# Protocol for evaluating the public health benefit of rilpivirine from the French Hospital Database on HIV Infection (FHDH)

# Problem description :

Rilpivirine is a molecule developed by Janssen and marketed by the same company since 2012 under the name (Edurant®) and is a reverse transcriptase inhibitor that received its MA in November 2011. In combination with other antiretroviral drugs it is indicated in adults living with human immunodeficiency virus type 1 (HIV-1), antiretroviral-naive with a viral load ≤ 100,000 copies / mL of HIV-1 RNA. A genotypic resistance test should guide its use. Rilpivirine is also marketed in France in 3 other fixed associations for the treatment of PLHIV:

* The combination rilpivirine + TDF + FTC (Eviplera®) has been marketed by GILEAD since 2012 and received its AMM in November 2011. At that date, this combination was indicated for the treatment of adult patients, infected with HIV-1, antiretroviral treatment naive, and with a viral load ≤ 100,000 copies / mL of HIV-1 RNA. Since November 2013, this combination is indicated for the treatment of adults infected with HIV 1 without mutations known to be associated with resistance to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), tenofovir or emtricitabine, and having a viral load ≤ 100,000 copies / mL of HIV-1 RNA.
* The combination of rilpivirine + TDF alafenamide + FTC (Odefsey®) is marketed by GILEAD in 2018 and received its AMM in April 2016. This combination is indicated for the treatment of adults and adolescents (aged 12 years at least 35 kg) infected with HIV-1 lacking a mutation known to be associated with resistance to the class of non-nucleoside reverse transcriptase inhibitors, tenofovir or emtricitabine and having a viral load ≤ 100,000 copies / mL of HIV RNA 1.
* The combination rilpivirine + dolutegravir (Juluca®) is marketed by GILEAD in October 2018 and received its AMM in April 2016. This combination is indicated for the treatment of human immunodeficiency virus type 1 infection (HIV). -1), in virologically controlled adults (HIV-1 RNA) Due to the marketing of this combination in France after December 2017, this fixed combination will not be taken into account in our study.

JANSSEN France has submitted a file to the Transparency Commission in 2017 for the renewal of rilpivirine on the list of reimbursable medicines to the Social Security and plans to file another in 2022. JANSSEN would like to have a follow-up study at long-term treatment of patients treated with rilpivirine in a real situation of prescription not to answer a request of the authorities of Health but for the results to be diffused in order to improve the medical knowledge of this product in France. The summary of the report will be sent to COREVIH.

This study will include rilpivirine under its INN (International Non-proprietary Name)

It should include:

a) describe the methods of prescription (indication, co-prescription, etc.) and the patients treated (demographics, antecedents, history of the disease, in particular previous treatments, etc.).

b) evaluate the impact of this medicinal product on the health of the population concerned.

c) number of consultations and hospitalizations

The French Hospital Database on HIV (French Hospital Database on HIV-FHDH) will answer the questions above.

## FRENCH HOSPITAL DATA DATABASE ON HIV INFECTION

## Objectives and issues of the cohort

The French hospital database on HIV infection is a hospital cohort, open, prospective, multicenter, including patients from 1989 [1]. It includes data from 125 centers and 182422 persons included until 31 December 2016.

One of the major assets of this base is its size. Thus, even as the incidence of all opportunistic manifestations has declined significantly, we can continue to study the clinical history of the disease and relate biological and clinical outcomes. The main research topics are:

* Therapeutic strategies: medium and long-term clinical evaluation, including use of observational causality ("comparative effectiveness") methodologies
* Morbidity and severe mortality AIDS and non-AIDS and the impact of HIV infection and antiretrovirals (including renal failure, fractures, malignancies and myocardial infarction)
* Public health and HIV infection in France
* Open theme: participating centers and external researchers can submit a project to the Scientific Council
* 2 focus groups: 1) Migrants, 2) Co-infection with hepatitis C virus

The FHDH Foundation participates in numerous collaborations, including ART-CC (Antiretroviral Cohort Collaboration), EUROCOORD (including CASCADE, since 2006 and COHERE since its creation in 2005) and HIV Causal (M Hernan, Harvard School of Public Health).

In addition to research, the database describes the epidemiology of HIV infection managed in hospitals in France, as illustrated in the epidemiology chapter of the expert report, and contributes to the evaluation of HIV infection. public health interest in antiretrovirals. Given its coverage (in the order of 53% of patients in care in 2009) [2] and its representativeness, the database is a valuable source for describing who HIV-infected patients are and who is cared for. the hospital and how their characteristics evolve over time. It contributes to the evaluation of the public health interest of antiretrovirals with tripartite contracts (INSERM, INSERM Transfert, Laboratory) in progress or realized.

