Incidence and factors associated with PrEP discontinuation in France

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Nina Garofoli
Directed by: Pr Jade GHOSN and Karen Champenois

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1/ Introduction

A) HIV epidemic context

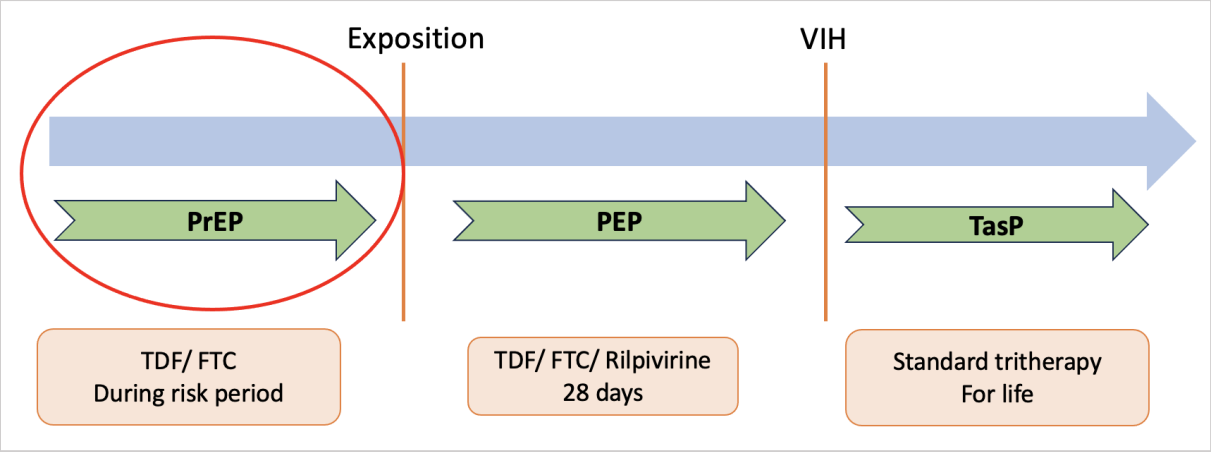
The Human Immunodeficiency Virus (HIV) is today the cause of a chronic disease, with effective and well tolerated antiretroviral treatments (ART). People living with HIV (PLWH), when treated early after infection, have almost the same life expectancy than the general population (1). A good adherence to treatment yields full suppression of viral replication, and subsequently prevents onward HIV transmissions from an HIV-positive individual on successful treatment to an HIV-negative sexual partner (2). However, PLWH are frequently diagnosed late in the course of the disease, leading to treatment initiation at a advanced stage of the disease, and potential contaminations of other people during the years when the disease was undiagnosed (3).
In France, the incidence rate of new HIV infections has only slightly decrease since 2000 (4), estimated around 6000 per year in 2022, despite expending prevention strategies (free of charge and ordonnance-free screening, universal Treatment as Prevention (TasP) consisting of treating every PLWH regardless of CD4 counts, Post-Exposure Prophylaxis, prevention campaigns, etc.). It is in that setting that the pre-exposure prophylaxis appeared in the 2000s.

B) Pre-exposure prophylaxis

1- What is HIV Pre-Exposure prophylaxis?

