Johnson & Johnson Pharmaceutical Research & Development*

Epidemiology Study Protocol

Observational Cohort Study Including a Nested Case-Control Study to Assess Rilpivirine (RPV) Utilization According to the European SmPC

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NOTE

The outline of this template is consistent with the Guidelines for Good Pharmacoepidemiology Practices (GPP) and The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

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SYNOPSIS

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a baseline viral load ≤ 100,000 HIV-1 ribonucleic acid (RNA) copies/mL. RPV will be available as two formulations on the European market: a single agent, marketed by Janssen-Cilag International NV, and a fixed-dose combination containing emtricitabine (FTC)/RPV/tenofovir disoproxil fumarate (TDF) marketed by Gilead Sciences International Ltd.

The CHMP has requested further assessment of the development of resistance and whether RPV is used in accordance with the Summary of Product Characteristics (SmPC).

The development of resistance and the utilization of RPV-containing products according to the products' SmPC will be assessed through a drug utilization study (DUS) conducted in HIV observational cohorts within Europe. Additionally, the DUS will provide context to the observed rates of virologic failure and development of resistance for patients initiating RPV treatment by describing the treatment outcomes of patients initiating efavirenz (EFV). The relative risk of virologic failure and resistant-associated mutations (RAMs) after initiating RPV-containing regimens will be estimated separately by comparing the incidence rates of virologic failure and RAMs among RPV-treated patients to the incidence of virologic failure and RAMs among EFV-treated patients. For all study objectives, frequency and rates will be reported for the RPV and EFV-treated groups separately, as well as for RPV relative to EFV.

The objectives of the DUS are to describe the following in the context of routine clinical practice:

Primary objectives:

- To describe the proportion of patients treated with RPV in accordance with the SmPC
  The proportion of patients treated with RPV in accordance with the SmPC will be described by estimating a proportion separately for each recommendation of patient treatment. The denominator for each proportion will consist of the number of all patients initiating RPV-containing regimens included in the study. Proportions will be estimated separately using the following numerators:
    - The number of patients naïve to HIV treatment regimens
    - The number of patients with documented pre-treatment screening for ARV RAMs
    - The number of patients initiating RPV-containing regimens with a baseline viral load ≤ 100,000 HIV-1 ribonucleic acid (RNA) copies/mL
- To describe treatment emergent RAMs in patients treated with RPV or EFV-containing regimens
- To describe virologic failure in patients treated with RPV or EFV-containing regimens

Secondary objectives:

- To describe the demographic characteristics, comorbidities, and medical condition of patients initiating RPV or EFV treatment
- To describe antiretroviral (ARV) treatment status (naïve/experienced) of patients prior to initiating RPV or EFV treatment
- To describe prior use of ARV treatment, if any, of patients initiating RPV or EFV-containing regimens
- To describe the frequency of pre-treatment RAMs for RPV and EFV among patients subsequently initiating RPV or EFV treatment respectively
- To describe viral load at start of RPV or EFV treatment
- To describe viral load over the course of RPV or EFV treatment

Observational Cohort Study Including a Nested Case-Control Study to Assess Rilpivirine (RPV) Utilization According to the European SmPC

- To describe HIV-treatment regimens and concomitant medications of patients initiating RPV or EFV-containing regimens
- To describe changes in HIV treatment and concomitant medication over the course of RPV and EFV treatment
- To describe reasons for switch of ARV treatment
- To describe adverse events over the course of RPV or EFV treatment

A DUS of HIV-positive patients captured in existing European cohorts initiating RPV treatment will be used to meet the study objectives. HIV cohorts provide detailed longitudinal information on patient demographics, HIV treatment regimens, treatment status (naïve/experienced), duration of therapy, clinical events, reason for discontinuation of HIV treatment, and adverse events. HIV cohorts included in the study will be determined by a feasibility assessment to evaluate the granularity of assessment of HIV resistance and variables needed to assess the use of RPV-containing products in accordance with the products' SmPC.

Additionally, a comparator cohort of EFV-treated patients will be included to provide contemporary context to utilization and outcomes observed within the RPV-treated group. The EFV treatment group will further elucidate which patient characteristics are more likely to influence health-care providers to channel patients to EFV or RPV containing regimens. Additionally, the EFV-treatment group will provide a better understanding of the observed rates of virologic failure, resistance patterns, and prescribing factors observed within the RPV-treatment group.

The DUS will identify a minimum of 600 patients newly initiating RPV-containing regimens and 600 patients newly initiating EFV-containing regimens and captured in one or more of the HIV cohorts currently established in Europe. Exposure to RPV-containing regimens will be measured by the presence of prescription records for the fixed dose combination (FDC) of RPV with emtricitabine/tenofovir (TRUVADA TM (Gilead)) or single agent tablets of RPV among the patient data. Exposure to EFV will be measured by the prescription records for the available formulations of EFV in patient data. Information on drug use, including dispensing date, dose prescribed, quantity dispensed and the length of drug supply, will also be captured from the prescription records in the cohort database. The sample size targets will produce an error rate of no more than 5% for the proportions estimated. A minimum of 600 RPV-treated patients will be included in the DUS to assess the proportion of appropriate use of RPV-containing regimens. The study period will start at the date of market availability of RPV-containing products in the participating counties and will end when in total 600 patients from each treatment group have been included in the study and followed for 12 months, until virologic failure, or lost to follow-up, whichever occurs first.

An evaluation of appropriate use will be conducted through an analysis describing and summarizing the prescribing patterns and use of RPV-containing products. The prescriptions will be summarized by patient demographics (age, sex, geography) and clinical characteristics (comorbidities and concomitant medications). In addition, the details of RPV-containing regimens use patterns will be described, including duration of use, persistence of therapy, and usage of other HIV treatments. This analysis will describe and summarize the utilization patterns of RPV-containing regimens with respect to viral load, CD4 counts, pre-treatment resistance testing, HIV treatment status (naïve/experienced), prior HIV treatment regimens, concomitant medications, and comorbidities. The analysis will ascertain the number of patients initiating treatment with RPV-containing regimens and the proportion of patients treated in accordance with the RPV SmPC. Proper prescribing will be summarized by patient demographics and potential confounders. Incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance will be calculated for the RPV and EFV-treated patients, separately. The three primary event rates of interest (incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance) will be analyzed in 3 separate sets of analyses. Additional descriptive analyses will include incidence rates for each drug calculated by dividing the number of events by the total person-exposure time and expressed as the number of events per person-year, and 95% confidence intervals.