### 2.2 Operation and organization of the Base

#### 2.2.1 Patients’ recruitment

To be included in the database, participants must meet three criteria: to be infected with HIV-1 or HIV-2, to be followed in a participating center (125 centers at the present time), and to have given their informed consent. in writing.

#### 2.2.2 Patients’ follow up

The information is collected at each hospitalization (conventional or day) and at each consultation of the subject, if a clinical and / or therapeutic event has occurred or at least every 6 months. If a subject changes his / her center but continues to be followed at a participating center, the anonymity number can be used to identify him in his new center. A study conducted in 1999 showed a rate of lost to follow-up (not reviewed in twelve months) for participants followed that year by 7.5%. Of the 7.5% of subjects lost to follow-up, 2.1% were remotely reviewed (present in the base available in mid 2006) and 5.4% were permanently lost from view, of whom 29.8% were in fact deceased [3]. In a recent article on the restoration of the CD4 / CD8 ratio after initiation of antiretroviral therapy between 2000 and 2010 [4], out of 10012 participants included, 846 were lost to follow-up during follow-up (ie no data in the last 18 months before the data update date of the center following the patient), ie a rate of 13% at 8 years.

As there is no contact between the management and analysis center of the base and the included patients, which are monitored in the different hospitals, it is not possible to set up procedures to minimize the losses of view. In recent articles, the loss of sight of the base is taken into account via competitive risk models (death and loss of sight being considered as competitive events of the event of interest), which limits the impact of the lost of sight on the results.

Matching with SNDS data should limit the impact of the loss of view and improve the completeness of morbidity and mortality data.

#### 2.2.3 Data collection

The data are collected from the medical records and then entered via the DOMEVIH software, owned by the Ministry of Health, by the Clinical Study Technicians (TEC) stationed in the various hospitals. In many services, a medical record software is set up (notably Nadis or DiamG). In this case, a gateway was developed to include data extracted from the local medical records database into the local DOMEVIH. Periodically (once a year), the TECs extract the DOMEVIH data for UMR-S 1136 via the secure transmission gateway set up by ATIH. During this extraction, the subjects are indexed by an anonymity number built from the surname, first name and day and month of birth.

Data is collected from medical records. They include invariable data (transmission group, date of first positive serology, notion of dated contagion, clinical and therapeutic antecedents of HIV infection, ...), clinical data (classifying diseases, other diagnoses, coded in CIM 10), biological (viral load and CD4, ...), and therapeutic (antiretroviral). Since 2005, alcohol and tobacco consumption, an HCV / HBV module for co-infected patients, lipid status, transaminases and the reason (s) for stopping ARVs have also been collected.

Before being incorporated into the database, the data are subjected to validation procedures allowing the elimination of unusable information (elimination of intra-center duplicates, verification of variables whose coherence is considered essential for the inclusion of the subject in the database). database or any monitoring sheet concerning it). Cross-center duplicates (people with the same anonymity number in different centers) are also identified. We then rely on the consistency of the data to determine if the identical anonymity numbers correspond to one and the same subject (true duplicates) or if they are different people (false duplicates). The data, integrated into a database managed under Oracle® Version 8.0, is analyzed using the SAS® Version 9.4 software.

### 3.2. Definition of patient groups

Three distinct groups of HIV-infected patients will be considered:

1. Antiretroviral-naive patients: patients who have never received ARVs
   1. All antiretroviral therapy naive patients
   2. Antiretroviral treatment naive patients divided into 2 categories:
      1. viral load (HIV-RNA) <100,000 copies / mL
      2. viral load (HIV-RNA) ≥ 100,000 copies / mL to identify patients' profiles with an off-label prescription
   3. Antiretroviral-naive patients subpopulation starting rilpivirine triple therapy

Only those who are naive to inclusion in the database and who are always naïve when initiating a rilpivirine-based treatment will be considered antiretroviral naive. A subject is considered to be naive at baseline if he has no history of treatment and a viral load (VL)> 50 copies / mL at this initiation to eliminate patients treated prior to inclusion in the base.

1. Pre-treated for virologic failure: patients who have previously received one or more antiretroviral therapy lines prior to initiation of rilpivirine therapy and switch to this treatment with a VL> 50 copies / mL.
   1. Antiretroviral pre-treated with virologic failure who switch for treatment with rilpivirine
   2. Subpopulation of antiretroviral pre-treated patients with virologic failure who switched to triple therapy or dual therapy with rilpivirine
2. Pre-treated for therapeutic success: patients who have already received one or more lines of antiretroviral treatment before initiation of rilpivirine treatment and who switch for this treatment with 2 VL≤50 copies / mL.
   1. Set of antiretroviral pre-treated patients with therapeutic success who switch for treatment with rilpivirine
   2. Antiretroviral pre-treated subpopulation for therapeutic success who switched to triple therapy or dual therapy with rilpivirine