to cART in HIV-infected subjects.

2.2. Secondary Objectives

- To prospectively evaluate the impact of the tenofovir-based STRon health related quality of life in HIV-1 infected patients. Health quality of life will be assessed using:
  - SF-6D[22], which is a validated utility score derived from SF-36.
  - Modified HAART Intrusiveness Scale (m-HIS) which is a validated questionnaire to measure the adequacy of the cART regimen regarding its compatibility with patients life style.[23]

- To evaluate concordance of the main adherence measure (CEAT-VIH) with:
  - Visual analogue scale (VAS) adherence questionnaire (prospectively).
  - Proportion of days covered (PDC) using the pharmacy's refill electronic database (retrospectively and prospectively).

- To evaluate the impact of tenofovir-based STR on selective adherence (defined as taking some but not all drugs) and non-adherence (defined as not taking any of the drugs in the regimen). These estimates will be obtained using pharmacy refills (retrospectively and prospectively)

- To evaluate the clinical and economic consequences of selective adherence and non-adherence (retrospectively and prospectively)

- To evaluate the impact of switching to tenofovir-based STR on effectiveness, safety and tolerability (retrospectively and prospectively).

- To compare persistence among patients on tenofovir-based STR with that observed in patients on other cART (retrospectively and prospectively).

- To estimate the impact of tenofovir-based STR on the probability of hospitalization (retrospectively and prospectively).

- To estimate the cost differential between cohorts, including:
  - The cART cost (retrospectively and prospectively).
  - Monthly (inpatient and outpatient) non-cART costs (prospectively)
  - Monthly total (SRT plus non-cART) costs (prospectively).

3. STUDY DESIGN

3.1. Study Overview

This is a multicenter, observational cohort study with retrospective and prospective follow up periods to evaluate the impact of tenofovir-based STR on adherence, health related quality of life, effectiveness, safety and tolerability. Additionally, it is intended to estimate the costs associated with the treatment and the cost-effectiveness of these STRs.
The study will be conducted in approximately 10-12 sites in Portugal with casuistic and expertise in the management of HIV infection. Sites without an electronic pharmacy refill database for HIV infected subjects will not participate in this study.
A total of 860 adult subjects infected with HIV-1 are expected to be included in this study (400 in the STR Cohort and 460 in the Control Cohort).
Subjects who meet eligibility criteria and give their written consent to participate will be enrolled and, at all circumstances during the prospective observation period, the Investigator's treatment decisions and management of the disease will be based on the local HIV/AIDS treatment guidelines and routine medical practice. Each site is expected to enrol the same number of patients in both cohorts.

3.2. Description of cohorts

The cohort under investigation (**STR Cohort**) will consist of subjects who, in the selected centers, switched or initiated a tenofovir-based STR (ATR, EPA or STB) up to 30th June 2015 (First STR became commercially available in Portugal in October 2008).
Subjects who, at the time of inclusion, are no longer receiving ATR will also be enrolled.
Within the STR Cohort, the sites should include all the patients that initiated EPA or STB up to 30th June 2015. By including all patients on EPA or STB and considering the current status of recruitment of ATR patients, it is expected to achieve a ratio of 1:1 between ATR and EPA/ STB patients at the study level.

The **Control Cohort** will comprise subjects who have initiated cART from 1st January 2008 up to 30th June 2015 with any multi tablet recommended regimen according to EACS Guidelines[11] in force at the time and **who never switched** to STRs up to 30th June 2015. The choice of the Control Cohort is based on DeJesus et al.[3] in which subjects switching to an ATR were compared to those who maintained their baseline regimen (all ARV regimens mentioned above). A random sampling technique at the site level will be used to select the remaining subjects in Control group (expected approximately 150 subjects, based on current recruitment) – see section 4.4.
During the statistical analysis, the STR Cohort will be matched with Control Cohort on a 1:1 ratio using the propensity score. The Control Cohort will require a 15% oversampling (460 patients) to account for losses during the post-PMS. The propensity score will be obtained using baseline and other retrospective information excluding any measures of adherence (outcome). The probability (propensity) to switch to STR will be computed using logistic regression and the cohorts matched using nearest neighbor (NN) matching algorithm.[24, 25]

3.3. Description of Observation Period

Observation period of the **STR Cohort:**

Baseline date for retrospective follow up:
Date of introduction of the first ARV regimen - The first ARV regimen should have started after 1st January 2008 and no later than 30th June 2015. (STR should have started up to 30th June 2015).
Enrolment date: the initiation of follow up for the prospective portion of the study.
End of follow up date for each subject: two years after the enrolment date.*

Observation period of the **Control Cohort:**

Baseline date for retrospective follow up: date of introduction of the first ARV regimen. The first ARV regimen should have started after 1st January 2008 and no later than 30th June 2015.
Enrolment date: initiation of follow up for the prospective portion of the study.
End of follow up for each subject: two years after the enrolment date (if at 24 of follow up, 24 months data has not been collected, the follow up will continue until the next visit, up to a maximum of 27 months after the enrolment date)

Subjects in both cohorts will be followed for two years from the date of enrolment, independently of having switched to or from ATR. This will allow the comparison of adherence and costs between the ATR path (ATR cohort) and the control cohort. The maximum duration of retrospective observation in both cohorts will be ~ 5 years and the maximum prospective observation period is 2 years.