Relative risks comparing the RPV-containing regimens with EFV-containing regimens and 95% confidence intervals will be calculated and appropriate stratified analyses will be conducted for virologic failure and emergence of treatment resistance. Poisson regression models will be used to adjust for the appropriate

factors that influence the risk of virologic failure and treatment-emergent resistance. Adjustments for imbalances between the treatment groups before receiving the first dose of RPV or EFV-containing regimens will be applied using accepted methods based on sample size availability and the observed overlap of key patient characteristics based on propensity score construction.

Given the recognized limitations of assessing food intake and treatment adherence in large observational studies conducted over several months, the feasibility of collecting food intake and treatment adherence data within the cohorts will be further explored. Currently, the HIV cohorts do not routinely collect data on ARV treatment adherence or pill intake with food. Optimally, HIV cohort data collection protocols will be modified for all RPV-treated patients to facilitate data collection on both ARV treatment adherence and pill intake with food at each patient visit. Under this scenario these measures will be added to the analysis described above. A nested case-control study will be conducted to address the CHMP's concerns on the effects of food intake on virologic failure among patient treated with RPV, while also evaluating ARV treatment adherence. The objective of the nested case-control analysis is to quantify the risk of virologic failure associated with adherence to ARV treatment and dietary instructions. Patients who experience virologic failure while under observation in the DUS will be selected into the study as cases. Patients who do not experience virologic failure while under observation and have similar experience with known confounders for virologic failure will be matched to cases using the incidence-density sampling method. This subgroup of patients from the DUS will be contacted and have their ARV treatment adherence and pill intake with food assessed through a one-time questionnaire assessing both adherence parameters over the past seven days. The methodology for the nested case-control study is provided in parallel with the DUS in this protocol.

ABBREVIATIONS

AACTG	Adult AIDS Clinical Trials Group
ARCA	Antiretroviral Resistance Cohort Analysis database
ARV	antiretroviral
BMI	body mass index
CHIC	Collaborative HIV cohort
CHMP	The Committee for Medicinal Products for Human Use
CI	confidence interval
CoRIS	Cohort of Spanish AIDS Research Network
DUS	Drug Utilization Study
EFV	efavirenz
FDC	Fixed dose combination
FTC	emtricitabine
FHDH	French Hospital Database on HIV
GPP	Good Pharmacoepidemiology Practice
HAART	highly active antiretroviral therapy
HIV-1	human immunodeficiency virus type 1
IRB	Institutional Review Board
J&JPRD	Johnson & Johnson Pharmaceutical Research and Development LLC.
MAR	missing at random
MCAR	missing completely at random
MNAR	missing not at random
M-PEMS	Modified Prescription Event Monitoring Study
NNRTI	non-nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OR	Odds ratio
PI	protease inhibitor
PSUR	Periodic Safety Update Report
RAM	resistance associated mutation
RMP	Risk Management Plan
RNA	ribonucleic acid
RPV	rilpivirine
SD	standard deviation
SERAD	Self-Reported Adherence
SHCS	Swiss HIV Cohort Study
SHCS-AQ	Swiss HIV Cohort Study Adherence Questionnaire
SMAQ	simplified medication adherence questionnaire
SmPC	Summary of Product Characteristics
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
TDF	tenofovir disoproxil fumarate
TDR	transmitted drug resistance
VAS	visual analog scale

1. INTRODUCTION

1.1. Background

Rilpivirine (RPV) is an NNRTI for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL. RPV will be available as two formulations on the European market: a single agent, marketed by Janssen-Cilag International NV, and a fixed-dose combination containing FTC/RPV/TDF, marketed by Gilead Sciences International Ltd. The CHMP has requested further assessment of the development of resistance and whether the product is used in accordance with the Summary of Product Characteristics (SmPC). The development of resistance and the utilization of RPV according to the SmPC will be assessed through a drug utilization study (DUS) conducted in HIV observational cohorts within Europe. Additionally, the DUS will provide context to the observed rates of virologic failure and development of resistance by describing the treatment outcomes of patients treated with efavirenz (EFV). The relative risk of virologic failure and resistant-associated mutations (RAMs) after initiating RPV-containing regimens will be estimated separately by comparing the incidence rates of virologic failure and RAMs among RPV-treated patients to the incidence of virologic failure and RAMs among EFV-treated patients.

Several factors have been shown to be associated with virological response to antiretrovirals (ARV) for the treatment of HIV-1, including the degree of immunodeficiency and level of plasma HIV RNA when therapy is initiated, antiretroviral experience, drug resistance, and type of and adherence to the therapeutic regimen (Hull, 2009).

Virological response to highly active antiretroviral therapy (HAART) regimens has been evaluated among patients enrolled in large, observational HIV cohorts. These studies have included evaluations of NNRTI and protease inhibitor (PI)-containing regimens (Paredes, 2000; Cozzi-Lepri, 2002) as well as short term and long term virological response when treated with NNRTI or PI-based HAART regimens (Mocroft, 2006). A few cohort studies have specifically examined virological failure among patients initiating nevirapine (NVP)-containing regimens or EFV-containing regimens. Phillips and colleagues conducted a study among 2203 patients in EuroSIDA who began a regimen with nevirapine or efavirenz after July 1997 (Phillips, 2001). A total of 1325 patients initiated NVP and 878 EFV. During a median of 8 months follow-up, 669 patients experienced virological failure giving an overall rate of 0.48 per year (0.83 per year if excluding those in first 6 months of follow-up who had baseline viral load >500

copies/ml). A total of 505 people on a NVP regimen experienced virological failure compared with 164 people on an EFV regimen, giving incidence rates of 0.55 per person-year and 0.35, respectively. A more recent EuroSIDA analysis examined virological outcome and drug resistance in 759 patients starting NNRTI-containing regimens (Bannister, 2008). A total of 287 (78.3%) of the 389 NVP patients and 168 (45.4%) of the 370 EFV patients experienced virological failure. NNRTI-resistant HIV was detected in 3% of patients at baseline. Out of the 131 patients still on an NNRTI and with resistance test results available at time of virological failure, NNRTI resistance was detected in 86% of patients and was similar between groups. The high levels of NNRTI resistance suggest that these drugs fostered selection pressure, and that patients had actually adhered to their regimens.

