NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	Impact of single tablet regimens on adherence and prescription errors – how big an issue and how relevant, in both clinical and economic terms.
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Gilead Study Director:	Name: Geraldine Reilly Telephone: +44 208 587 2303 Mobile: +44 7788 188779
Marketing Authorization Holder	Gilead Sciences International Limited Flowers Building, Granta Park Abington, Cambridge CB21 6GT, UK.
MAH contact person	Filipa Aragao
Gilead Qualified Person Responsible for Pharmacovigilance:	Name: Dr Anne-Ruth van Troostenburg de Bruyn Telephone: +44 1223 824641 Mobile: +44 7887 450620

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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	adverse event
ART	Antiretroviral Treatment
BID	Twice daily
DSPH	Drug Safety & Public Health
eCRF	Electronic case report form
EMA	European Medicines Agency
EU	European Union
FDC	Fixed dose combination
GDP	Gross domestic product
GEE	Generalized estimation equations
GLM	Generalized linear models
GLMM	Generalized linear mixed models
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GVP	Good Pharmacovigilance Practices (guidelines for)
HIV	Human immunodeficiency virus
HMA	Heads of Medicine Agency
ICH	International Conference on Harmonization
IEC	Independent ethics committee
II	Integrase inhibitor
MM	Marginal models
NA	Non-adherence
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OIA	Overall inadequate adherence
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PI/r	Ritonavir -boosted Protease Inhibitor
PP	Purchasing power
PPP	Purchasing power parity
QD	Once daily
SA	Selective adherence
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SSR	Special situation report
STR	Single Tablet Regimen
SUSAR	Serious Unexpected Suspected Adverse Reaction

Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cases	Group of individuals with the condition of interest
Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Confounder	Extraneous factor that accounts for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders
Confounding by indication	A patient characteristic that is related to the outcome of interest and which influences treatment choice (exposure)
Controls	Group of individuals without the condition of interest but are otherwise similar to cases, or unexposed to or not treated with the agent of interest
Date at which a study commences	Date of the start of data collection
Effect modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier
End of data collection	The date from which the analytical dataset is completely available
Exposure	A variable whose effect is of interest and is being studied
External validity	Whether or not the results from the study can be generalized to other populations
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
Odds ratio	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Prevalence	Proportion of persons with the exposure/outcome at a specific point in time
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Relative Risk (RR)	A general term that can refer to the ratio of 2 risks or the ratio of 2 rates
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Start of data collection	Date from which information on the first study subject is first recorded in the study dataset

3. RESPONSIBLE PARTIES

Table 1. Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
Project Management	Jacqueline Ewan Senior Program Manager, Clinical Operations Gilead Sciences Ltd Flowers Building, Granta Park Abington, Cambridge UK	+44 1223 897416 +44 7787 538987
Drug Safety	Janette Tenys Associate Manager DSPH Gilead Sciences Inc 333 Lakeside Drive Foster City, California USA	+1 (650) 522-5103
Data Management	Hannah Sharp Senior Clinical Data Associate, Gilead Sciences Ltd Flowers Building, Granta Park Abington, Cambridge UK	+44 1223 897 405
Medical Oversight	Felipe Rogatto Associate Director Medical Affairs Gilead Sciences Europe Ltd 2 Roundwood Ave, South Building Stockley Park, Uxbridge UK	+44 208 587 2431
Statistics/Epidemiology	Robertino Mera-Giler Senior Director Epidemiology Gilead Sciences Inc 333 Lakeside Drive Foster City, California USA	+1 (650) 522 5056

4. PROTOCOL SYNOPSIS

Gilead Sciences International Limited
Flowers Building, Granta Park
Abington, Cambridge
CB21 6GT, UK.

Title:	**Impact of single tablet regimens on adherence and prescription errors – how big an issue and how relevant, in both clinical and economic terms.**
Rationale and Background:	Antiretroviral therapy (ART) involves the use of a combination of multiple classes of drugs, including Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), ritonavir-boosted Protease Inhibitors (PI/r), and Integrase Inhibitors(II), and has several goals including suppression of viral replication below detectable limits and increase of CD4+ T-lymphocyte cell counts. Successful ART has been hampered by complicated regimens, high pill burden, drug-drug interactions, and frequent short- and long-term adverse effects {26182}. To overcome these important barriers, a daily pill count reduction was obtained by combining a full regimen into single pill fixed-dose combinations, known as single tablet regimens (STR). This study will investigate two types of medication errors – one at the patient level (adherence) and one at the Healthcare provider level (prescription errors). Adherence is of utmost importance in achieving a high proportion of successful treatments. In fact, the association between adherence to ART and therapeutic success has been demonstrated {27740} {27741} {27765}. On the other hand, poor adherence may lead to drug failure, viral mutations and development of drug resistance {27741} {2642} {5523} {27742} {27743}. Investigators hypothesize that selective adherence (SA) accounts for a non-negligible portion of overall inadequate adherence (OIA) and that both SA and non-adherence (NA) are clinically and economically relevant. STRs are, by definition, SA-free regimens. Three analyses have recently appraised this value of STRs suggesting that STRs are associated with higher rates of viral suppression and higher CD4 {27766}, lower probability of hospitalization and lower annual costs {27766} {21957} {27767} {19} {20} {21}. ART medication errors may have serious long-term consequences, including the development of drug resistance, treatment failure, or

	death {27744}. Depending on the source of information, medication error rates related to ART regimens among hospitalized patients reported in the literature, can go up to 72% {27722} {27768} {27745}. Of these, prescription errors are a major problem and account for 70% of medication errors that could potentially result in an adverse event {27745}. The study is split into two parts – an adherence study and a prescription errors sub-study. The aim of the adherence study is to evaluate the potential benefits of STR in enhancing adherence, and its clinical and economic consequences, in the European context. The aim of the prescription errors sub-study is to quantify prescription errors and identify those that can be avoided by the use of STRs.
Research Question and Objectives:	**Research questions:** This study aims to determine whether STRs, as SA-free regimens, will: • improve adherence and generate clinical and economic benefits; • prevent prescription errors. **Primary Objective:** • To assess the impact of STRs, as compared to non-STRs, on adherence in HIV-1 infected patients. **Secondary Objectives** • To assess the direct effect of STR versus non-STR on o virological failure o hospitalization o ART plus hospitalization costs • To assess the effect of NA and OIA (overall and STR versus non-STR) on o virological failure o hospitalization o ART plus hospitalization costs • To quantify ART prescription errors
Study Design:	This retrospective, non-interventional study focuses primarily on patient adherence to ART. Adherence will be evaluated in a matched retrospective cohort study. Two cohorts will be considered: STR (defined as a regimen containing single tablet regimens presently recommended by the European AIDS Clinical Society (EACS) Version 7.0 October 2013 {27774} or Stribild) and non-STR (defined as a regimen containing multi-pill once daily combinations presently recommended by the European AIDS Clinical Society (EACS) Version 7.0 October 2013 {27774}). In order to maximize homogeneity between the two cohorts and reduce the impact of treatment-selection bias we will be applying a propensity score