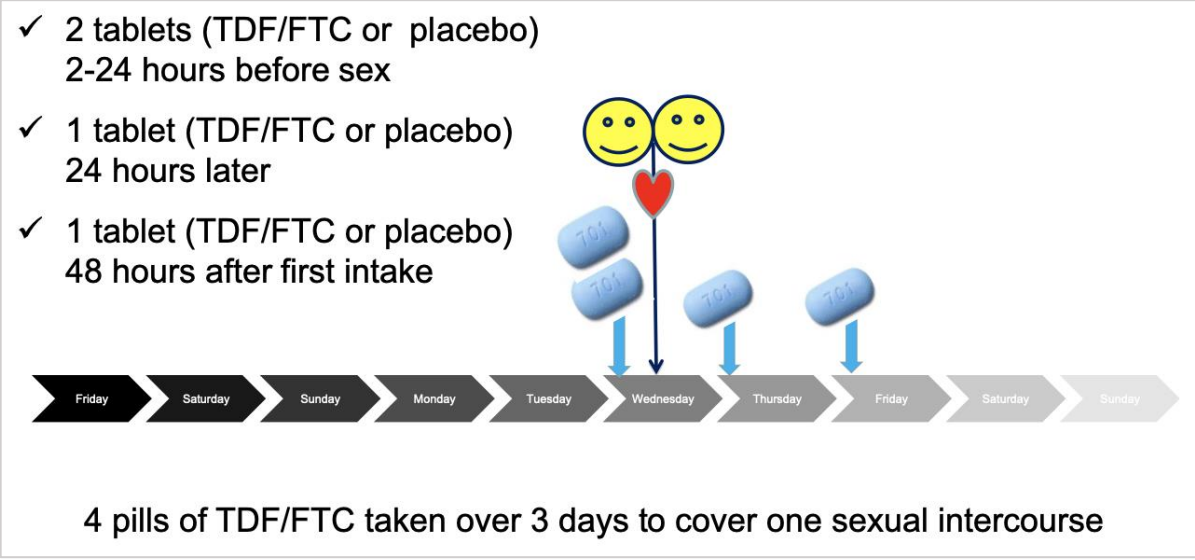
HIV Pre-Exposure Prophylaxis (PrEP) is an antiretroviral treatment given to an HIV-negative individual before an exposition at risk of HIV acquisition, to prevent the infection. Thus, it is different from the Post Exposure Prophylaxis (PEP), taken within 48 hours following a potential contamination with HIV, and from the classical curative triple antiretroviral combination for PLWH (Figure 1). In France, it has been recommended for use since 2016 for HIV negative people at risk of HIV infection, i.e. men who have sex with men (MSM) reporting condomless anal intercourses, sero-discordant couples when the HIV-positive partner has not yet reached full viral suppression on ART, intravenous drug users, but also, every individuals with numerous sexual partners and condomless sex (5). Originally, PrEP was exclusively introduced by medical specialists within specialized centers as the Centre Gratuit d'Information de Dépistage et de Diagnostic (CeGIDD) and hospital infectious disease departments. Since 2017, general practitioners can prescribe PrEP refill and follow PrEP users, and since 2021, they are allowed to initiate PrEP, facilitating its access and the follow-up (6). To date, in France, PrEP consists in one validated antiretroviral dual combination with one pill of TRUVADA® (TDF 245mg/FTC 200mg: Tenofovir DF and Emtricitabine), taken either daily (continuous regimen) or on-demand, before and after the exposition at risk of HIV acquisition (Figure 2). Nevertheless, this second regimen is only recommended for MSM or transgender women, because it has not been proved efficacious for women due to the different penetration, accumulation and elimination of the drugs in the anal mucosa and the vaginal mucosa (7).

Figure 1: HIV prevention schedule



Since 2010, we know that PrEP is effective to prevent HIV acquisition (8). The first trial to prove PrEP effectiveness with oral daily TDF/FTC was the iPrEX trial, showing a 44% reduction of risk of HIV, and this reduction of risk increased to over 90% in the subgroup of people with good adherence (9). It appeared that this efficacy was largely dependent of users' adherence. Indeed, PrEP must be taken at least seven consecutive days to be effective. During the following years, many studies focused on PrEP adherence, with 3 main ways to measure it: self-reporting (with questionnaires), counting pills at each visit, and the most accurate, measuring blood concentration of Tenofovir DF and Emtricitabine. Many trials and real-life studies confirmed the greater than 90% efficacy, when the treatment is taken correctly (10)(11)(12).

Figure 2: On-demand regimen



Source : Molina et al., IPERGAY study

The PrEP is prescribed for HIV negative people and regular screening of HIV must be performed every 3 months. The PrEP prescription is part of a global action for HIV prevention, and in that way, it is associated with a 3-monthly follow-up, with, at each visit, questioning about risk exposition, recalling of other measures of prevention (condoms), screening and treatment of sexually transmitted infections (STIs) (*Chlamydia trachomatis* and *Neisseria gonorrhea* in the anal, urine and pharyngeal sites, Syphilis, viral hepatites, and others in case of symptoms), screening of clinical or biological side effects, and incitation of vaccinations (13).

Potential side effects are gastro-intestinal disorders, dizziness, renal injuries (14), and diminution of bone mineral density without raising the risk of fracture (15). That is why the creatinine level must be checked regularly.