Several large HIV cohort databases have investigated the prevalence of transmitted drug resistance (TDR). Among 525 chronically infected treatment-naïve patients in the EuroSIDA cohort, the overall prevalence of TDR was 11.4% from 1996-2004 (Bannister, 2008). In the German HIV-1 Seroconverter cohort of 1276 patients, the overall prevalence of TDR was 12.4% from 1997 through 2007. NRTI associated resistance was identified most frequently (6.3%), followed by NNRTI resistance (2.4%) and PI resistance (2.1%) (Bartmeyer, 2010). In the Swiss HIV cohort of 822 newly infected patients identified from 1996-2005, the overall prevalence of TDR was 7.7% for any ARV drug, 5.5% for NRTIs, 1.9% for NNRTIs, and 2.7% for PIs (Yerly, 2007). A recent investigation by the UK Collaborative Group in HIV drug resistance reported a decline in the rate of TDR in treatment-naïve recently and chronically infected patients from around 14% in 2001-2002 to around 8% by the end of 2004 (Dunn, 2007).

The level of adherence to antiretroviral therapy (ART) is one of the critical factors in achieving viral suppression, avoiding viral rebound, increasing CD4 cell counts, and minimizing the risk of development of AIDS-defined illnesses that may result in death among HIV-infected patients on ART (Cambiano, 2010). Patient self-reports via questionnaires or interviews is the most frequently used measure of treatment adherence to HAART. More quantitative measures exists, such as electronic monitoring devices, pill counts, and pharmacy prescription refill monitoring; however use of these methods is limited by high cost, labor intensity, and other issues (Nieuwkerk and Oort, 2005). Self-report questionnaires that have been used in the clinical setting and validated include the simplified medication adherence questionnaire (SMAQ), the visual analog scale (VAS), the Adult AIDS Clinical Trials Group (AACTG) questionnaire, and the Self-Reported Adherence (SERAD) (Deschamps, 2008). While self-reports offer significant correlation

with viral load, this measurement method tends to underestimate nonadherence. An adherence questionnaire (SHCS-AQ) was introduced into follow-up of the Swiss HIV Cohort Study (SHCS) in July 2003 to assess overall doses missed and drug holidays over the past 4 weeks. The SHCS-AQ has been validated in a small study that compared the European HIV treatment questionnaire, a visual analog scale, and electronic monitoring. Using virological failure as the gold standard, the SHCS adherence questionnaire in the validation study performed slightly better than either electronic monitoring or a combination of the SHCS-AQ and a VAS with a sensitivity of 88% and a specificity of 79% (Deschamps, 2008). Despite its importance, there are no readily available measures of treatment adherence beyond notes of issues with treatment adherence given as the reason for treatment failure ordinarily used in routine clinical practice, nor are there methods available for comparison of adherence levels across large patient populations captured in the multiple HIV cohorts.

Patient adherence to food requirements also affects optimal bioavailability of the RPV regimen and is a component of adherence to the SmPC. The Sponsor have evaluated methods of adherence measurements of dietary intake (weighing and measuring of food, 24-hour recall, and food diaries) considered to have reliable face validity, content validity, construct validity, and reliability (Vitolins, 2000). Assessment of patient adherence to the RPV-containing products' SmPC would require careful measurement that is not practical within large observational studies such as modified prescription event monitoring studies (M-PEMS) or DUS. Traditionally, clinical studies designed to measure dietary adherence have involved weighing and measuring all food and drinks consumed. Such labor-intensive methods are impractical within an M-PEMS or DUS due to both frequency of the required measures and length of follow up proposed in the studies. Another method for measuring dietary adherence is 24-hour recall, where patients are asked to recall food intake during the previous day. Interviews are typically conducted by trained interviewers or nutritionists. Although this method is less complex than weighing and measuring it is not practical for measuring dietary adherence in large groups included in M-PEMS or DUS due to the high variability of diet day to day and the required frequency of patient interviews. Dietary records or food diaries are also used to measure food adherence. These are detailed records of the types and quantities of food and beverages consumed during a specified period. The specified period is usually 3-7 days. This method puts considerable burden on the patient, particularly over the anticipated course of rilpivirine therapy, and is not practical within an M-PEMS or DUS.

Given the recognized limitations of assessing food intake and treatment adherence in large observational studies conducted over several months, the feasibility of collecting food intake and treatment adherence data within the cohorts will be further explored. Options to be explored will include using one of the accepted methods of measuring ARV treatment adherence and pill intake with food in a smaller sample of patients within the HIV cohorts.

In summary, a DUS (using data from multiple existing HIV cohorts in Europe) will be conducted in order to address the CHMP concerns on the potential for development of virologic resistance and potential for improper prescribing or use (according to the SmPC). HIV cohorts have a demonstrated history of assessing virologic failure, RAMs, and associated risk factors. This DUS will provide significant real-world data on (amongst other parameters) ARV drug resistance, frequency of resistance testing, viral load at the start of treatment, prior use of ARV treatment, reasons for switch of ARV treatment, adverse events, concomitant medications and comorbidities. Currently, the HIV cohorts do not routinely collect data on ARV pill adherence or pill intake with food. The feasibility of collecting data on ARV treatment adherence and pill intake with food within the HIV cohorts for each patient at each visit will be assessed. Additionally, a nested case-control study will be conducted to assess the effects of ARV treatment adherence and pill intake with food on the risk of virologic failure with RPV will be assessed. As the nested case-control analysis will assess a smaller sample of RPV-treated patients that have already been identified as part of the DUS, details on the study design are included in this protocol.