**End of recruitment period is expected on 30th September 2016. Therefore, the end of the observation period is expected to occur in 30th September 2018.*

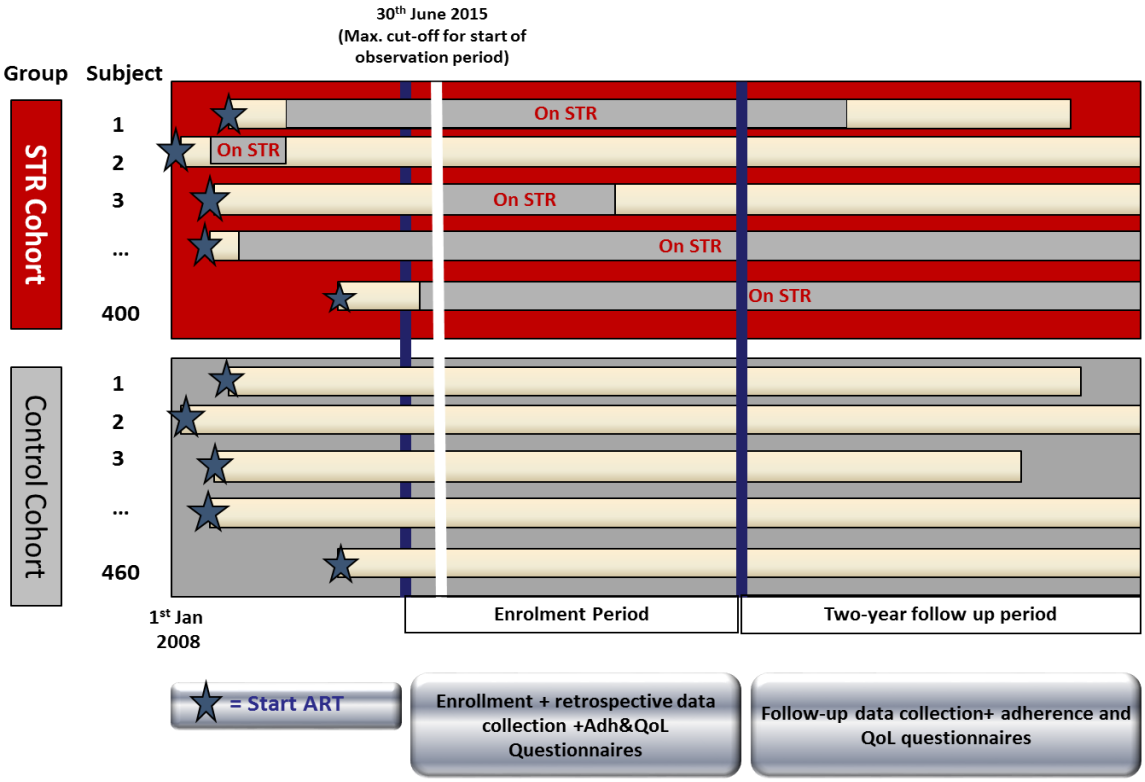

Figure 1 – Study Scheme

3.4. Study Duration

The estimated length of time needed to complete the entire study, from enrolment of the first subject to completion of the 2 years of observation of the last subject is approximately 5 years. However, the recruitment period may be extended in case the overall planned number of subjects is not reached within this timeframe.

4. SUBJECT POPULATION

4.1. Target population

Adult HIV-1 infected subjects who initiated cART between 1st January 2008 and 30th June 2015 according to EACS Guidelines[11] in force at the time.

4.2. Inclusion Criteria

Subjects must meet ***all*** of the following inclusion criteria to be eligible for documentation in this study:

1. Subjects who give written informed consent.
2. HIV-1 infected subjects, aged 18 years or older at time of introduction of first cART.
3. Availability of complete antiretroviral therapy clinical history and pharmacy refills (pharmacy's electronic database).
4. Subjects who initiated therapy with a regimen containing one boosted protease inhibitor (PI/r) plus two Nucleoside Reverse Transcriptase Inhibitors (2NRTI) or one Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) plus 2NRTI or one integrase inhibitor (INSTI) boosted or not plus 2NRTI, according to the EACS Guidelines in force at the time.

    - **Specific inclusion criteria for the STR Cohort:**

    a) **Subjects who started tenofovir-based STR** up to 30th June 2015 (not necessarily on STR at the time of enrolment). Note: subjects who switched from one STR to another STR can also be enrolled.

    b) Treatment with STRs according to Summary of Product Characteristics.

    - **Specific inclusion criteria of Control Cohort:**

    c) Subjects who have never had a pharmacy refill of a tenofovir-based STR up to the time of inclusion in the study.

4.3. Exclusion Criteria

Subjects who meet ***any*** of the following exclusion criteria are not to be included in this study.

1. Subject who had participated in an interventional study during the retrospective period. Those who, during the follow-up period enter in an interventional study will be considered in the statistical analysis up to the moment of inclusion in the interventional study.

4.4. Subject Selection

Subjects who meet eligibility criteria will be enrolled and, at all circumstances during the prospective observation period, the Investigator's treatment decisions will be based on routine clinical practice and in accordance with ATR label. There will be no protocol-mandated subject visits or laboratory tests during the observation period. Nevertheless, in the context of real clinical practice, asymptomatic HIV patients attend to the consultation every 4-6 months. Therefore, it is expected to collect follow up data related with study endpoints, subject's vital status and use of STR and control cART at least every six months.

A total of 10-12 investigational sites are expected to participate in this study, each one will contribute to the study's global number of subjects (860, 400 in STR cohort and 460 in Control Cohort).

The subject selection will involve the following steps, to be initiated as soon as hospitals' approval has been granted at each site:

- **Search in Pharmacy's electronic records** – the pharmacist will search the pharmacy electronic database in order to identify all the subjects who had their first pharmacy refill record from 1st January 2008 (inclusive) and 30th June 2015 (inclusive).

- **Division in two groups** – The list of patients drawn from the pharmacy records will be divided into two groups: 1) subjects who have started tenofovir-based STR at some point up to 30th June 2015; 2) subjects who have never been on STR up to 30th June 2015.

- **Check of eligibility criteria by physician** - The pool of subjects previously identified in the pharmacy will then be checked by the study's physician who will select all the subjects who meet all protocol's eligibility criteria (except for informed consent).