	matching (PSM) approach. The statistical unit of analysis will be the patient-regimen. Data will be collected on patient-regimens that have been given for at least 90 days at any time between 1st January 2009 and 31st December 2013. This is the observation period. All data introduced into the eCRF will be de-identified to maintain subject confidentiality. A study number will be assigned for each subject and patient-regimen. Within the STR group, priority will be given to non-Atripla patient-regimens so these will be selected first if available.
Sub-study design	A sub-study will review and quantify prescription errors. Only centers where prescription data is available will be included in the prescription errors sub-study. ART prescription errors will be evaluated by a retrospective review of medication orders during the first 48 hours of hospitalization (for any cause) for patients with HIV infection admitted to each participating center between 1st January 2012 and 29th December 2013. Each center participating in this sub-study will aim to include 40 hospitalization episodes. Prescription errors will be classified as: 1). absence / incomplete regimen 2). incorrect dosage (including renal dose adjustment) 3). incorrect schedule 4). incorrect formulation 5). duplication of ART therapy 6). non-recommended drug-drug combinations (ART-ART and ART-non-ART). In this sub-study, two cohorts will also be considered: STR and non-STR however, unlike the adherence study, any ART regimen may be included. This is an analytical cross-sectional study aimed at identifying the proportion of hospital episodes in which prescription errors occur. A random sample of 40 hospitalization episodes will be selected according to the methods described below. Data will be collected by manual review of subject clinical records and types of errors classification will be performed by the investigator.
Population:	**Adherence study** HIV-1 infected adults who received ART between 1st January 2009 and 31st December 2013 for at least 90 days. **Inclusion criteria:** • HIV-1 infected • Aged 18 or above at the beginning of the observation period

	• Able and willing to provide informed consent • At least one pharmacy refill in 2013 • Being followed at the center at the time of recruitment • Has been on an ART regimen containing Stribild or one that is recommended by EACS v 7.0 {27774}(which contains two NRTI plus one NNRTI **or** two NRTI plus one PI/r) and which was taken once daily for at least 90 days on 31st December 2013 • Availability of a complete electronic history of pharmacy refills throughout the observation period **Exclusion criteria:** • Subject participation in an interventional study during the observation period • Subject on a non-pill formulation during the observation period • Subject on off-ART periods (ART holidays) during the observation period **Patient-regimens permitted** For each subject to be included in the study, all regimens containing Stribild or all EACS v7.0 {27774} recommended ART regimens (which contain two NRTI plus one NNRTI or two NRTI plus one PI/r), and which were taken once daily for at least 90 days during the observation period, will be included in the analysis. EACS v7.0 alternative regimens will not be included, with the exception of regimens containing Stribild. These characteristics define a valid patient-regimen. The regimen(s) may start before the beginning of the observation period or end after the observation period provided at least 90 days are within the observation period. In the case of a patient-regimen that continued after the end of the observation period, the patient-regimen will be censored at the date of the last refill within the observation period. The regimen duration to be considered is from the first refill of that regimen within the observation period to the last refill of that regimen during the observation period. January 1st 2009 will, for study purposes, be considered the start of the regimen duration for patient-regimens that started before the observation period. **Prescription errors sub-study:** Subjects enrolled in the sub-study do not need to be participating in

	the adherence study in order to be eligible. **Inclusion criteria:** • HIV-1 infected patients who were hospitalized, at least for a minimum of 48 hours between 1st January 2012 and 29th December 2013 and who received, or should have received, an ART regimen during the first 48 hours of the hospitalization episode; • Aged 18 or above at the beginning of the hospitalization episode; • Able and willing to provide informed consent • Availability of complete history of medication (ART and non-ART) prescribed during the first 48 hours of the hospitalization episode. **Exclusion criteria:** • Subject participation in an interventional study during the observation period
Variables:	**Primary endpoints:** • Confounder adjusted odds of attaining > 90% adherence in the STR cohort versus the non-STR cohort as measured by medication possession ratio based on pharmacy refills **Secondary endpoints:** • Confounder adjusted average OIA and NA levels in each cohort • Confounder adjusted odds of becoming unsuppressed (defined as two sequential measures of HIV RNA >50 copies/mL within the observation period) among subjects with HIV RNA ≤50 copies/mL at the start of the regimen if the regimen started during the observation period, or at the start of the observation period if the regimen started before the observation period, in STR versus non-STR groups • Confounder adjusted odds of becoming unsuppressed (defined above) among subjects with HIV RNA ≤50 copies / mL at the start of the regimen if the regimen started during the observation period, or at the start of the observation period if the regimen started before the observation period, according to patient-regimens adherence level (NA and OIA) • Confounder adjusted odds of resistance development among those who become unsuppressed (defined above), by STR vs. non-STR and adherence level

	• Confounder adjusted odds of hospitalization in STR versus non-STR groups • Confounder adjusted odds of hospitalization according to patient-regimens adherence level (NA and OIA) • Confounder adjusted actual (i.e. OIA adjusted) average monthly ART plus hospitalization cost in STR versus non-STR groups • Confounder adjusted actual (i.e. OIA adjusted) monthly ART plus hospitalization costs by patient-regimens adherence level (NA and OIA) • Proportion of hospitalization episodes with ART prescription errors overall and in STR versus non-STR groups • Percentage of prescription errors, overall and STR versus non-STR. The list of confounders to be included is detailed in the variables to be collected section. All variables collected will be considered as confounders except the dependent or related dependent variable in question for each endpoint.
Data Sources:	Centers participating in the Adherence study must have the complete history (within the observation period) of pharmacy refills available electronically in the hospital records. Subjects' clinical records will be the main source for the remaining data to be collected. For centers participating in the Prescription errors sub-study, registration of ART errors, in either paper or electronic format, is required. The main source of data is thus the subject clinical record.
Study Size:	**Adherence study** 700 STR subjects and 805 non-STR subjects is the sample size needed to enable a final sample size for analysis of 2060 patient-regimens (assuming an average of 1.5 patient-regimens per subject), after matching on a variable ratio with a propensity score approach. This is necessary to achieve a power of 80% for detecting a difference of 0.02 in the proportion of subjects with adherence > 90% between the two cohorts, with a two sided test with a significance level of 0.05, determined using the methodology proposed by Sahai and Khurshid {27760}. **Prescription errors sub-study** Due to the nature of the study design a formal size determination could not be performed. Each center will aim to include 40 inpatient care episodes of HIV-1 infected subjects that occurred between 1st

	January 2012 and 29th December 2013. There is no minimum number of subjects required since the unit of observation is the hospitalization episode. The subjects enrolled onto the sub-study do not need to be participating in the adherence study in order to be eligible.
Data Analysis:	Baseline characteristics will be reported using descriptive statistics. In general, when presenting descriptive statistics, the following parameters will be presented: • for qualitative data: absolute and relative frequencies. Proportions, and 95% confidence intervals for parameters of interest, 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: use of mean, standard deviation, median, 25th and 75th percentiles (interquartile range IQR), minimum and maximum and number of non-missing cases (95% confidence intervals for parameters of interest). **Adherence study:** Appropriate methods to deal with matched samples will be used. Suitable methods are Conditional Logistic Regression, Generalized Linear Mixed Models (GLMM) and Marginal Models (MM) with Gaussian or Logistic links. **Prescription errors sub-study:** The number of errors per hospitalization will be modeled with Generalized Linear Models (GLM). If significant correlation between hospitalizations from the same subject/hospital is found, then appropriate methods to address such data structure will be used. Suitable methods are GLMM and MM. **For both the main study and the sub-study:** Missing data will not be imputed. In case of parametric procedures the underlying statistical assumptions, such as normality, will be checked. In case of severe violations of assumptions, transformations will be attempted as appropriate, and nonparametric methods may 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%. Matching will be done using a propensity score approach on a variable ratio. The propensity score will be obtained using baseline and other retrospective information excluding

	any measures of adherence (outcome). The probability (propensity) to be in the STR group will be computed using logistic regression and the cohorts matched using nearest neighbor (NN) matching algorithm {27765} {27775}.