1.2. Overall Rationale for the Study

The CHMP has requested an assessment of the use of RPV-containing products by prescribers as well as patients in accordance with the SmPC. The development of resistance and the utilization of RPV-containing products according to the products' SmPC will be assessed through a drug utilization study (DUS) conducted in HIV observational cohorts within Europe. HIV cohorts included in the study will be determined by a feasibility assessment to evaluate the granularity of collection of HIV resistance data and of the variables necessary to assess the proper use of RPV in accordance with the products' SmPC.

1.3. STUDY OBJECTIVES

1.3.1. Primary Objectives:

The primary objectives were specifically chosen to meet the CHMP request to assess appropriate use of RPV-containing products. For all primary objectives, frequency and rates will be reported separately for the RPV and EFV-treated groups.

- To describe the proportion of patients treated with RPV-containing products in accordance with the SmPC. The proportion of patients treated with RPV in accordance with the SmPC will be described by estimating a proportion separately for each recommendation of patient treatment. The denominator for each proportion will consist of the number of all patients initiating RPV-containing regimens included in the study. Proportions will be estimated separately using the following numerators:
    - The number of patients naïve to HIV treatment regimens
    - The number of patients with documented pre-treatment screening for ARV RAMs
    - The number of patients initiating RPV-containing regimens with a baseline viral load ≤ 100,000 HIV-1 ribonucleic acid (RNA) copies/mL
- To describe treatment emergent RAMs in patients treated with RPV or EFV-containing regimens
- To describe virologic failure in patients treated with RPV or EFV-containing regimens

The primary objective of the nested case-control analysis is to quantify separately the risk of virologic failure associated with ARV treatment adherence and pill intake with food.

1.3.2. Secondary Objectives:

The secondary objectives were specifically chosen to assist in meeting the CHMP request to assess appropriate treatment of patients with RPV-containing products in accordance with the SmPC or to provide context to events observed within the RPV-treatment group. For all secondary objectives, frequency and rates will be reported separately for the RPV and EFV-treated groups, as well as for RPV relative to EFV.

- To describe the demographic characteristics, comorbidities, and medical condition of patients initiating RPV or EFV treatment

- To describe antiretroviral (ARV) treatment status (naïve/experienced) of patients prior to initiating RPV or EFV treatment
- To describe prior use of ARV treatment, if any, of patients initiating RPV or EFV-containing regimens
- To describe the frequency of pre-treatment RAMs for RPV and EFV among patients subsequently initiating RPV or EFV treatment respectively
- To describe viral load at start of RPV or EFV treatment
- To describe viral load over the course of RPV or EFV treatment
- To describe HIV-treatment regimens and concomitant medications of patients initiating RPV or EFV-containing regimens
- To describe changes in HIV treatment and concomitant medication over the course of RPV and EFV treatment
- To describe reasons for switch of ARV treatment
- To describe adverse events over the course of RPV or EFV treatment

2. OVERVIEW OF STUDY DESIGN

2.1. Study Design

This DUS will be implemented in one or more large HIV cohorts established in Europe. Data will be collected longitudinally and recorded in the HIV cohorts' databases. A minimum of six hundred patients will be entered into the study based on the prescribing of RPV-containing regimens, either as a single agent or as a FDC. An additional minimal number of 600 patients will be entered into the study based on the prescribing of EFV-containing regimens. Retrospective data available in the HIV cohorts will be used to describe patient clinical characteristics prior to receipt of RPV-containing regimens or EFV-containing regimens.

Data will be collected in an observational manner such that the management of the patient is determined by the patient and the caregiver and not influenced by the DUS protocol. The DUS will evaluate care as it is provided. It will capture data on a heterogeneous population treated with RPV-containing regimens or EFV-containing regimens in a comprehensive manner without exclusions to assure representativeness of the populations treated with RPV or EFV-containing regimens.

All patients initiating RPV treatment will be eligible for inclusion in the DUS. Patients initiating EFV treatment will also be eligible for inclusion in the comparator group based on the date of EFV treatment initiation. Relevant IRB/EC and HA approvals will be secured prior to initiating the study.

2.1.1. Nested Case-Control Study Design

A nested case-control study will be conducted to evaluate the effects of ARV treatment adherence and pill intake with food on the risk of virologic failure with RPV. Information on food intake associated with taking RPV and ARV treatment adherence during the last 7 days will be collected retrospectively through a self-reported questionnaire in a smaller sample of RPV-treated patients nested within the DUS. Patients will be informed that their responses are confidential and have no consequences for their treatment. Cases for the case-control study will comprise all RPV-treated patients who experience virologic failure. For each case, four control patients without virologic failure will be chosen using incidence density sampling from the defined cohort of RPV-treated patients in the DUS. Incidence density sampling involves matching each case to a sample of those who are at risk at the time of case occurrence. This sampling method has been found to result in an unbiased estimate of the incidence rate ratio. The control patients will be matched on potential confounders for virologic failure, eg. age, sex, weight or body mass index (BMI), ethnicity, CD4 cell count, pre-treatment viral load, route of HIV infection, co-infection with hepatitis B/C, HIV treatment status (naïve/experienced), and depression. Risk of virologic failure associated with adherence to ARV treatment and dietary instructions will be quantified.

2.2. Study Design Rationale

A DUS design using existing HIV cohorts was chosen to assess proper prescribing and effectiveness of RPV-containing products in routine clinical practice in Europe and to provide the greatest access to HIV prescribers. HIV cohorts operating in Europe and using electronic medical record-based databases have proven to be an important resource for post-marketing observational studies in HIV. These studies are generally not subject to additional informed consent and may be completed expeditiously.

An important strength of these cohorts relevant to the proposed DUS is their ability to evaluate conditions under which HIV drugs are prescribed in large numbers of patients. Data from these cohorts are useful in evaluating treatment patterns and appropriateness of treatment. The design was also chosen due to the robust patient numbers available within

the HIV cohorts in Europe that capture the experience of patients with HIV. Multiple HIV cohorts will be evaluated for inclusion in the DUS to meet the study objectives and sample size requirement of 600 patients exposed to RPV-containing regimens and 600 patients exposed to EFV-containing regimens.

The proposed HIV cohorts have been established in Europe specifically to facilitate research in HIV infected patients. Data salient to meeting the CHMP request are available within the HIV cohorts and do not require additional data collection or interaction with physicians or patients with the exception of robust food intake and adherence measures. It is important to note that one of the reasons these cohorts were established was because traditional resources for patient identification were insufficient in identifying HIV infected patients due to HIV infected patients seeking treatment outside of payer systems and from health care providers other than general practitioners.