2- Focusing on discontinuations

The HIV seroconversions observed among PrEP users, attributed to PrEP failure, were probably due to poor adherence or PrEP discontinuations. In the French PREVENIR cohort, that followed PreP users for a median time of 22 months, the 6 seroconversions all occurred in individuals who had discontinued PrEP for weeks, despite continuing condomless sexual intercourses (16). Indeed, some PrEP users sometimes stop the treatment when they find themselves out of risk, without medical consideration (17). It goes with the notion of seasonal risk, adapting the treatment to the risk. On one hand, this allows for a certain flexibility for people who are not at a constant risk of HIV exposure, and who sometimes have long periods without exposure; it prevents from PrEP side effects during the period without risk. But on the other hand, it limits PrEP effectiveness when users misjudge their risk of HIV infection. Therefore, it is important for users who discontinue PrEP to stay in contact with a health center, so that the treatment could be easily restarted in case of later re-exposure to HIV.

Reasons for discontinuation were identified in a meta-analysis in 2021 (18) : particularly the low perceived risk of contracting HIV, the stigmatization as a PrEP user, the cost of the treatment, the potential side effects, or the pill burden. But in the studies included in this meta-analysis, main discontinuations were observed within the first month of follow-up and the proportion of discontinuation varied according to the studies. Rusie et al. also highlighted the potential difficulties of keeping up with quaterly consultations (19). Some characteristics of PrEP users seem to be associated with PrEP discontinuation: younger age, women and transsexual genders are the three main risk factors described (20)(21)(22).

Another issue about PrEP users is the lost to follow-up (LTFU) people (23). It is not rare that someone who does not need PrEP anymore just stops attending medical visits, without informing the care center about treatment discontinuation. But many other reasons can lead to follow-up discontinuation: a relocation, a transfer to another center, a follow up with general practitioner. Other causes of follow-up difficulties include lack of time or wrong beliefs regarding PrEP. It is important to limit the LTFU persons to make sure that discontinuation is an informed and consciously taken decision. The Centers for Disease Control and Prevention (CDC) recommends an HIV testing at the moment of the discontinuation (13). Usually, the persons LTFU are reached out to by care providers to promote continuation of follow up. But

many cannot be reached, and the important amount of LTFU subjects makes the estimation of PrEP discontinuations more difficult.

C) Objective of the study

The main objective of the study was to estimate the incidence rate of PrEP discontinuations in 3 PrEP centres in France. The secondary objectives were to describe the causes of discontinuation reported by PrEP users, and to assess the characteristics of users associated with PrEP discontinuations.

2/ Material and methods

A) Study design

A retrospective cohort was constructed from hospital databases, in two Parisian PrEP centers (Bichat and Tenon hospitals) and one in the Northern France (the hospital center of Tourcoing). The data of the PrEP users who initiated PrEP between January 1st, 2016 (the beginning of PrEP recommendation in France) and June 30th, 2022, and who attended at least two PrEP visits within 6 months, were included. Participants were followed-up until December 31st, 2022. We did not include participants after June 30th, 2022, to avoid immortality bias.

B) Outcome

In most studies on the topic, a follow-up discontinuation was defined by 2 consecutive missing visits (16), i.e. at least 6 months without visits, and 3 months without treatment since a prescription for 3 months of treatment was given at each visit. As we attempted to have the approximative date of PrEP discontinuation in our study, given by the PrEP users, **we defined a PrEP discontinuation as a treatment free period of three months.**

C) Data collection

For each hospital center, data extraction was conducted from the software database, including participant key characteristics. Subsequently, I meticulously reviewed every visit records of each PrEP user to identify specific variables of interest (outlined below). The three centers used 3 distinct software plateforms, each presenting the data differently, which necessitated data the standardization of the data. To ensure data privacy, each PrEP user was assigned a unique identifier number for pseudonymization purpose.

Each PrEP user had one of these status at the end of his follow-up (Figure 3) :