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

5. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
<1>	[DD Month YYYY]	[Enter Text]	[Enter Text]	[Enter Text]
<2>	[DD Month YYYY]	[Enter Text]	[Enter Text]	[Enter Text]
<n>	[DD Month YYYY]	[Enter Text]	[Enter Text]	[Enter Text]

Protocol Modifications

Protocol modifications may only be made by Gilead Sciences. Approval must be obtained before changes can be implemented.

6. MILESTONES

Milestone	Planned Date
Start of data collection	01 Sep 2014
End of data collection	01 Dec 2014
Final report of study results	01 Mar 2015

7. BACKGROUND AND RATIONALE

7.1. Background

Approximately 35.3 million people are infected with the human immunodeficiency virus (HIV) worldwide, of whom 25.9 million are eligible to receive ART according to WHO guidelines. HIV can be suppressed by combination ART consisting of three or more antiretroviral drugs. {27515}

In order to achieve a successful treatment rate, adherence is of utmost importance. Adherence to ART has been shown to be associated with maintained viral suppression {20920} {27747} {16557} and inherent reduction in infectivity of the individual {27748}, lower resistance development {27770}, higher immunological recovery/maintenance {27749}, slower disease progression and mortality {27765} {27744} {16555}, increase in quality of life {27750}, reduced resource utilization {27751} and lower costs {20290} {27752} {27755}. STRs have been created to potentiate adherence and have been shown to be associated with lower mortality and slower rates of progression to AIDS {27765} {16661} {27769}. Several guidelines recommend the usage of fixed-dose combinations for the treatment of HIV infection {27746} {27774} {27777, 27778} {27779} {27780}.

While a vast amount of literature has analyzed the clinical and economic impact of adherence, fewer studies have looked deeper into the issue of selective adherence (SA).

In 2005, Gardner et al. {27753} used pharmacy refill data to quantify SA (defined in that analysis as a >5% difference in adherence between 2 components of an antiretroviral regimen lasting at least 60 days), to identify its determinants and its clinical consequences. In their analysis the authors found that SA occurred in 47 of 322 patients (15%) and on 51 of 438 regimens (12%) and that regimens with a fixed-dose combination were less likely to have selective drug administration (OR = 0.5; 95%CI: 0.2 – 0.99). As factors associated with SA, the authors presented lower baseline CD4 lymphocyte count, therapies with three daily doses, and the presence of significant adverse events {27753}.

In 2008, Gardner et al. {27754} investigated the occurrence of SA to ART (defined as any difference in self-reported adherence to individual antiretroviral regimen components) and assessed its predictors and association with virological failure and resistance. This was a secondary analysis of a prospective clinical trial and SA was assessed by means of a questionnaire. In their analysis, the authors found that SA was reported at least once by 403 of 1379 subjects (29%), over 60 months median follow-up.

In 2012, Cohen et al. {21957} evaluated NA and SA, based on pharmacy claims from a large commercially insured population of treated HIV patients in the US (LifeLink database). The authors found that SA accounts for between 40% and 52% of OIA in non-STR based regimens (depending on the third agent class), while obviously being null in STR regimens. Also in 2012, the same authors {21957} evaluated NA and SA, based on pharmacy claims from Medicaid enrollees with HIV in the US (MarketScan Medicaid Multi-State Database) and found

that SA accounts for between 30% and 43% of OIA in non-STR based regimens (depending on the third agent class).

Also in 2012, two additional studies, both based on pharmacy refill data, were presented regarding SA. Antinori et al. {27766} evaluated NA and SA in Italy and found that SA accounts for between 13% and 48% of OIA, depending on the third agent class; Vera et al. {27767} evaluated NA and SA in one center in Portugal and found that SA accounts for 24% of OIA in once daily (QD) regimens and approximately 15% of OIA in multi-pill fixed-dose combination (FDC), non-FDC and twice-daily (BID) regimens.

7.2. Rationale

The aim of this study is to evaluate the potential benefits of STR on two types of medication errors – one at the patient level (adherence) and one at the Healthcare provider level (prescription errors):

- To evaluate whether use of an STR can enhance adherence, assessing its clinical and economic consequences, in the European context,

- To quantify prescription errors and identify those that can be avoided by the use of STRs.

Adherence has generally been reported as either the level of adherence to a single component of a multi-drug regimen or as the average level of adherence to multiple components {27754}. Nonetheless, inadequate adherence may take two forms: non-adherence (NA), defined as not taking any of the regimen's components, and selective adherence (SA), defined as taking some but not all of the regimen's components. Whenever NA or SA occurs, the patient cannot be considered to fully adhere to ART and as such, overall inadequate adherence (OIA) may be defined as the sum of NA and SA.

Among the predictors of SA, CD4 lymphocyte count {27753}{27753}, adverse drug events {27753} regimen complexity (number of daily intakes, absence of fixed-dose combination, number of drug components) {27766} {21957} {27767} {27753} {27754} and ART medication errors {27744} have been identified. ART prescription and dispensing by non-specialists and tight stock management (especially in a context of economic constraints) may also contribute to SA but no studies have yet been published on these themes.

In the case of the STR, SA is by nature not possible and as such all OIA will be NA. Three analyses have recently appraised this value of STRs suggesting that STRs are associated with higher rates of viral suppression, higher CD4 {27766}, lower probability of hospitalization and lower annual costs {27766} {21957} {27767}. When using pharmacy refill data to measure adherence, medication possession is what is actually measured. In that case, NA is defined as the proportion of days (out of total regimen duration within observation period) the patient did not have any of the components of the regimen in his possession. SA is defined as the proportion of days (out of total regimen duration within observation period) the patient did not have some (but had other) components of the regimen in his possession. OIA is the proportion of days (out of total regimen duration within observation period) the patient did not have any or did not have some (but had other) components of the regimen. Because a patient may have a drug in his

possession and not take it, our estimate provides a lower bound to actual intake. Actual OIA may indeed be higher than what is estimated but it cannot be lower.

ART medication errors may have serious long-term consequences, including the development of drug resistance, treatment failure, or death {27744}. Depending on the source of information, medication error rates related to ART regimens among hospitalized patients reported in the literature can go up to 72% {27744} {27768} {27745}.

Prescription errors are a major problem among medication errors, they account for 70% of medication errors that could potentially result in adverse events. Although rarely fatal, they can affect patients' safety and quality of healthcare {27745}. According to the definition presented by Aronson {27764}, a prescription error can be defined as "a failure in the prescription writing process that results in a wrong instruction about one or more of the normal features of a prescription." However, most of the studies published consider prescription errors as medication errors, which is a broader concept.

Neuner et al {27776} reported that medication errors with ART and opportunistic infections' drugs occur in 50% of admissions, with the majority of these errors (65%) not being recognized or resolved during the admission. In 2012, Yehia et al. {27744} found a total of 145 ART medication errors in 110 admissions on the first day (29%) and 22 errors in 21 admissions on the second day (7%). Pettit et al. {27768} also reported a significant association ($p < 0.001$) between medication errors and protease inhibitor drugs (PIs).