European HIV cohorts capture care as given and are generalizable to the population likely to be exposed to RPV-containing regimens. The proposed design does not interfere with the physician's decision regarding what to prescribe for the individual patient. Patients receive the drug in everyday practice and are not a highly selected group of patients who may not be representative of the 'real-world' population. The use of multiple cohorts located in several different countries increases the generalizability of the observed rates of use by physicians. The major strength of using the HIV cohorts for a DUS is the protocols for data collection have been specifically designed for HIV research (www.hicdep.com). Data are systematically collected on all clinical aspects salient to HIV care. These data include laboratory variables for HIV viral load, CD4+ counts, drug resistance information, concomitant medications, adverse events, and detailed information on HIV treatment. Additionally, patients are followed in the cohort until death or loss to follow-up from the cohort. Data are collected independent of the proposed DUS and are not subject to physician recall or potential biases involving self-reported drug prescribing or patient management. These data are collected longitudinally and in a time-dependent manner so that variation in time-dependent variables can be assessed. This is particularly important when considering the outcome of virologic failure and potential factors contributing to loss of virologic control. Finally, these data are collected electronically and do not place additional burden on the treating physician or patient.

Additionally, a comparator group of EFV-treated patients will be included in this study to provide contemporary context to utilization and outcomes observed within the RPV-treated group. The EFV-treated group will provide insight into patient characteristics

likely to influence health-care providers to channel patients to EFV-containing regimens or to RPV-containing regimens. Additionally, the EFV treatment group will provide a better understanding of the observed rates of virologic failure and prescribing factors observed within the RPV-treated group.

2.2.1. Nested Case-Control Study Design Rationale

Given the recognized limitations of assessing food intake and treatment adherence in large observational studies conducted over several months, the feasibility of collecting food intake and treatment adherence data within the cohorts will be further explored. Options to be explored will include using one of the accepted methods of measuring ARV treatment adherence and pill intake with food in a smaller sample of patients within the HIV cohorts. A nested case-control design was selected to improve computational and operational efficiency of comparisons of virologic failure as a function of adherence to treatment and food recommendations. This design also facilitates the selection of a comparison group with similar clinical experience with respect to potential confounders.

3. STUDY POPULATION

3.1. Patient Selection

The study population will be drawn from the population of patients enrolled in one or more European HIV cohorts. Eligible patients must be new users of RPV-containing regimens at the initiation of therapy (inception cohort). Patients eligible for the comparator cohort must be new users of EFV-containing regimens. Data will be included for analysis based on the availability of RPV-containing regimens in each country. Patients in the EFV-treated group will be eligible for selection from each HIV cohort if they initiate an EFV-containing regimen after the availability of an RPV-containing regimen is observed within the respective cohort. The study period will start at the date of market availability of RPV-containing regimens in the participating counties and will end when in total 600 patients from each treatment group (RPV and EFV) have been included in the study and followed for 12 months, until virologic failure, or lost to follow-up, whichever occurs first.

3.1.1. Inclusion Criteria

Patients who initiate therapy with RPV or EFV-containing regimens during the study period will be identified. Initiation of therapy is defined as first prescription for RPV or EFV-containing regimens documented in the HIV cohort. Patients will be included in the study if they meet all of the following criteria:

- Have documented enrollment in the HIV cohort database prior to the start of RPV or EFV-treatment regimens;
- Have received at least one prescription for RPV-containing regimens or EFV-containing regimens

3.1.2. Exclusion Criteria

No specific exclusion criteria will be applied in this study.

3.1.3. Data Source(s)

3.1.3.1. Feasibility Assessment of European databases

An evaluation will be conducted of the following available HIV cohorts in Europe for their suitability for meeting the study objectives:

- EuroSIDA
- UK Collaborative HIV cohort (CHIC), with linkage to the UK HIV drug resistance database and the UK Register of HIV Seroconverters
- Danish HIV cohort
- German HIV-1 Seroconverter cohort
- Italian Antiretroviral Resistance Cohort Analysis database (ARCA)
- French Hospital Database on HIV (FHDH)
- Cohort of Spanish AIDS Research Network (CoRIS)

4. STATISTICAL METHODS

4.1. Sample Size and Study Precision

4.1.1. DUS Sample Size and Study Precision

The sample size targets will produce an error rate of no more than 5%. A minimum of 600 patients exposed to RPV-containing regimens will be included in the DUS to assess the proportion of appropriate use of RPV formulations. The error rate under these assumptions and an observed proportion of appropriate use of 95% is estimated at +/- 0.02.

Proportion of appropriate use (%)	95% CI error (+/-) with 400 patients	95% CI error (+/-) with 600 patients
70	0.04	0.04
75	0.04	0.03
80	0.04	0.03
85	0.03	0.03
90	0.03	0.02
95	0.02	0.02

4.1.2. Nested Case-Control Sample Size

The power and detectable odds ratio for the nested case-control study will be based on the number of patients experiencing virologic failure while under observation in the DUS. The power ranges for detectable odds ratios based on the observed number of cases at alpha=0.05 is given Table 1 below. For example, based on an alpha of 0.05, a control to case ratio of 4:1, and an adherence level of 80% or greater in 50% of patients, approximately 40 cases would be needed for a minimally detectable odds ratio of 3.0 with 80% power. For a minimally detectable odds ratio of 2.0, approximately 90 cases would be needed.

Table 1. Sample size and study power for minimally detectable odds ratio assuming a two-sided test, 5 percent alpha level, an adherence level of 80% or greater in 50% of patients, and a 4:1 ratio of controls to cases.