- **Conduct site-level random sampling (for Control Cohort only)** – It is likely that the number of subjects identified for the Control Cohort is higher than the number of subjects required per protocol at each site (roughly the same number

of subjects included in the STR Cohort). In this circumstance, each site should select a sample of subjects from their eligible population. For this purpose, a sampling mechanism will be used. Subjects listed in the Control Cohort list will be randomly selected by using Microsoft Excel®, as described below:

- The list of subjects' unique identifiers will be put in a column of an empty sheet;
- A second column will be created to the left (it must be to the left) of the subjects' identifiers by writing "=RAND()" in each cell and random numbers from 0 to 1 will appear;
  (note in the Portuguese version of Excel the RAND function is designated as "=ALEATORIO()")
- The column with the random numbers will be copied and pasted as values in the same cells, so the random numbers won't change;
- Finally, the "Sort" button from the "Sort and Filter" group in the "Data" ribbon will be clicked (both "smallest to largest" or "largest to smallest" sorting may be used) and a randomly sorted list of subjects' identifiers will be obtained.

- For all the subjects who sign the consent form, the investigator will assign a sequential study number to each subject enrolled in each cohort. The Investigator will record all subjects who meet study eligibility criteria but are not enrolled in the study in the "Subject Non-participating Log".

  Note: in order not to affect negatively the recruitment rate, matching procedures (between cohorts) will not be implemented during the subject selection procedures. This matching will be performed during the statistical analysis using the propensity score matching method. This method will tend to maximize homogeneity between the two cohorts and to reduce the impact of treatment-selection bias.

4.5. Criteria for premature discontinuation

Subjects who discontinue STR or other cART (control cohort) during the observation period, regardless of the reason (e.g. safety, tolerability or lack of efficacy, switch to other STR), should continue to be followed until the end of follow-up period (2 years after the enrolment date). This will allow the comparison of adherence and costs between the STR path (STR cohort) and the control cohort.

Reasons for discontinuation of the observation period include:

- Subject withdraws consent;
- Subject's death;

- Subject's lost to follow up: Investigator lost contact with the subject during the observation period and no subsequent clinical information was obtained;
- Sponsor's decision - The study may be terminated or suspended by the Sponsor at any time. If the study is terminated or suspended, the Sponsor will promptly inform the Investigator and the Regulatory Authorities (if applicable). The Independent Ethics Committee (IEC) will be promptly informed and the reason(s) for the termination or suspension will be provided by the Investigator /Institution.
- Investigator's decision (e.g. subject's participation in an interventional study)
- Inclusion in an interventional study

If a subject discontinues the study prematurely, the reason must be noted in the case report form.

5. STUDY ENDPOINTS

5.1. Primary endpoint

Adherence

- Mean score of CEAT-VIH questionnaire in the subgroup of subjects of the STR cohort who are on STR at the time the questionnaire is administered, compared to the mean score of the same questionnaire among subjects in the control cohort. Comparison will be performed at enrolment, 12 months and at 24 months, after adjusting for baseline variables and other confounders.

5.2. Secondary endpoints

Quality of life

- Mean score of SF-6D in the subgroup of subjects of the ATR cohort who are on tenofovir-based STR at the time the SF-36 questionnaire is administered, compared to the mean score of the same index among subjects in the control cohort. Comparison will be performed at enrolment, 12 months and at 24 months, after adjusting for baseline variables and other confounders.

- Mean score of m-HIS questionnaire in the subgroup of subjects of the STR cohort who are on tenofovir-based STR at the time the questionnaire is administered, compared to the mean score of the same questionnaire among subjects in the control cohort. Comparison will be performed at enrolment only, after adjusting for baseline variables and other confounders.

Adherence

- Mean score of VAS questionnaire in the subgroup of subjects of the STR cohort who are on tenofovir-based STR at the time the questionnaire is administered, compared to the mean score of the same questionnaire among subjects in the control cohort. Comparison will be performed at enrolment, 12 months and at 24 months, after adjusting for baseline variables and other confounders.

- PDC based on confirmed pharmacy refills among patients of the STR cohort - while on tenofovir-based STR - compared to the PDC among subjects in the control cohort. Comparison will consider a patient regimen as the unit of observation, will only include patients-regimens of at least 90 days and will be performed at enrolment, 12 months and 24 months after adjusting for baseline values and other confounders.

- PDC based on confirmed pharmacy refills among patients on a tenofovir-based STR- compared to the PDC among subjects on a two-pill regimen. Comparison will consider a patient-regimen as the unit of observation, will only include patients-regimens of at least 90 days and will be performed based on the

retrospective period and based on the complete (retrospective plus prospective periods, jointly), after adjusting for baseline variables and other confounders.

Effectiveness, safety and tolerability (data collected during retrospective and prospective follow-up)

- Time from tenofovir-based STR initiation to virologic failure (defined as detectable viral load [HIV-1 RNA level ≥50 copies per milliliter] at least 4 weeks apart) after viral suppression has been achieved or unreached viral suppression - using the first lab result available after 24 weeks of tenofovir-based STR initiation).
- Annual median changes in CD4+ T-lymphocyte cell counts (absolute and percentage) in each cohort (retrospectively and prospectively)
- For patients with 2 or more lines of therapy (including at least one STR regimen and one non-STR regimen), comparison of CD4+ T-lymphocyte value assessed prior and each year post-switch to tenofovir-based STR.
- Differences in persistence by ARV regimen (persistence is the time between the date of regimen initiation and the occurrence of at least one of the following events: missing more than 90 days of antiretroviral medication or having any change in the ARV regimen including switch or addition).
- Time from tenofovir-based STR initiation to treatment discontinuation due to toxicity (defined by the investigator)
- Time to development of resistance in the STR cohort versus the control cohort
- Confounder adjusted, incidence of grade 3 or 4 adverse events per person-year of observation, in the prospective period.
- Confounder adjusted, incidence of increase in the sum of genotypic sensitivity scores (over all drugs) per person-year of observation (retrospective and prospective.