Most errors are caused by a lack of expertise with prescribing ART, failure to reconcile home or transfer medications, poor or no written or verbal communication between physicians, overlooking decision support software alerts and/or lack of ownership for HIV therapy when treating patients' primary problem {27744}. The correction of medication / prescription errors requires an intervention by the pharmacist and a discussion with the physician. In the Pettit et al. study, the majority of pharmacist interventions (68%) were related to dosage modification {27768}.

8. RESEARCH QUESTIONS AND OBJECTIVES

This study was designed to estimate the impact of each type of regimen (STR and non-STR) on adherence and prescription errors (sub-study) and to assess the impact of adherence on hospitalization and clinical and economic outcomes.

In order to do so, several research hypotheses were formulated:

1. that SA accounts for a non-negligible portion of OIA and that both SA and NA are clinically and economically relevant;

2. that STRs, as SA-free regimens, will improve adherence and generate clinical and economic benefits;

3. that STRs are, by nature, of value in avoiding prescription errors.

In this context, the aim of this international retrospective study is to evaluate the potential benefits of STR in enhancing adherence, and its clinical and economic consequences in the European context. The study also aims at quantifying prescription errors and identifying those that can be avoided by the use of STRs.

8.1. Primary Objective

To retrospectively evaluate the impact of STR on adherence (NA and OIA) in HIV-1 infected subjects. Adherence will be assessed through pharmacy registries (ART refill data), which is one of the possible ways to evaluate adherence rates to ART in HIV-infected subjects but is the only possibility considering the retrospective design of the study. Adjusting for baseline variables and other confounders will be performed.

8.2. Secondary Objectives

- To retrospectively assess the efficacy consequences of NA and OIA, after adjusting for baseline characteristics and other confounders, overall and by cohort, on the odds of becoming unsuppressed, in subjects with and without resistance development. The protocol definition of unsuppressed is: HIV RNA>50 copies/mL in two consecutive measures within regimen duration, occurring within the observation period; among patient-regimens with HIV RNA ≤50 copies/mL at the start of the regimen if the regimen started during the observation period, or at the start of the observation period if the regimen started before the observation period.

  In order to evaluate the odds of becoming unsuppressed (with or without resistance development), laboratory / monitoring data shall be collected.

- To retrospectively assess the effect of NA and OIA on the odds of hospitalization, after adjusting for baseline characteristics and other confounders, overall and by cohort.

In order to answer this objective, hospitalization data of all patient-regimens included in the study shall be collected.

To retrospectively assess the impact of NA and OIA on mean monthly ART plus hospitalization costs (Gross Domestic Product [GDP] Purchasing Power [PP] converted current prices), after adjusting for baseline characteristics and other confounders, overall and by cohort.

Ideally, hospitalization and ART costs will be collected at the center level. If not possible, hospitalization costs will be collected from publicly available national lists of diagnosis-related groups (DRGs) and ART costs from IMS databases of each participating country.

To assess the impact of STR versus non-STR on:

1. becoming unsuppressed (defined as above)
2. being hospitalized
3. costs (ART plus hospitalization costs)

To retrospectively quantify ART prescription errors during the first 48 hours of hospitalization of HIV-1 adult patients, overall and according to the cohort. Prescription errors will be evaluated by reviewing all prescriptions made during the first 48 hours of every hospitalization episode included. Investigators shall review all medication orders during this period to identify ART prescription errors. Errors will be classified as

1. Absence / incomplete regimen – when the regimen prescribed is incomplete (e.g. when the physician prescribes only one PI/r) or when the regimen is not prescribed although it should have been.
2. incorrect dosage (including renal dose adjustment) – when the dosage of a component/co-formulation of the regimen is not correct, i.e. the dosage prescribed does not exist
3. incorrect schedule – when the schedule mentioned by the physician is not adequate to the regimen prescribed
4. incorrect formulation – when the pharmaceutical form prescribed is not available
5. duplication of ART therapy
6. non-recommended drug-drug combinations (ART-ART and ART-non-ART), as suggested by Yehia et al. {27744, 22}. Non-recommended drug-drug combinations (between antiretroviral agents and/or antiretroviral agents and other drugs simultaneously) are available on the HIV Drug interaction website and are shown in red as contra-indicated:www.hiv-druginteractions.org/Interactions.aspx

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective non-interventional study that has two outcomes: adherence (the primary focus) and prescription errors (sub-study). While all centers will participate in the Adherence study, only centers where prescription data is available will be included in the Prescription errors sub-study. In order to do so, several research hypotheses were formulated:

that SA accounts for a non-negligible portion of OIA and that both SA and NA are clinically and economically relevant

that STRs, as SA-free regimens, will improve adherence, and generate clinical and economic benefits

that STRs are, by nature, of value in avoiding prescription errors.

According to these research hypotheses, study endpoints were established.

Primary endpoint:

Odds of attaining > 90% adherence in the STR cohort versus non-STR cohort, after adjusting for baseline variables and other confounders, with adherence measured by medication possession ratio based on pharmacy refills.

Secondary endpoints:

Adherence

Average OIA and NA levels, in the STR cohort versus non-STR cohort, after adjusting for baseline variables and other confounders, with adherence measured by medication possession ratio based on pharmacy refills.

Average OIA level, according to the number of pills in the regimen (1, 2-3, 4+), after adjusting for baseline variables and other confounders, with adherence measured by medication possession ratio based on pharmacy refills.

Clinical impact

Odds of becoming unsuppressed (HIV RNA >50 copies /mL in two consecutive measures within regimen duration occurring within the observation period) among subjects who had HIV RNA ≤50 copies/mL between 1st January 2009 and the start of the regimen (whichever is latest); in STR versus non-STR groups, after adjusting for baseline characteristics and other confounders, using laboratory/monitoring data;

Odds of becoming unsuppressed (defined as above) according to subject adherence level (NA and OIA), after adjusting for baseline characteristics and other confounders, using laboratory/monitoring data;

Odds of becoming unsuppressed (defined as above) with resistance development according to subject adherence (NA and OIA), after adjusting for baseline characteristics and other confounders, using laboratory/monitoring data (n.b. may not be feasible).

Hospitalization

Odds of being hospitalized in STR versus non-STR groups, after adjusting for baseline characteristics and other confounders, using monitoring (hospitalization) data;

Odds of being hospitalized according to subject adherence level (NA and OIA), after adjusting for baseline characteristics and other confounders, using monitoring (hospitalization) data.

Costs

Average monthly ART plus hospitalization costs, adherence (OIA) adjusted, in each STR versus non-STR groups at GDP Purchasing Power Parity (PPP) converted current prices, after adjusting for baseline characteristics and other confounders;

Monthly ART plus hospitalization costs according to subject adherence level (NA and OIA), adherence (OIA) adjusted at GDP PPP converted current prices, after adjusting for baseline characteristics and other confounders.

Ideally, hospitalization and ART costs will be collected at the center level. If not possible, hospitalization costs will be collected from publicly available national lists of DRGs and ART costs from IMS databases of each country.

Prescription errors audit

Number of prescription errors in ART orders in the first 48 hours of hospitalization, overall and according to the cohort. Errors will be classified as:

1. absence / incomplete regimen
2. incorrect dosage
3. incorrect schedule
4. incorrect formulation
5. duplication of ART therapy
6. non-recommended drug-drug combinations (ART-ART and ART-non-ART), as suggested by Yehia et al {27744} and available on the HIV drug interaction website shown in red as contra-indicated; www.hiv-druginteractions.org/Interactions.aspx.