	Detectable OR						
Cases	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**5**
0	0.0249979	0.0249979	0.0249979	0.0249979	0.0249979	0.0249979	0.0249979
10	0.0788996	0.1456193	0.2129961	0.2757540	0.3321963	0.3821915	0.4649655
20	0.1199695	0.2577778	0.3968270	0.5174057	0.6151327	0.6920104	0.7982529
30	0.1603557	0.3671945	0.5590526	0.7033559	0.8024057	0.8678758	0.9386928
40	0.2006102	0.4692415	0.6894629	0.8283160	0.9066258	0.9489490	0.9838703
50	0.2406664	0.5610976	0.7878403	0.9052049	0.9585720	0.9817546	0.9961780
60	0.2803320	0.6415215	0.8586668	0.9496126	0.9825155	0.9938649	0.9991643
70	0.3193976	0.7103878	0.9078456	0.9740491	0.9929161	0.9980363	0.9998286

80	0.3576683	0.7682871	0.9410123	0.9869870	0.9972264	0.9993967	0.9999667
90	0.3949750	0.8162206	0.9628471	0.9936230	0.9989453	0.9998210	0.9999938
100	0.4311767	0.8553823	0.9769310	0.9969370	0.9996089	0.9999484	0.9999989

4.2. Measurements

4.2.1. Exposure Definition and Measures

Exposure to RPV will be determined by the presence of prescription records for the FDC of FTC/RPV/TDF or single agent of RPV among patient data. Relevant drug codes will be used to identify RPV-containing regimens in the HIV cohorts. The baseline date for exposure follow-up (index date) for a patient within a given treatment group will be defined by first prescription of RPV or EFV-containing regimens. Duration of exposure will be based on dispense date and days of supply for each dispensed prescription. Exposure to RPV or EFV-containing regimens will be considered discontinued if the prescription is not refilled within a specified interval of time (e.g. twice the days' supply) of the previous prescription. Switches from one drug to another will be captured and time on drug will be defined by the exposure periods. The total length of exposure to a given drug will be the time between start and stop periods of exposure to the same drug.

4.2.1.1. Exposure Definition in Nested Case-Control Study

For the nested case-control analysis, exposure will be based on 1) level of daily medication adherence, and 2) level of adherence to food recommendations. Cases and matched controls that are selected will be asked to retrospectively report via a questionnaire how often they took their HIV medication during a specified time period and how often RPV was taken with food. A single item querying the number of prescribed doses the participant had missed in a specified time period will be used, as follows:

> *"How many doses of your complete HIV regimen did you miss in the last 7 days?"*
>
> *"For those days you missed, what component of your HIV regimen did you miss?" (If applicable)*
>
> *"How often did you take RPV with food in the last 7 days?"*

Since RPV dosing is once-daily, number of doses taken is equivalent to number of days the medication is taken. A 7-day recall period is proposed for this analysis as it has the advantage of including a weekend, during which adherence is often problematic. Further,

longer recall periods (7-day vs. 1-3 day) may yield more useful data for once-daily ART dosing since there are too few dosing times in a very brief recall period to capture variations in adherence behaviors (Simoni, 2006).

Level of daily medication adherence will be expressed as a continuous measure of percentage of doses taken calculated as [(prescribed doses – missed doses)/prescribed doses x 100]. Level of adherence to dietary instructions will be estimated based on appropriate use; the proportion of doses taken that were accompanied by food calculated as [(doses taken with food/total doses taken) x 100]. Adherence data will then be converted to dichotomous indicators of adherent versus nonadherent patients. The cut-off threshold is arbitrary and has ranged from 75% to 100% in the published literature (Simoni, 2006; Wilson, 2009). Based on findings from a meta-analysis, Nieuwkerk and Oort suggest that for thresholds determined a priori, choosing a threshold below 95% would be more appropriate (Nieuwkirk and Oort, 2005). For this analysis, patients who have greater than an 80% level of adherence will be categorized as adherent. Patients will be classified as adherent vs. nonadherent with respect to treatment adherence and adherence to food recommendations, separately based on the 80% level of adherence.

4.2.2. Outcome Definition and Measures

Outcome definitions for the DUS will include:

- HIV viral load prior to initiating RPV-containing regimens or EFV-containing regimens as well as over the course of therapy
- Virologic failure defined for treatment naïve patient as plasma HIV-1 RNA levels >500 copies/ml after 6 months of regimen initiation if baseline viral load is >500 copies/ml. For patients undetectable at baseline virologic failure is defined as 2 consecutive plasma HIV-1 RNA levels >500 copies/ml after starting the regimen.
- HIV treatment status (naïve/experienced) at RPV or EFV treatment initiation
- Prior use of ARV treatment, if any
- NNRTI drug resistance at RPV or EFV treatment initiation as well as over the course of therapy
- Proportion of patients who have resistance testing prior to initiating RPV or EFV therapy as well as over the course of therapy

- Concomitant medications prior to initiating RPV or EFV therapy as well as over the course of therapy
- Comorbidities prior to initiating RPV or EFV therapy as well as over the course of therapy
- Reason for discontinuation of RPV or EFV-containing products
- Reason for switch of ARV treatment
- Adverse events over the course of RPV or EFV therapy

4.2.3. Case Definition for Nested Case-Control Study

Cases will be selected based on occurrence of virologic failure as defined in the DUS, and controls will be selected based on absence of virologic failure.

4.2.4. Potential Confounders and Effect Modifiers

Potential confounders and effect modifiers will be collected from the databases and assessed to determine their association with the outcomes of interest. These covariates will be used to perform adjusted analyses and to describe the treatment groups. Patient factors to be considered will include, but are not limited to, demographics, comorbidities and concomitant medications that might influence appropriate use. Risk factors will be identified in the database using pre-specified diagnosis and/or treatment codes.

- Age
- Sex
- Weight or BMI
- CD4 at treatment initiation and at treatment failure
- Ethnicity
- Route of HIV infection
- Co-infection with hepatitis B/C or TB
- Depression

4.2.5. Length of Follow-up

Each patient will be followed for 12 months from the initiation of RPV or EFV-containing regimens, or until death, loss to follow-up within the cohort, or virologic failure, whichever occurs first. Time varying variables will be recorded at each patient visit.

4.3. Analyses

4.3.1. Descriptive Analysis

This DUS is descriptive in nature; and frequency and rates of virologic failure, baseline resistance, and treatment emergent resistance will be reported separately for the RPV and EFV-treated groups.

4.3.2. Specific Comparisons

Specific comparisons will be made with respect to patient clinical characteristics, rates of virologic failure, baseline resistance, and treatment emergent resistance between the RPV and EFV-containing regimen treatment groups.