Costs and hospitalization

- Impact of tenofovir-based STR on the probability of hospitalization, after controlling for baseline characteristics and other confounding factors (retrospectively and prospectively).
- Cost differential in the two cohorts (difference in medians and means) at current prices, after adjusting for baseline characteristics and other confounders:
  - Monthly cART cost (retrospectively and prospectively).
  - Monthly (inpatient and outpatient) non-cART costs (prospectively).
  - Monthly total cost (SRT+ non-ART) (prospectively).

6. MEDICINAL PRODUCTS

6.1. Handling of prescribed drugs

Tenofovir-based STRs (ATR, EPA and STB) should be used according to the approved local label. All cART will be prescribed by the Investigator according to the local standard of care of HIV infected subjects. Subjects will obtain commercially available cART as they would in routine clinical practice. No medication will be supplied by Gilead Sciences. For detailed information of tenofovir-based STRs see respective SmPC.

6.2. Prior and concomitant medications

The Investigator will prescribe and manage any concomitant treatments according to his/her clinical decision and taking into account the approved local STR's SmPC.

7. STUDY VARIABLES

After confirmation of eligibility criteria and written informed consent is given by the patient, the Investigator will collect the following data, based on relevant medical/laboratory records and patient's examination:

Variables to be collected	
Period of analysis	From cART initiation until end of observation period
Demographics	- Date of birth (dd/mm/yyyy) - Gender (male, female, transgender) - Race (White, Asian, Black or African heritage, other) - Country of origin (Portugal, Brazil, PALOP, Eastern Europe, Other)
Baseline characteristics	- Date of HIV diagnosis (dd/mm/yyyy) - Most likely mode of Infection (injection drug user, heterosexual sex, homosexual sex, unknown, other) - CDC Classification at date of diagnosis (A1, A2, A3, B1, B2, B3, C1, C2, C3) - Date of AIDS diagnosis, if applicable (dd/mm/yyyy) - Highest attained education level (none - cannot write or /and read, elementary school, high school, university or higher) - Profession
Characteristics to be evaluated at cART initiation, at the moment of inclusion, and at Months 12 and 24)	- Illegal drugs dependency with current consumption (yes, no), - Alcohol dependency with current consumption (yes, no) - Smoker with current consumption (yes, no) - Current opioid substitution treatment (no, methadone, buprenorphine) - Mental disorder (not present, controlled, uncontrolled) - Has someone meaningful/close to talk to regarding his/her HIV status and treatment? (yes no) - Employment status (student, permanent, temporary, unemployed, retired, other) - Shift Worker (yes, no) - Average number of nights away from home per month - Housing (no permanent home, stable housing) - Present CDC Classification (A1, A2, A3, B1, B2, B3, C1, C2, C3) - Date of AIDS diagnosis, if applicable (dd/mm/yyyy) - Date of study discontinuation, if applicable (dd/mm/yyyy) - Reason for discontinuation, if applicable (protocol violation; withdrew consent, lost to follow-up, investigator's discretion, death, other) - Height (cm) and weight (Kg) - Abdominal perimeter (cm) - Diabetes mellitus(yes, no) - Systolic blood pressure (mmHg) - Diastolic blood pressure (mmHg) - Hypertension (yes, no) - Medicated with anti-hypertensive drugs (yes, no) - Corticotherapy (yes, no)

	- Established cardiovascular disease (yes, no) - Hyperlipidemia (yes, no) - Nephropathy (yes, no) - Proteinuria (yes, no) - Asthmatic (yes, no) - Chronic obstructive pulmonary disease (yes, no) - Femural neck T Score (SD) - Lumbar Spine T Score (SD) - Previous bone fracture (yes, no) - Previous femur neck fracture (yes, no) - Rheumatoid arthritis (yes, no) - Secondary osteoporosis (yes, no) - Osteopathic disorder (yes, no) - Neuropsychiatric disorder (yes, no) - Tuberculosis (yes, no) - Hepatitis B (yes, no) - Hepatitis C (yes, no) - Other co-infection (yes: specify, no)
Antiretroviral treatment	For the first cART: • Date of initiation of cART (dd/mm/yyyy) • For each drug/co-formulations: scientific name (which includes active principles, dosages, pharmaceutical forms), posology (times per day, dosage each time) For the following cART: • Date of cART change, i.e., any change in components or formulation (dd/mm/yyyy) • Reason for cART change (viral suppression unreached, virological failure after suppression has been achieved, CD4+ T lymphocyte cell count related, toxicity, simplification, pregnancy, other - specify) • For each drug/co-formulations: scientific name (which includes active principles, dosages, pharmaceutical forms), posology (times per day, dosage each time)
Laboratory parameters (Prospective and Retrospective)	For each test: • Date of test (dd/mm/yyyy) • Parameter name and corresponding value • CD4 absolute (/mm3) • CD4 % • HIV RNA (copies/mL) • Ratio CD4/CD8 • AST (IU/L) • ALT (IU/L) • Triglycerides (mg/dL) • Total Cholesterol(mg/dL) • HDL Cholesterol (mg/dL) • LDL Cholesterol (mg/dL)