In order to collect this information, all prescriptions made during the first 48 hours of every hospitalization of all patient-regimens included shall be reviewed.

Taking into consideration the endpoints defined, the investigators believe that the study will answer the research questions.

Since this is a retrospective study that will only use data from subjects' clinical files and from prescription / laboratory and pharmacy files, treatment decisions will have already taken place, according to local treatment guidelines and/or routine clinical practice, and will not be influenced by the protocol.

9.2. Population

The population being studied are HIV-1 infected adult patients on ART, recruited from centers in Italy, Portugal, Spain and UK by Investigators that have expertise in the management of HIV infection.

Adherence study

HIV-1 infected adults who received ART between 1st January 2009 and 31st December 2013 for at least 90 days.

Inclusion criteria:

- HIV-1 infected
- Aged 18 or above at the beginning of the observation period
- Able and willing to provide informed consent
- At least one pharmacy refill in 2013
- Being followed at the center at the time of recruitment
- Has been on an ART regimen recommended by EACS v 7.0 {27774}, which contains two NRTI plus one NNRTI **or** two NRTI plus one PI/r, or Stribild, and which was taken once daily for at least 90 days on 31st December 2013.
- Availability of a complete electronic history of pharmacy refills throughout the observation period.

Exclusion criteria:

- Subject participation in an interventional study during the observation period
- Subject on a non-pill formulation during the observation period
- Subject on off-ART periods (ART holidays) during the observation period.

Prescription errors sub-study:

Subjects enrolled in the sub-study do not need to be participating in the adherence study in order to be eligible.

Inclusion criteria:

- HIV-1 infected patients who were hospitalized, at least for a minimum of 48 hours between 1st January 2012 and 29th December 2013 and who received, or should have received, an ART regimen during the first 48 hours of the hospitalization episode;
- Aged 18 or above at the beginning of the hospitalization episode;
- Able and willing to provide informed consent
- Availability of complete history of medication (ART and non-ART) prescribed during the first 48 hours of the hospitalization episode.

Exclusion criteria:

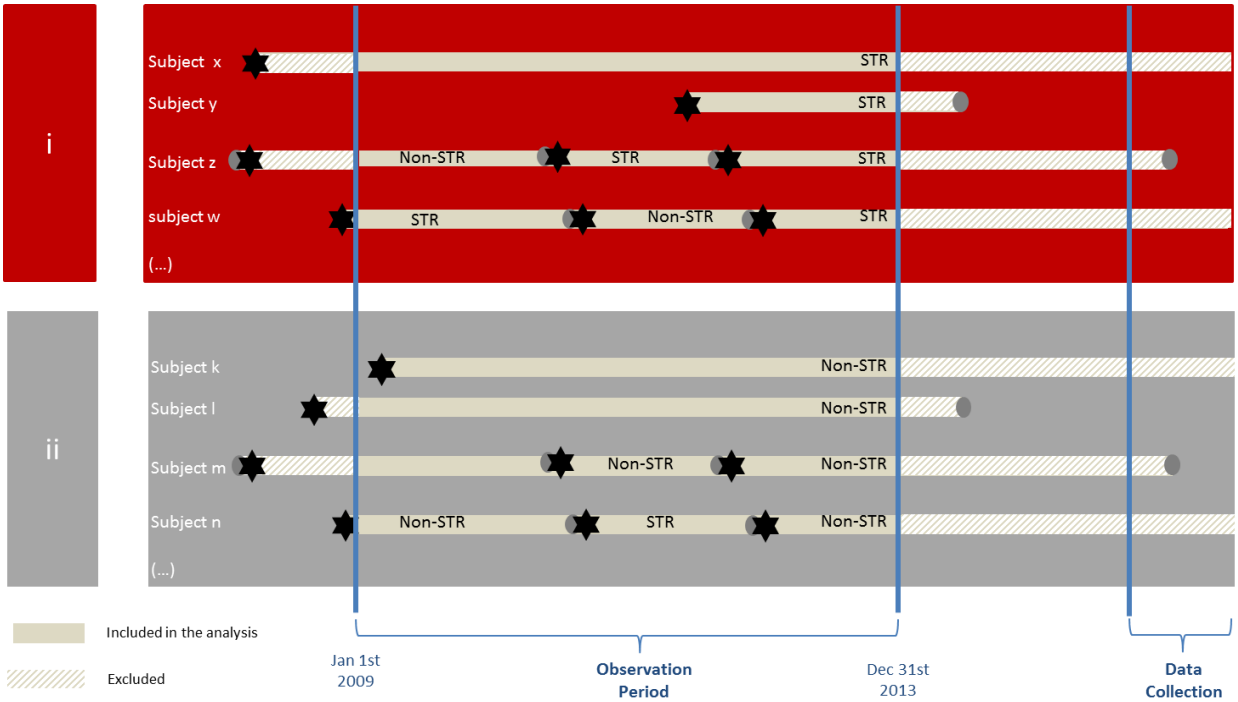
- Subject participation in an interventional study during the observation period

9.3. Subject Selection

Adherence study

For each included subject, data will be collected for all patient-regimens lasting for at least 90 days during the observation period, that either include Stribild or are EACS v7.0 recommended, once daily regimens containing two NRTI plus one NNRTI or two NRTI plus one PI/r. Two cohorts will be considered: (i) STR and (ii) non-STR (Figure 1).

Figure 1. Study Scheme of Adherence study.



Legend: ★ start of patient-regimen; ⬮ end of patient-regimen; i) STR; ii) non-STR.

STR and non-STR subjects are defined, for administrative purposes, according to the type of regimen they were receiving on 31st December 2013. Note that these STR and non-STR groups of subjects are defined only for subject selection purposes. Once subjects are selected, the

relevant unit of analysis is a patient-regimen and both matching and the statistical analysis will be performed at the patient-regimen level.

A single subject may contribute to the analysis with 1 or more patient-regimens. Moreover, a subject selected as part of the STR group (because he was on STR on 31st December 2013) may contribute in the analysis for both the STR and the non-STR group as the example of subject Z or W, in Figure 1 above.

Data will be collected on patient-regimens that were ongoing between 1st January 2009 and 31st December 2013, this is the observation period, and subjects must have had at least one pharmacy refill in 2013. All patient-regimens must have started before 30th September 2013 to ensure a minimum duration of at least 90 days, as determined in the inclusion criteria. Although patient-regimens may have been started before the beginning of the observation period and may still be in progress at the end of this period, for the purposes of this study, generally only data from the observation period shall be collected. The data collection period is the time during which the centers will enroll eligible subjects and enter the data onto the eCRF.

The patient-regimen selection for the adherence study will involve the following steps, to be initiated as soon as hospital approval has been granted at each site:

1. Search in Pharmacy's electronic records – the pharmacist will search the pharmacy electronic database in order to identify all patients who have at least one ART refill in 2013.