4.3.3. Nested Case-Control

A nested case-control analysis will be performed to estimate the odds of virologic failure associated with ARV treatment adherence and separately with adherence to pill intake with food by comparing the exposure level (>80% vs. ≤80%) of each case with that of individually matched controls. The odds ratio of virologic failure and 95% CI will be reported for nonadherent patients compared with adherent patients with respect to daily medication adherence and adherence to dietary instructions, separately.

4.4. Missing Data Handling

An evaluation of missing data will be conducted to assess the assumptions under which inference is valid. Missing data will be categorized into: missing completely at random (MCAR) in which there is no difference in subjects with missing data and those with complete data; missing at random (MAR) in which missing data are based on known or observed values of the collected variables, but not unmeasured data; and missing not at random (MNAR) where missing data is dependent on variables not measured. The evaluation will consist of comparing the distribution of the observed variables for patients with complete data with the distribution of observed variables for patients with missing data. Strategies for managing missing data may include limiting the analysis to patients with complete data or missing data imputation to estimate the value of the missing data.

4.5. Statistical Analysis Plan

4.5.1. Analysis of Baseline Characteristics

Baseline characteristics including demographics, medical history and use of medications at cohort entry will be described separately for the RPV and EFV-treated groups. The analysis will report the frequency distribution (number and percentage of patients) for categorical variables and descriptive statistics (median, mean, standard deviation [SD]) for continuous variables. Descriptive statistics will be used to evaluate and compare the baseline characteristics of the treatment groups and analyze the prescribing patterns of RPV-containing regimens and EFV-containing regimens. Characteristics to be analyzed will be covariates and all potential confounding factors listed in Section 4.2.3.

4.5.2. Analysis of Appropriate Use

This analysis will describe and summarize the prescribing of RPV and EFV-containing regimens. The analysis will ascertain the number of patients exposed to RPV-containing regimens and EFV-containing regimens. The prescriptions will be summarized by patient demographics (age, sex, geography) and clinical characteristics (comorbidities and concomitant medications). In addition, the details of RPV and EFV-containing regimens use patterns will be described including duration of use, persistence of therapy, and usage of other HIV treatments.

This analysis will describe and summarize the utilization patterns of RPV-containing regimens and EFV-containing regimens with respect to viral load, CD4 counts, pre-treatment RPV-containing regimens resistance testing, adverse events, HIV treatment status (naïve/experienced), prior HIV treatment regimens, concomitant medications, comorbidities, and route of infection. The analysis will ascertain the number of patients initiating RPV-containing regimens and the proportion of patients treated in accordance with RPV products' SmPC. Proportions will be estimated separately for each recommendation of patient treatment. The denominator for each proportion will consist of the number of all patients initiating RPV-containing regimens included in the study. Proportions will be estimated separately using the following numerators:

- The number of patients naïve to HIV treatment regimens
- The number of patients with documented pre-treatment screening for ARV RAMs

- The number of patients initiating RPV-containing regimens with a baseline viral load ≤ 100,000 HIV-1 ribonucleic acid (RNA) copies/mL

Proper prescribing will be summarized by patient demographics and potential confounders.

4.5.3. Additional analysis on virologic failure and emergence of resistance

Additional analyses will be conducted to evaluate outcomes within twelve months of initiating RPV or EFV-containing regimens. Specific analyses to be conducted are as follows:

- The proportion of patients with virologic failure within twelve months of RPV-containing regimens initiation or EFV-containing regimens initiation
- The proportion of patients with treatment emergent RPV or EFV RAMs within 12 months of NNRTI initiation

The decision to prescribe RPV-containing regimens or EFV-containing regimens will be influenced by the treatment recommendations, patient characteristics, the prescriber assessment of the health status and risk profile, and the local policies and formularies. Thus, when planning to compare rates of virologic failure and emergence of resistance, it will be important to first determine whether the populations are comparable. The parameters available in the HIV cohorts will be used to investigate the relative importance of patient characteristics or risk factors that may be used to identify which patients are selected to receive RPV-containing regimens compared with EFV-containing regimens.

The evaluation of appropriateness of a comparison of RPV-exposed patients with EFV-exposed patients will be based on the consistency of the clinical experience of the two treatment groups. This assessment will be conducted based on distribution of propensity scores for receipt of RPV-containing regimens or EFV-containing regimens.

The evaluation of clinical experience will assess the patients' clinical and demographic characteristics in relation to receipt of RPV or EFV-containing regimens. Information will be captured on the patients' clinical and demographic characteristics that could be predictive of RPV treatment appropriateness. This information will be incorporated into multivariate models to identify a group of patients with similar characteristics to the RPV-containing regimens cohort but treated with EFV-containing regimens. All patients

will be assigned a propensity score ranging from 0 to 1 that represents the fitted probability of receiving RPV-containing regimens. The scores from EFV-treated patients will be plotted against those for RPV-treated patients. Overlap in the treatment groups based on sample size estimates of approximately 600 patients per treatment group in the propensity space must exist for a comparison of outcomes of interest between the two groups.

Incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance will be calculated for the RPV and EFV-exposed patients. The three primary event rates of interest (incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance) will be analyzed in 3 separate sets of analyses. Additional descriptive analyses will include incidence rates for each drug calculated by dividing the number of events by the total person-exposure time and expressed as the number of events per person-year, and 95% confidence intervals. Analyses of virologic failure will be stratified by HIV treatment status (naïve/experienced) at treatment initiation.

Relative risks comparing the RPV-containing regimens with EFV-containing regimens and 95% confidence intervals will be calculated and appropriate stratified analyses will be conducted for virologic failure and emergence of treatment resistance. Poisson regression models will be used to adjust for the appropriate factors that influence the risk of virologic failure and treatment-emergent resistance. Adjustments for imbalances between the treatment groups before receiving the first dose of RPV or EFV-containing regimens will be applied using accepted methods based on sample size availability and the observed overlap of key patient characteristics based on propensity score construction.