	• Fasting Serum glucose (mg/dL) • Fasting Serum insulin (mg/dL) • HbA1c (%) • Hemoglobin (g/dL) • Platelets (x10^9/L) • Leukocytes (x10^9/L) • Conjugated bilirubin (mg/dL) • Total bilirubin (mg/dL) • Alkaline phosphatase (mg/dL) • Albumin (g/dL) • Prothrombin time (seconds) • International normalized ratio (INR) • Serum calcium (mg/dL) • Serum phosphate (mg/dL) • Serum creatinine (mg/dL) • Fasting serum insulin (mcroU/ml) • Urine: Proteinuria - single sample, proteinuria - in the 24h, glycosuria - single sample, glycosuria - in the 24h, phosphaturia - single sample, phosphaturia - in the 24h. • HLA-B*5701 (Yes, No, Unknown) With the above data and height and weight, the CRF will automatically calculate and present: • Body mass index (value and resulting category) • Metabolic syndrome (value and resulting category) • Cockcroft – Gault Glomerular filtration rate (mL/min and resulting category) • CKD-EPI Glomerular filtration rate (mL/min and resulting category) • MDRD Glomerular filtration rate (mL/min and resulting category) • FRAXmTS (% and resulting category) • FRAXhTS (% and resulting category) • FRAXm (% and resulting category) • FRAXh (% and resulting category) • Framingham (% and resulting category) • Score (% and resulting category) • Glycaemia/insulin ratio (value and resulting category)
Resistance profile	For each test: • Date of test (dd/mm/yyyy) • Was the REGA 8.0 algorithm used? (yes, no: specify) • GSS score (REGA 8.0 algorithm) for each drug • Mutation detected (yes: specify, no)
Inpatient care (provided by hospital administration)	For each episode: • Date of admission (dd/mm/yyyy) • Date of discharge (dd/mm/yyyy) • Discharge destination (home, to other institution as an inpatient, to home care support, discharge against

	physician's opinion, deceased, unknown) • Event code (DRG)
Antiretroviral treatment pharmacy refills (provided by pharmacy)	For each drug of each regimen of each individual: • Prescribing date (dd/mm/yyyy) • Date of refill (dd/mm/yyyy) • International non-proprietary name (INN) (include fixed dose combinations and allow for new drugs and drugs withdrawn) • Quantities dispensed
Adverse reactions to a Gilead Sciences product (Retrospective)	• Adverse reaction description • Event code (ICD9 - provide search motor for list) • Seriousness (yes, no) • Start and End date (dd/mm/yyyy) • Action taken to cART (dose not changed, dose reduced, drug interrupted, dose increased, drug withdrawn, not applicable, unknown) • Other action taken (none, medication required, other treatment required, hospitalized / prolonged hospitalization) • Severity (according to DAIDS Dec 2004 classification)
Clinical diagnosis - any condition that started before baseline and which were not resolved at time of baseline	• Condition description • Event code (ICD9 - provide search motor for list) • Seriousness (yes, no) • Start date (dd/mm/yyyy) • End date (dd/mm/yyyy) – to be filled if applicable during prospective follow-up • Is it associated with chronic comorbidity? (yes, no) • If so, which? (ICD9 - provide search motor for list) • Is it an opportunistic infection? (yes, no) Is it an AIDS-defining event? (yes, no)
Period of analysis	**During prospective follow-up only**
Adverse events/Clinical diagnosis	For each episode • Adverse event description • Event code (ICD9 - provide search motor for list) • Seriousness (yes, no) • Start and End date (dd/mm/yyyy) or ongoing • Relation to Gilead drug • Action taken to cART (dose not changed, dose reduced, drug interrupted, dose increased, drug withdrawn, not applicable, unknown)Other action taken (none, medication required, other treatment required, hospitalized / prolonged hospitalization) • Severity (according to DAIDS Dec 2004 classification) • Is it associated with chronic comorbidity? (yes, no) o If so, which? (ICD9 - provide search motor for list) • Is it an opportunistic infection? (yes, no) • Is it an AIDS-defining event? (yes, no)
Pregnancy (if applicable)	• Last menstrual period (dd/mm/yyyy)

	• Date of pregnancy confirmation (dd/mm/yyyy) • Estimated date of delivery (dd/mm/yyyy)
Death (if applicable)	• Date of death (dd/mm/yyyy) • Immediate cause of death
Period of analysis	**During follow-up only (at inclusion, 12 and 24 months)**
Adherence to cART (pharmacy refills provided by pharmacy)	• CEAT-VIH at inclusion, 12 and 24 months • VAS at inclusion, 12 and 24 months
Quality of life	• SF-36 and corresponding SF-6D score at inclusion, 12 and 24 months • Modified-HIS (at inclusion only)
Appointments	For each appointment • Date (dd/mm/yyyy) • Emergency? (yes, no)
Non cART drugs	For each drug prescribed: • Prescribing date (dd/mm/yyyy) • International Non-proprietary Name - INN) • Dosage • Pharmaceutical form • Long term treatment duration (yes, no) • Provided by the hospital? (yes, no)
Other Outpatient Tests and Procedures	For each test: • Date (dd/mm/yyyy) • DRG code (provide search motor for list from Portaria n.º 132/2009, 30 de Janeiro, Diário da República, 1.ª série — N.º 2, p. 660-758)

8. ADVERSE EVENTS AND TOXICITY MANAGEMENT

8.1. Definition of Adverse Events, Adverse Reactions and Serious Adverse Events:

8.1.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol mandated procedures, lack of efficacy, overdose or drug abuse/misuse reports. Pre-existing events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed. The condition that led to the procedure may be an adverse event and should be reported

- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the initiation of treatment does not need to be recorded in the CRF unless it relates to the questions on the HealthScan CRF.

8.1.2. Adverse Reactions

An **adverse reaction** (AR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or authorized medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose or occupational exposure where applicable.

8.1.3. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose:

- Results in death;

- Is life-threatening; Note, the term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe;

- Results in-patient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity;

- Is congenital anomaly/birth defect; or

- Is a medically important event or reaction. AEs requiring medical and scientific judgment to determine if expedited reporting is appropriate. Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment should be exercised in deciding whether an event is a Medically Important Event. Examples of Medically Important Events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a Medically Important Event and subject to expedited reporting requirements.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself. Therefore, if death occurred, the event that led to death needs to be reported as an SAE.