2. Separate these patients into two cohorts according to the regimen they were receiving on December 31st 2013 (STR cohort and non-STR cohort)

3. Perform center level random sampling – It is likely that the number of subjects identified above is higher than the number of subjects agreed in the present protocol (average of 80 subjects in the STR and 90 subjects in the non-STR cohort, per center). In such case, each investigational center will select a sample of subjects from their population, instead of including the entire population. Therefore, a sampling mechanism will be used. Participating subjects will be randomly selected from the list of subjects and stratification by cohort will be considered (stratified random sampling). In stratified random sampling, separate random samples will be selected from the two cohorts created (STR and non-STR). Each center will prepare two separate lists with subjects' unique identifiers (subject hospital number) for each cohort. The random samples will be obtained using Microsoft Excel®:

    - 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;

    - 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;

- Repeat the procedure for the other cohort.

In the STR cohort, priority will be given to non-Atripla subjects. As such, if a center has more than the number of pairs to be included, e.g. 80 subjects on Eviplera or Stribild, the methodology described above applies directly to the population of subjects on Eviplera or Stribild. If a center does not have any other STR except for Atripla, the methodology described above applies directly to the population of subjects on Atripla. If a center has less than 80 subjects on Eviplera or Stribild then these are included and the remaining will be selected using the methodology described above, from the population of Atripla subjects.

The non-STR cohort will be oversampled to a 1:1.15 ratio, so 90 subjects need to be selected.

The subjects to be selected are the first ones from each sorted list of the random numbers. For example, if 80 subjects are to be selected in the STR cohort, the top 80 in the list are to be included.

For the selected subjects, check Inclusion and Exclusion criteria. If one subject does not meet the criteria, replace that subject with the next on the list (subject 81 in the example above). Repeat as necessary replacing each subject which does not meet the criteria by the next in the list. The same procedure should be followed if a subject meets the criteria but does not sign the informed consent.

Note that subjects are being selected instead of patient-regimens, so it is not obvious how many patient-regimens will be included. Nonetheless, considering that an average of 1.5 regimens in a 5 year period is likely to occur, then the 700 STR subjects and the 805 non-STR subjects will yield more than enough patient-regimens to reach the required patient-regimen sample size.

A Propensity Score Matching (PSM) approach will be applied subsequently on the merged dataset from all sites in order to maximize homogeneity between cohorts and reduce the impact of treatment-selection bias. A variable ratio between cohorts will be considered, so that 700 STR subjects are selected as cases and 805 non-STR as controls. The propensity score is defined as a subject’s probability of receiving a specific treatment (STR) conditional on the observed covariates {27771}. When propensity scores are used in matching, treatment effects are unbiased when treatment assignment is strongly ignorable {27756}. On the other hand, treatment assignment is strongly ignorable if treatment cohorts and the outcome variable are conditionally independent given the covariates. This independence assumption will not hold in situations where there are variables not included as propensity score covariates that are correlated with outcome events and time dependent treatment selection {27757}.

The PSM procedure will include 4 steps:

1. Model choice: The propensity score will be computed using binary regression with a logit or a probit link function, depending on model fitting statistics. Statistical based criteria will be used to specify the covariates, such as the degree of association with STR odds.

2. Matching algorithm choice: The nearest neighbor algorithm or the nearest neighbor within a specified caliper distance algorithm will be used as a matching algorithm. The nearest neighbor matching selects for matching to a given STR subject the non-STR subject whose propensity score is closest to that of the STR subject. Nearest neighbor matching within a specified caliper distance is similar to nearest neighbor matching with the further restriction that the absolute difference in the propensity scores of matched subjects must be below some pre-specified threshold (the caliper distance) {27758} {27759}. The choice between one of these approaches will rely on how much data will be collected.

3. Sample balance diagnosis: Sample balance will be checked using the methods proposed by Ho et al. including standardized means, comparing higher-order moments, propensity-score summary statistics or empirical quantile-quantile plots for each variable {27772}.

4. Matching: Assign the matching membership and retain the propensity score for the case where further adjustment is needed.

Prescription errors sub-study

In this sub-study, unit of analysis will be a hospitalization episode of HIV-1 infected adult (due to any reason) in which there was a prescription of ART during the first 48 hours. Two cohorts will be considered: (i) STR and (ii) non-STR. Subjects will be enrolled that were hospitalised between 1st January 2012 and 29th December 2013.

For the prescription errors sub-study, subject selection will involve the following steps, to be initiated as soon as hospital approval has been granted at each site:

1. Search in the hospital registry to identify all hospitalization episodes of HIV-1 infected patients with admission date 1st January 2012 and 29th December 2013.

2. Check Inclusion criteria – once identified, the Investigator will check whether those hospitalization episodes meet the inclusion criteria.

3. Perform center level random sampling – It is likely that the number of eligible episodes identified above is higher than the number of episodes the center is willing to include. In such case, each investigational center will select a sample of 40 episodes from their population, instead of including the entire population. Therefore, a sampling mechanism will be used. Episodes to be included will be randomly selected from the list of eligible episodes and stratification by cohort will be considered (stratified random sampling). In stratified random sampling, separate random samples will be selected from the two

cohorts created (STR and non-STR). Two separate lists with episodes' unique identifiers for each cohort will be prepared. The random samples will be obtained using Microsoft Excel®:

- The list of episodes' 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 patient-regimens' identifiers by writing "=RAND()" in each cell and random numbers from 0 to 1 will appear;
- 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 episodes' identifiers will be obtained;
- Repeat the procedure for the other cohort.

The episodes to be selected are the first ones from each sorted list. As a guidance rule, even samples of episodes from each cohort should be obtained. Information of eligible hospitalization episodes shall be recorded on the eCRF.

9.4. Variables

Adherence study

After confirmation of eligibility criteria, investigators will collect the following data for each subject selected, based on clinical/pharmacy/prescription records. Each selected subject may have one or more valid patient-regimens. Data on all valid patient-regimens should be collected. A valid patient-regimen is defined in the Inclusion Criteria Section.

Table 2. Adherence study– Variables to be collected

Demographics	- Subject initials (where permissible) - Date of birth (where permissible) - Gender (male, female, transgender) - Race (White, Asian, Black or African heritage, other)
Baseline characteristics	- Most likely mode of HIV infection (injection drug user, heterosexual sex, homosexual sex, unknown, other) - Date of ART initiation - Number of virological failures (HIV RNA >50 copies/mL in two consecutive measures after HIV RNA <50 copies/mL has been achieved in that regimen) as of January 1st 2009 - HIV RNA (copies /mL) at ART initiation - CD4 count at ART initiation and CD4 nadir (if available)
Patient-regimen characteristics (characteristics to be evaluated at each	- Illegal drugs dependency with current consumption - Alcohol dependency with current consumption

valid regimen initiation) Note: For the purpose of evaluating these characteristics; if the regimen started after January 1st 2009, the day of initiation should be considered and if the regimen started before January 1st 2009, January 1st 2009 should be considered	- Smoker with current consumption - Current opioid substitution treatment (use of methadone, buprenorphine or buprenorphine/naloxone) - Mental disorder (present, controlled or uncontrolled) - AIDS status - Hepatitis C - Charlson comorbidity Index
Antiretroviral treatment prescription (for each valid patient-regimen)	- For each drug/co-formulation: scientific / generic name (which includes active principles, dosages and number of pills per day) - Date of discontinuation, if available
Laboratory parameters (all CD4 and HIV RNA tests performed during the observation period)	For each test: - Date of test - corresponding value
Resistance profile (all tests performed during the observation period)	For each test: - Date of test - Was the REGA 8.0 algorithm used? - Genotype Sensitivity Score (Susceptive, intermediate or resistant) for each drug
Inpatient care (all episodes performed in the observation period)	For each episode: - Date of admission - Admission diagnosis - Date of discharge - Destination at discharge - Event code (DRG) - ICD-9 or ICD-10 code (primary and secondary) - Total cost of hospitalisation, including medications
Antiretroviral treatment pharmacy refills (for each valid patient-regimen)	For each drug of each regimen: - Date of refill (dd/mm/yyyy) - scientific / generic name (which includes active principles, dosages, pharmaceutical forms), - Quantity dispensed
Adverse Drug Reactions	For each episode - Adverse Drug Reaction description - Seriousness - Start and End dates or ongoing - Relation to Gilead drug
Pregnancy (if applicable)	- Last menstrual period - Date of pregnancy confirmation - Estimated date of delivery or outcome if available at the time of the review