4.5.4. Nested Case-Control Analysis

A nested case-control methodology will be used to quantify the risk of virologic failure associated with adherence to ARV treatment and dietary instructions. For each identified case of virologic failure, four controls without virologic failure will be selected using incidence-density sampling from RPV-treated patients within the HIV cohorts. The control patients will be matched on potential confounders for virologic failure, eg. age, sex, weight or BMI, ethnicity, CD4 cell count, pre-treatment viral load, route of HIV infection, co-infection with hepatitis B/C, HIV treatment status (naïve/experienced), and depression. Conditional logistic regression will be used to estimate the odds ratio of virologic failure associated with ARV treatment adherence and separately with adherence to pill intake with food by comparing the exposure level (>80% vs. ≤80%) of each case with that of individually matched controls. The odds of virologic failure and 95% CI will

be reported for non-adherent patients compared with adherent patients, with respect to daily medication adherence and adherence to dietary instructions, separately. Variables that were used in matching will be included in all regression models. Other potential confounders will be evaluated using a change-in-estimate criterion to determine inclusion or exclusion. Variables will be included in subsequent multivariable models if adjustment for the given variable, in a model with exposure status and that single variable, produces a change of 10% or more in the odds ratio for the outcome. Additional risk factors evaluated may include drug and/or alcohol abuse, prior ART use, and prior virologic failure, if available

4.6. Data Quality Assurance

A summary of the data holder's internal data quality procedures will be requested and reviewed. The data holder is responsible for implementing and maintaining quality assurance and control systems to ensure that this DUS is conducted and data are generated, documented, and reported in compliance with applicable regulations and guidelines.

4.6.1. Validation Procedures

A literature review will be conducted to identify external validation studies performed in the database.

5. STUDY LIMITATIONS

The proposed study is based on analysis of medical and prescription records from databases maintained by HIV cohorts in Europe. The following limitations should be considered:

There is potential misclassification of the diagnosis or the outcomes of interest.

Attribution of loss of virologic control to failure to follow RPV-containing products' SmPC may not be feasible given the multiple factors and dynamics salient to virologic control

Measurement of adherence to treatment regimens are difficult to assess with reliability beyond prescription refills. Reasons for switch of ARV treatment may be captured inconsistently across the HIV cohorts. Adverse events during the course of RPV or EFV-treatment will be described in aggregate; it is not possible or appropriate to assess the causality of individual cases.

Daily measurement of patient food intake with RPV-containing regimens is highly problematic in any study given the time required to measure diet consistently and accurately over the course of the study period. Associations between patient diet measurement and loss of virologic control are likely highly unreliable given misclassification of diet and consistent measurement of dietary intake. Furthermore, a thorough measurement using complicated instruments of the patient's dietary intake may result in changes in dietary behavior to an extent that the behavior becomes unrepresentative of true intake in the 'real world' setting.

Self-report of treatment adherence is susceptible to recall bias and social desirability bias. Self-reported measures reflect only short-term or average adherence and may often overestimate it, particularly when queried retrospectively.

DUS include bias related to the observational nature of the data and potential lack of data due to loss to follow-up or essential data not collected as routine fields. These studies are also subject to real-world prescribing practices that may not provide sufficient patient numbers to meet study goals of ascertainment within a reasonable timeframe. The feasibility evaluation and design assessment of the study are intended to better understand and adjust for these limitations as well as to estimate the probability to meet study goals of ascertainment within a reasonable timeframe.

Allocation of treatment is not subject to randomization. Patients will likely be channeled to treatment based on several measured and unmeasured characteristics and based on treatment guidelines. For example, treatment guidelines for the FDC of EFV are likely to channel ARV-treatment experienced patients into the FDC as opposed to the single agent formulation of EFV. This potentially introduces associations between exposures and outcomes that are confounded and may result in imbalances in the exposure groups when comparing EFV-containing regimens and RPV-containing regimens.

All comparative analyses will be conducted under the assumption that unmeasured or missing effect modifiers, risk factors, or confounders are distributed equally across the RPV and EFV treatment groups and that the effects of these unmeasured or missing variables are non-differential with respect to treatment.

6. ETHICAL ASPECTS

6.1. Privacy of Personal Data

Confidentiality of patient records will be maintained at all times. All analyses of data will be performed using appropriately de-identified data without access to personal

identifying information. All study reports will contain aggregate data only and will not identify individual patients or physicians. Medical record abstraction, if available, will only be performed after receiving a waiver of authorization from the relevant data holder's privacy board and approval from an Institutional Review Board (IRB). At no time during the study will the sponsor receive patient identifying information.

7. ADMINISTRATIVE REQUIREMENTS

7.1. Adverse Event Reporting

This study is designed to assess the appropriate use of RPV-containing regimens based on aggregate analyses. The sponsor will report aggregate findings as study reports, not as individual spontaneous reports. In this study, it is not possible or appropriate to assess the causality of individual cases. Instances where individual patient data review identifies adverse events or serious adverse events, which may be attributable to RPV, e.g., if a chart indicates a physician or other health care professional considered the event possibly related to the regimen, the events will be entered to the Sponsor's Safety database and adverse reactions will be reported as individual case safety reports under expedited timelines as appropriate per company standard operating procedures.

7.2. Study Completion/Termination

7.2.1. Study Completion

The study will be completed once a minimum of 600 patients have entered each of the RPV and EFV treatment groups and have been followed individually for 12 months from RPV or EFV-containing regimen initiation, death, virologic failure, or loss to follow-up to the HIV cohort, whichever comes first. Interim analyses will be conducted to check the number of RPV-treated patients captured in the DUS and to review the estimated timeframe that will be needed to obtain the required sample size. Updates on patient accrual and timelines for study completion will be provided as part of Periodic Safety Update Reports (PSURs) and Risk Management Plan (RMP) updates. A descriptive report on patient counts and the safety profile of RPV-containing regimens with respect to appropriate use by prescribers and patients will be prepared in alignment with the PSUR schedule.

7.2.2. Study Termination

Study termination will be determined based on the projected ability of the study to meet sample size requirements using the health care database.

7.2.3. Dissemination and Communication of Study Results

Study results will be disseminated and communicated through the final study report. Study progress will be provided in the PSURs and RMPs for RPV-containing products. Additionally, findings of potential scientific or public health importance will be disseminated through conference presentations or journal articles as appropriate.

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