- The subject may not have been on investigational medicinal product at the time of the occurrence of the event. Dosing may have been given as treatment cycles or interrupted before the onset of the SAE.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, is life-threatening, or meets any of the other definitions of a SAE, then it is a SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis (and not the individual signs/symptoms) should be documented as the AE and/or SAE.

A distinction should be drawn between seriousness and severity of AEs. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed for severity. An AE is defined as "serious" when it meets one of the predefined outcomes described above in this Section.

8.2. Assessment of AEs and SAEs

The Investigator or qualified designee is responsible for assessing AEs and SAEs for causality and severity, for final review and confirmation of accuracy of event information and assessments.

8.3. Assessment of Causality for Study Drugs and Procedures

The relationship to investigational medicinal product therapy should be assessed using clinical judgment and the following considerations:

No: Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

Yes: A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Or, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

8.4. Investigator Requirements and Instructions for Reporting AEs and SAEs to Gilead

During the retrospective review period, all ADRs (nonserious adverse drug reactions) and SADRs (serious adverse drug reactions) related to a Gilead Science product must be reported to Gilead in the electronic case report form (eCRF) database and to Contract (or clinical) Research Organization (CRO) as instructed.

During the prospective follow up phase of the study, all AEs and SAEs, regardless of cause or relationship to Gilead Science product or other antiretroviral therapy must be reported in the eCRF database and to the CRO as instructed.

Follow-up and monitoring of ongoing AEs and SAEs will continue until the last day on study or until the investigator and Gilead Sciences determine that the subject's condition is stable. Gilead Sciences may request that certain AEs or SAEs be followed until resolution.

Investigators are not obligated to actively seek SAEs after the patient follow-up period. However, if the investigator learns of any SAEs that occur after study participation and the event is deemed relevant to the use of investigational medicinal products, he/she should promptly document and report the event to the CRO.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF Completion Guideline.

- All SAEs will be recorded on the "Serious Adverse Event Report" report form and submitted by faxing the SAE report form within 24 hours of the investigator's knowledge of the event to the attention of the CRO.

Eurotrials (CRO) Fax:+351 213 825 452

Email:joao.silva@eurotrials.com

If required the Portuguese contact of Gilead DSPH is:

Alexandra Santos
Pharmacovigilance Responsable Person
Mobile: +351 916 474 982

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur with personal subject details de-identified, without losing the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded in the event description section of the SAE form. Any medications necessary for treatment of SAEs that are reported for the prospective period of the study must be recorded on the Non-ART Drugs page of the subject's eCRF and the event description section of the SAE form.

8.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Commission Clinical Trials Directive (2001/20/EC) and relevant updates, and other country specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory authorities reports of Serious Adverse Events, Serious Adverse Drug Reactions (SADRs) or Suspected Unexpected Serious Adverse Reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead Sciences or specified designee will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the Investigator's Brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the IEC of SUSAR reports as soon as is practical, where this is required by local regulatory authorities, and in accordance with the local institutional policy.

8.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Clinical laboratory abnormalities and other abnormal parameters will be assessed for their severity according to the table included in appendix 13.1.

8.7. Special Situations Reports

8.7.1. Definitions of Special Situations

Special situation reports include pregnancy reports, reports of medication error, abuse, misuse, or overdose, reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints.

A pregnancy report is used to report pregnancies following maternal or paternal exposure to the product.

Medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient or consumer.

Abuse is defined as persistent, sporadic or intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects.

Misuse is defined as any use of a medicinal product in a way that is not in accordance with the protocol instructions or the local prescribing information and may be accompanied by harmful physical and/or psychological effects.

An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labelling (as it applies to the daily dose for the subject/patient in question).

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

8.7.2. Instructions for Reporting Special Situations

8.7.2.1. Instructions for Reporting Pregnancies

The Investigator should report all pregnancies to Eurotrials (CRO) using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the adverse event term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in the Adverse and Serious Adverse Events section. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to Gilead Sciences.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Eurotrials (CRO) using the Pregnancy Outcome Report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

8.7.2.2. Reporting Other Special Situations

All other Special Situation reports must be reported on the Special Situations Report Form and forwarded to Eurotrials (CRO) within 24 hours.

All clinical sequelae in relation to these special situation reports that occur during the prospective period of the study will be reported as AEs at the same time using the AE eCRF. Any serious clinical sequelae in relation to these special situation reports that occur while the subject is taking a Gilead product during the retrospective and prospective periods of the study will be reported as SAEs at the same time using the SAE report form.

9. STATISTICAL CONSIDERATIONS

9.1. General procedures

In general, when presenting descriptive statistics the following parameters will be presented:

- For qualitative data, absolute and relative frequencies. Percentages will be based on the total number of subjects with non-missing values unless specified otherwise. Counts for missing values will be also tabulated but missing values will not be considered in the percentages.
- In case of quantitative data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum and number of non-missing cases (95% confidence intervals for parameters of interest).

Missing data will not be imputed. Throughout the study, a valid case approach will be assumed.

In case of parametric procedures the underlying assumptions will be checked. In case of severe violations of assumptions, nonparametric methods will be used instead.

Exploratory post-hoc subgroup analyses may be performed if appropriate.

All statistical tests will be two-tailed considering a significance level of 5%.

In order to maximize homogeneity between the two cohorts and reduce the impact of treatment-selection bias a propensity score matching (PSM) approach will be applied in the statistical analysis.

The propensity score will be computed using logistic regression. Matching algorithm is nearest neighbor.[24]

9.2. Comparisons intra-patient (individual cohorts)

Comparisons intra-patient for two paired quantitative variables (e.g. measures pre and post switch within STR cohort) will be carried out using linear models or Wilcoxon Sign-Rank test if normality assumption is not accepted. Additionally, mixed models may be used in the analysis of repeated measures.