Prescription errors sub-study

After confirmation of eligibility criteria, investigators will collect the following data for each hospitalization episode selected, based on clinical/pharmacy/prescription records:

Table 3. Prescription errors sub-study- variables to be collected

Individual characteristics (at the beginning of each hospitalization episode)	- Subject initials (where permissible) - Date of birth - Gender (male, female, transgender) - Race (White, Asian, Black or African heritage, other) - Non ART concomitant medications
Inpatient care (for each hospitalization episode)	- Date of admission - Admission diagnosis - Date of discharge - Discharge diagnosis - Destination at discharge - ICD-9 or ICD-10 code (primary and secondary) - DRG code Admitting service: HIV/AIDS, Medicine, Surgery, Obstetrics and Gynaecology, Neurology / Psychiatry, Other - Degree of the prescribing physician: Assistant / Junior doctor, Graduated Assistant / Registrar, Senior Graduated Assistant / Consultant, Other - Transferred within the first 48 hours? If so where to and when? - ART prescribed in the first 48 hours: active substances, dosage of each, scheduling

Prescription errors audit (for each error)	- Type of error:
	  - (1) absence / incomplete regimen
	  - (2) incorrect dosage [including renal dose adjustment]
	  - (3) incorrect schedule
	  - (4) incorrect formulation
	  - (5) duplication of ART therapy
	  - (6) non-recommended drug-drug combinations (ART-ART and ART-non-ART)
	- Drug-drug interactions will be evaluated according to the HIV drug-drug interaction website and are shown in red as contra-indicated;
	  (www.hiv-druginteractions.org/Interactions.aspx)
	- Was the error resolved?

Adverse Drug Reactions	For each episode - Adverse Drug Reactions description - Seriousness - Start and End dates or ongoing - Relation to Gilead drug
Pregnancy (if applicable)	- Last menstrual period - Date of pregnancy confirmation

	- Estimated date of delivery or outcome if available at the time of the review

9.5. Data Sources

Sources to be analyzed for data collection include subject's clinical files and prescription / laboratory / pharmacy files and accounting data.

Centers participating in the Adherence study have to have the complete history (within the observation period) of pharmacy refills available electronically.

For centers participating in the Prescription errors sub-study, registration of ART errors, in either paper or electronic format, is required.

9.6. Study Size

Adherence study

The sample size needed to achieve a power of 80% for detecting a difference of 0.02 in the proportion of patients with adherence > 90% (adherent patients) between the two cohorts, with a two sided test with a significance level of 0.05, was determined using the methodology proposed by Sahai and Khurshid {27760}. The number of discordant pairs (the ones with more than 90% adherence in only one of the 2 cohorts) was estimated using data reported in Airoldi et al.{16102}. In this study patients in a non-STR regimen had an average adherence rate of 97% and after changing to an STR regimen a rate of 98%. Assuming the reported standard deviation of 11%, a 0.74 and 0.77 proportion of adherent patients was estimated for non-STR and STR regimens, respectively, which represent the marginal probabilities of adherence. Therefore, if one assumes that patients who adhere to non-STR also adhere to the STR regimen, the probability of adherence to STR conditional to non-adherence to non-STR is 0.02. In order to be less conservative, it was assumed a probability of 0.01 of being adherent to non-STR and non-adherent to STR.

Since a multivariate analysis will be performed, the suggestion by Katz {27773} of adding 10 observations per covariate included in the logistic regression was considered. A potential 20% loss of patient-regimens due to missing values on covariates was considered, as well as an inclusion of 10 covariates in the logistic regression model. In addition a 15% oversampling on the non-STR cohort was considered to enable a final sample size, post PSM, of 1030 pairs of patient-regimens. Hence 700 subjects will need to be included in the STR cohort and 805 subjects will need to be included in the non-STR cohort.

A preliminary evaluation of the availability of the centers to collect data was performed. Taking into account this information, an average of 80 subjects in the STR cohort and 90 subjects in the non-STR cohort, will be needed per center to achieve the power considered in the sample size determination presented above. It is possible that some centers will have less than 80 subjects to include in the STR cohort. In those cases, data from all these subjects should be collected and

other centers may include more than 80 subjects to ensure the overall 2060 patient-regimens sample size is reached.

Prescription errors sub-study

Due to the nature of the study design, a formal sample size determination was not performed. Each center will collect data on approximately 40 hospitalization episodes randomly selected as described in the 'Setting' section.

9.7. Data Management

For each subject enrolled, investigators will record the data (collected from subject's clinical files and prescription / laboratory / pharmacy files) 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 eCRF.

Investigators should 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, and pharmacy refill and prescription errors information.

All data will be kept anonymous during this process.

A Data Management Unit will be responsible for designing and validating the web-based eCRFs. 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 a Statistics Unit in order to perform the statistical analysis and report.

9.8. Data Analysis

The following general approach will be used:

for qualitative data - absolute and relative frequencies will be used. 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 used.

Missing data will not be imputed.

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%.

The statistical analysis will account for the panel structure of the data.

Adherence study

Appropriate methods to deal with paired samples will be used. Suitable methods are Generalized Linear Mixed Models (GLMM), such as the Linear Mixed Model (for continuous outcomes, such as ART plus hospitalization costs), Poisson Mixed Model (for count outcomes, such as the number of days covered by treatment) or Logistic Mixed Model (for binary outcomes, such as the proportion of subjects with > 90% adherence). These models might be used as well when analyzing panel data. Other options might be to use Marginal Models (MM) which rely on Generalized Estimation Equations (GEE) for parameter estimation {27761} {27762}.

In order to reduce bias in treatment effect estimation, a propensity score will be obtained and covariate adjustment using the propensity score will be performed. In other words, the propensity score as well as the variable denoting the ART class will be entered in the appropriate regression model (for instance, binary logistic regression).

Prescription errors sub-study

The number of errors will be modeled with Generalized Linear Models (GLM). If significant correlation between hospitalizations from the same subject/hospital is found, then appropriate methods to address such data structure will be used. Suitable methods are GLMM and MM.

9.9. Quality Control

Prior to study start, investigators are 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, investigators must inform Gilead immediately about this request. It is important that investigators and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. Investigators and institutions will allow the appropriate regulatory authorities direct access to source documents to perform this verification.

9.10. Limitations of the Research Methods

This study has the characteristic disadvantages of retrospective studies, namely, selection bias, information bias, and other confounding variables.

In order to reduce selection bias, subject's eligibility criteria have been well defined, however this is not a type of bias easy to prevent and measure.