In case of intra patient binary or ordinal data, logistic regression will be used. Mixed models with the logit link will be sued for repeated measures.

9.3. Comparisons inter-patient (matched cohort)

Matched comparisons will use conditional logistic regression when the outcome is binary or ordinal.
For further exploration of parameters of interest, multivariate panel data modeling will be conducted, as required.
Generalized mixed models may be used in the analysis of repeated measures.

9.4. Time to event data

Time to event data will be analyzed using survival analysis. Kaplan-Meier curves will be computed for calculation of medians, quartiles and corresponding 95% confidence intervals. Statistical comparisons between curves will be conducted using log-rank test. Cox's regression and parametric regression models will be used if a multivariable approach is relevant.

9.5. Cost-effectiveness analysis

Generalized linear models and Lin's regression will be used to estimate costs. Cost-effectiveness analysis will be performed using a discrete events microsimulation model. The primary cost-effectiveness analysis will be STR versus control but other cost-effectiveness analysis may be performed.

9.6. Effectiveness analysis and cost analysis

- Complete descriptive analysis and evaluation of endpoints with respect to the retrospective period
- Complete descriptive analysis and evaluation of endpoints with respect to retrospective period + 1 year of prospective follow-up
- Complete descriptive analysis and evaluation of endpoints with respect to retrospective period + 2 year of prospective follow-up
- Evaluation of the evolution of QoL and adherence at 3 different time points (from enrolment to 12 and from 12 months to 24 months) for both STR and control cohorts.
- Comparison of PDC, proportion of days completely not covered and proportion of days partially covered by some but all drugs of the regimen among patients in the STR cohort, who remained on tenofovir-based STR for at least 90 days, to the PDC among subjects in either the ATR cohort or the control cohort who remained on TDF/FTC+EFV for at least 90 days. Comparison will be performed based on the retrospective period and based on the complete (retrospective plus prospective periods, jointly), after adjusting for baseline variables and other confounders.
- Comparison of PDC, proportion of days completely not covered and proportion of days partially covered by some but all drugs of the regimen among patients who remained on STR for at least 90 days, to the PDC among subjects who remained on non-STR for at least 90 days. Comparison will be performed based on the retrospective period and based on the complete (retrospective plus prospective periods, jointly), after adjusting for baseline variables and other confounders.
- Evaluation of the clinical and economic impact of selective and/or non-adherence)
- Comparison of effectiveness, tolerability and safety in STR subjects switching from PI/r vs switching from NNRTI.
- Analysis of the determinants of QoL at 12 and 24 months.
- Analysis of the predictors of switch to STR at inclusion (retrospective), 12 and 24 months.
- Analysis of the relationship between adherence rates and resistance at inclusion (retrospective), 12 and 24 months.
- Analysis of the impact of switch to STR on cART and non-cART costs (STR cohort) at inclusion (retrospective), 12 and 24 months.

- Analysis of the impact of initial CD4 T lymphocyte cell count on costs and mortality at inclusion (retrospective) and 24 months.
- Estimation of the total annual cost per CD4 T lymphocyte cell count class at inclusion (retrospective) and 24 months.Intra-individual adherence comparison pre and post switch (components vs STR and 2NRTIs+PIr vs STR®) among subjects who have been on tenofovir-based STR for at least one year (at inclusion, 12 and 24 months).
- Determinants of adherence through the analysis of retrospective and prospective data in both cohorts.
- Clinical and economic impact of simplification from cART regimens with higher pill burden (e.g. boosted PI/r or NNRTI [nevirapine] on safety, effectiveness and quality of life and adherence patient reported outcomes).

Other analyses may be performed based on the variables collected. The requirement to perform these analyses will be discussed between the Steering Committee and Gilead.

9.7. Sample Size

The power to detect a difference in adherence proportion of 0.025, assuming a sample size of 400 in each cohort (400 patients in the STRs cohort, in a proportion of 1:1 for ATR and EPA or STB, and 400 in the Control cohort), a standard deviation of the difference of 0.110[4] and using a test to compare two proportions with a 0.05 two-sided significance level was calculated at 0.89. In addition, a 15% oversampling on the Control cohort should be considered to enable a final sample size, post PSM, of 400 pairs of patients. Hence, 400 subjects will need to be included in the STRs cohort and 460 subjects will need to be included in the non-STR cohort.
The sample size calculation did not take into account the number of covariates in the statistical modelling analysis.

10. DATA HANDLING

10.1. Data collection

For each subject enrolled, the investigator will record the data into an electronic Case Report Form (eCRF) specifically designed for this study. Each investigator will be assigned with a unique log-in and password for accessing the electronic CRF.
The investigator must keep source documentation for each subject included in the study, consisting of case and consultation notes (hospital, clinic medical records or patient diary) containing demographic and medical information, results of any tests or assessments performed as part of routine clinical practice, QoL and cART adherence questionnaires. Pharmacy refills will be provided directly from the hospital pharmacy and will be inputted in the eCRF. Inpatient episodes will be provided directly from the hospital administrative records and will be inputted in the eCRF
All the data collected into the eCRF must be consistent with these source documents.
A data-entry will provide assistance at site-level for collection of retrospective data into a database specifically designed for this study according to the information provided by the pharmacist and investigator. Subsequently, the data-entry will visit each site regularly for collection of prospective data. All data will be kept anonymous during this process.

10.2. Data management

A Data Management Unit will be responsible for designing and validating the web-based case report forms. A detailed data validation plan that will identify missing data, out-of-range data, and other data inconsistencies will be implemented in the electronic platform prior to study start.
Once all information is introduced in the database, data will be reviewed. Queries will be prepared in case data inconsistencies are found and will be resolved by each investigator. After the data validation, the database will be locked and sent to Statistics Unit in order to perform the statistical analysis and report.

11. ETHICAL, DATA PRIVACY AND ADMINISTRATIVE CONSIDERATIONS

11.1. Study conduct

This study will be conducted in accordance with the requirements defined in this protocol and also in accordance the Declaration of Helsinki, the Good Pharmacoepidemiology Practices (GPP), local laws and the regulatory requirements for reporting of serious adverse events.

Considering this is an observational study, a study specific insurance is not applicable.

11.2. Independent Ethics Committee (IEC) review

This protocol will be submitted to all the Ethics Committees (IEC) of the Hospitals involved in this study. The IEC approval should be obtained in written, prior to study initiation at each site. Any change or addition to the protocol can only be performed in a written protocol amendment that must be approved by Gilead Sciences and IECs before implementation.

11.3. Informed Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods and objectives of the study. The Investigator must use an IEC-reviewed consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent. A copy of the signed and dated written Informed Consent Form will be provided to the patient (or the patient's legally acceptable representative).

11.4. Confidentiality

The data collected under this study will be treated in compliance with the Portuguese law for personal data protection (Data Protection Act – 67/98 of 26th October). The study will be submitted to the Portuguese Data Protection Authority (CNPD – Comissão Nacional de Protecção de Dados) for authorization of data processing.
The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties.
The Investigator agrees that all information received from Gilead Sciences, including but not limited to this protocol, CRFs and any other study information, remain the sole and exclusive property of Gilead Sciences during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead Sciences. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain. Please consult the Study Agreement for further details on this issue.

11.5. Study Agreement

Prior to study initiation, GILEAD (or Designee) and the Investigator will also sign a Study Agreement stating the terms of the collaboration namely the study recruitment goals and the fees to be assigned.

11.6. Steering Committee

The Scientific Steering Committee (SSC) is an external group of infectious disease/HIV medicine-experts whose role is to provide input on study protocol, to periodically monitor the progress of the study, including logistical and operational aspects, to evaluate the quality of the data being collected in the study, and to assist the sponsor in the development of any remedial plans of action, as necessary. The SSC may propose changes to the study design and conduct including follow-up duration, as the committee deems necessary based on emerging safety data. Additionally, the members of the SCC will be involved in the presentation of abstracts, posters or contribute to scientific papers resulting from this study.

11.7. Study implementation and monitoring

Eurotrials, Scientific Consultants will be the CRO responsible for the study implementation, submission to applicable EC/Institutions and regular contacts with investigators for this purpose.
Before the start of activities Eurotrials will conduct Initiation Visits in order to train the investigational team on the protocol, safety reporting and other protocol-related procedures.
During the study Eurotrials will also be responsible for conducting periodic monitoring visits at each site every three months to ensure that the protocol is being followed and the data recorded in the CRF is accurate and consistent with source data. A Monitoring Plan will define which procedures should be followed during the monitoring visits. At any time during the course of the study, the investigator (or site staff) may contact the monitor in order to clarify any study procedures.

11.8. Quality Assurance

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct this study in accordance with its requirements, and also to give access to all relevant data and records to GILEAD (or designee) monitors, auditors, GILEAD Clinical Quality Assurance representatives, Ethics Committee and regulatory authorities, if required.
The study site may be subject to review by the Ethics Committee, and/or to quality assurance audits performed by the Sponsor or its designated representative, and/or to inspection by appropriate regulatory authorities. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform GILEAD immediately

about this request. It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. The investigator and institution will allow the appropriate regulatory authorities direct access to source documents to perform this verification.

11.9. Study files and retention of records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) Investigator's study file, and (2) subject clinical source documents.
The Investigator's study file will contain the protocol/amendments, EC approval, informed consent, and other appropriate documents. These study files shall be archived for at least 2 years after the last patient was documented by the Investigator. They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator.
The subject clinical source documents consist of the usual patient files kept at the site of the Investigator and falls within the local regulations for such files and documents.

11.10. Publication policy

Upon study completion and finalization of the statistical report, the results of this study will be communicated to all investigators.
GILEAD is the sole proprietor of the data resulting from this study and has the right to publish it at any time.
GILEAD recognizes the Investigator's right to utilize data derived from the study for teaching purposes, communication at congresses and scientific publications. Nevertheless, only cleaned, checked and validated data will be used. To that effect, it is essential that the parties exchange and discuss, prior to any publication or communication, the draft manuscript or communication made by the Investigator.
Each site has full rights to present and publish results from its own data set. Overall study data will be presented and subsequently published being the authors the Principal Investigators of the sites participating in the study cited by an order related to the percentage of achievement of study recruitment goals, as described in Study Agreement.
Therefore, the Investigator undertakes not to make any publication, communication or release pertaining to the results of the study or a part of it, without the prior written consent of GILEAD.

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13. APPENDICES

13.1. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

13.1. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Infant, **2 – ≤ 7 Days**	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, **1 Day**	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
Activated Partial Thromboplastin (APPT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to 135 mEq/L 130 to 135 mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin) **Adult and Pediatric ≥ 7 Days**	10.6 to 11.5 mg/dL 2.64 to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to 1.76mg/dL 1.2 to 1.4 mEq/L 0.58 to 0.72 mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.5 mg/dL to < LLN 0.80 mmol/L to < LLN 3.0 to 3.5 mg/dL 0.96 to 1.14 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	2.0 to < 2.5 mg/dL 0.63 to < 0.80 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 2.0 mg/dL 0.31 to < 0.63 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	> 1.0 to 1.5 × ULN NA NA	> 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	> 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperuricemia	7.5 to 10.0 mg/dL 444 to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below	6–10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1-2+	3+	4+	NA

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak-ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	**Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	**Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	**Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	**Necrosis (involving dermis and deeper tissue)**
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC
GENITOURINARY

	Grade 1	Grade 2	Grade 3	Grade 4
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

	Grade 1	Grade 2	Grade 3	Grade 4
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.