Additionally, a propensity score approach (matching or regression) will be considered to balance the covariates in the four cohorts and therefore to reduce the impact of treatment selection bias.

Due to lack of matching procedure, the sub study is subject to selection bias. Information bias can be prevented by using standard measurement instruments, like eCRF. However this study will have a source of information biases related to the possible lack of registry of some data that is impossible to be prevented or reduced.

9.11. Other Aspects

9.11.1. Joint Investigator/Sponsor Responsibilities

9.11.1.1. Access to Information for Monitoring

The study monitor is responsible for review of a sample of the eCRFs at set intervals throughout the study to verify adherence to the protocol and the completeness of the data being entered on the forms. The investigator will provide the study monitor with access to any subject records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.11.1.2. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The investigator will ensure that this study is conducted in accordance with the principles of the International Conference on Harmonization (ICH) Pharmacovigilance Planning E2E guidelines, and with the laws and regulations of the country in which the research is conducted.

The investigator will conduct this study in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. Independent Ethics Committee (IEC) Review

The sponsor will submit this protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study subject activities until approval from the IEC has been documented and provided as a letter to the investigator.

Any subsequent modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC approval will also be submitted for IEC approval prior to use.

10.3. Informed Consent

The need for subject's informed consent for retrospective non-experimental studies depends on each country's legislation however, as monitoring of patient records will be performed by Gilead's representative, consent for participation in the study should be obtained.

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 prior to study participation and before commencing with any study-related activities. The investigator must utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements.

10.4. Confidentiality

The data collected under this study will be treated in compliance with each country law for personal data protection.

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only a unique identifier (as allowed by local law) and a unique study identification code should be recorded on any study-related document.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, eCRFs, and any other study information, remain the sole and exclusive property of Gilead 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. 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.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

11.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, 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 lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in a clinical study are also considered AEs.

As this is a retrospective, non-interventional study not all medical events noted in the subject's medical records will be collected. However, where recorded in the subject's medical notes, adverse events that occur during the period under review and that are associated with a Gilead drug will be captured. These are known as adverse drug reactions, as defined in section 11.1.1

11.1.1. Adverse Drug Reactions

An **adverse drug reaction** (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved 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.

11.1.2. Serious Adverse Events

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

Death

Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

In-patient hospitalization or prolongation of existing hospitalization

Persistent or significant disability/incapacity

A congenital anomaly/birth defect

A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be

exercised to determine whether such an event is a reportable under expedited reporting rules. 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; and 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.

A Serious Adverse Drug Reaction (SADR) is an Adverse Drug Reaction that meets the criteria for being serious as detailed above.

In this study we are only collecting adverse drug reactions and serious adverse drug reactions that occur during the period under review and that are associated with a Gilead drug.

Clarification of Serious Adverse Events

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

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation that are deemed to be related to a Gilead drug must be recorded as an ADR (both serious and non-serious, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms and related to a Gilead drug must also be recorded as an ADR (both serious and non-serious) if they meet the definitions as described in Sections 11.1.1 and 11.1.2**.** If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub investigator is responsible for final review and confirmation of accuracy of event information and assessments. Only ADRs and SADRs will be collected from the medical records. Events that the investigator considers to be related to a Gilead drug and that occur during the period of review should be recorded on the eCRF.

11.2.1. Assessment of Causality for Study Drugs

Since this is a retrospective study the investigator should note the relationship to a Gilead product as documented in the subject's medical notes. In general, the assessment of the relationship to drug therapy is based in the following considerations:

No: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, concomitant medication).

Yes: There is a reasonable possibility that the event may have been caused by the medicinal product.

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

11.3. Special Situations Reports

11.3.1. Definitions of Special Situations

Special situation reports include reports of pregnancy; medication error, abuse, misuse, or overdose; lack of effect; adverse reactions in infants following exposure from breastfeeding; and adverse reactions associated with product complaints and occupational exposure. A pregnancy report is used to report any pregnancy that occurred during the period under review.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject 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). Overdose cannot be established

when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product labelling.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

11.3.2. Instructions for Reporting Special Situations

11.3.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur during the period under review and the outcome of the pregnancy where recorded in the medical notes are to be reported to Gilead DSPH using the Pregnancy Report Form once they have been identified in the subject's medical record.

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 (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) where reported in the medical notes must be reported as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 11.4.

The outcome, where available, should be reported to Gilead DSPH using the Pregnancy Outcome Report Form.

11.3.2.2. Reporting Other Special Situations

All other special situation events that are captured in the medical notes of the subject during the period under review must be reported on the Gilead Non-Interventional Study Special Situation Report Form (appendix 1) and forwarded to Gilead DSPH within 24 hours of knowledge of the event. These reports must consist of situations that involve Eviplera, Stribild or Atripla and any other Gilead medication, but do not apply to non-Gilead medications.

11.4. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

All SADRs associated with Eviplera, Stribild or Atripla, or any other Gilead drugs, that occur during the period under review, will be recorded on the Gilead Non-Interventional Study

AE/SAE Study Report Form (appendix 1) and will be reported to Gilead DSPH within 24 hours of knowledge of the event. ADRs associated with Eviplera, Stribild or Atripla, or any other Gilead drugs, that occur during the period under review, will be recorded on the eCRF only.

SADR/SSR reports should be forwarded to the Gilead DSPH email address or fax below:

DSPH Representative: Fax: +1 650-522-5477
E-mail: Safety_FC@gilead.com

11.5. Investigator and Sponsor Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all AEs and SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs), and special situation reports (SSRs) as determined by country-specific legislation or regulations where the study is conducted and other applicable countries. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for AEs, SAEs and SSRs will be determined by Gilead using reference safety information specified in the relevant local label.

12. RESPONSIBILITIES / PLANS FOR DISSEMINATING STUDY RESULTS

12.1. Investigator Responsibilities

12.1.1. 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. 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, IEC 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.

12.1.2. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures described in this protocol.

12.2. Sponsor Responsibilities

12.2.1. Protocol Modifications

Protocol modifications may be made only by Gilead. The sponsor must submit all protocol modifications to the IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

12.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII. Note that an abbreviated report may be prepared in certain cases. The final CSR will be submitted within 12 months of study completion.

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to

withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

Gilead shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

12.3. Joint Investigator/Sponsor Responsibilities

12.3.1. Access to Information for Monitoring

The investigators will provide the study monitors with access to any subject records needed to verify the entries on the eCRFs.

12.3.2. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and IECs.

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14. APPENDICES

Appendix 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	GF-21043J	[DD Month YYYY]	Non-Interventional Study AE/SAE Study Report form
2	GF-21043K	[DD Month YYYY]	Non-Interventional Study Special Situations Report form

Appendix 2. Study Acknowledgement

GILEAD SCIENCES INTERNATIONAL LIMITED
FLOWERS BUILDING, GRANTA PARK
ABINGTON, CAMBRIDGE
CB21 6GT, UK.

Impact of single tablet regimens on adherence and prescription errors – how big an issue and how relevant in both clinical and economic terms
FINAL, 16th May 2014

This protocol has been approved by Gilead Sciences International Limited. The following signatures document this approval.

Geraldine Reilly	
Gilead Study Director Author	Signature
19th May 2014	
Date	
Dr Anne–Ruth van Troostenburg de Bruyn	
Gilead EU QPPV	Signature
19th May 2014	
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number