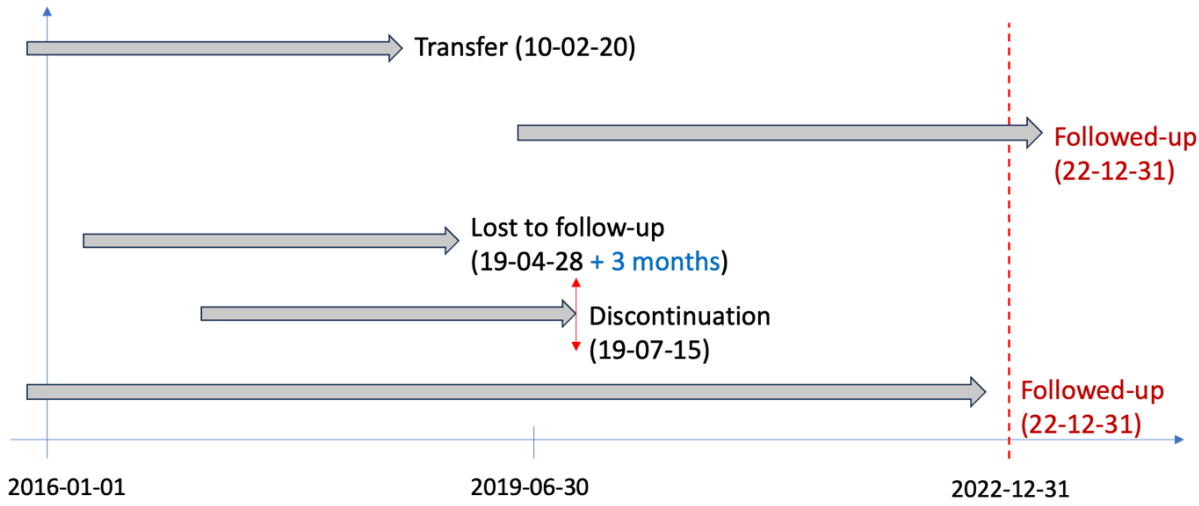
- “Followed-up” if he was still followed in the center on December 31st, 2022. Every person with a last visit on July 1st, 2022, or after, and without notion of discontinuation

or transfer, was considered followed up on December 31st, 2022 (because a six-month interval between two visits was classical).

- "Discontinued PrEP" if a stop of 3 months or more of the treatment was mentioned in any visit of the PrEP user. The date of the first discontinuation was the date of the end of follow-up.
- "Transfered" if the continuation of PrEP follow-up with a general practitioner or in another center was mentioned at the last visit. The date of the last visit was the date of the end of the follow-up.
- "Lost to follow-up" if the last visit of the PrEP user was before July 1st, 2022, and without mention in the database of a transfer or a discontinuation of treatment. Three months were added to the date of the last visit for the date of follow-up end because 3 months of treatment were prescribed at this visit.

To estimate more precisely the incidence rate of PrEP discontinuations, we differentiated PrEP discontinuations from follow-up discontinuations. A PrEP discontinuation was defined by a 3-month-period without taking the treatment, explicitly attested by the individual. In case of follow-up discontinuation without explanation in the dataset, we defined the person as LTFU. The PrEP discontinuation was expressed as a censored variable to consider the length of follow-up and the LTFU. We only included the first follow up in case of multiple follow-ups for a person, to avoid bias (related to the same individual being followed-up many times) and because of the low proportion of stop/ restart.

Figure 3: Possible status of PrEP users at the end of follow-up



Variables of interest

We collected factors potentially associated with HIV infection according to the literature, among users' characteristics, sexual behavior or PrEP use. All data were prospectively collected by the physician at each visit of the participant. Some data were entered in ticking a questionnaire directly in the computarised medical form, other were written in the medical report of the visit. I read all the medical reports to complete the database.

Variables collected at the PrEP initiation for each participant

- Country of birth, grouped into 6 geographic regions (France, Western countries, Sub-Saharan Africa, Latin America and Caribean, Eastern Europe and Asia, and Middle East and North Africa)
- Year of arrival in France : if the participant was not born in France
- Gender distinguished cis men, cis women, transsexual men to female (MtF), and transsexual female to men (FtM). Because of the very low number of transsexual FtM, these two latter groups were analysed together.
- Sexuality, classified as either heterosexual or MSM+, which means men who have sex with men and transgender women who have sex with men
- Age at PrEP initiation was collected, and then turned into in a categorized variable according to quartils and median (4 categories)
- Having a main partner (yes/no)

Variables collected when occured at least once during the follow-up

- Reacreative drug use including cocaine, amphetamines and methamphetamines, GHB/ GBL, ecstasy, LSD, ketamine, heroin, and cathinones
- Practice of slam (yes/no), consisting of injecting drug during sexual intercourse
- Sex work (yes/no)

Variables relative to PrEP use

- Date of PrEP initiation
- Date of the end of the follow-up
- Status at the end of follow-up (described before)
- If the status at the end of follow-up was “PrEP discontinuation”, reason(s) for discontinuation reported by the participant were stated

Variables collected at each visit

- Date of the visit
- PrEP regimen: daily, on-demand, or mixed if both ways were used in the past 3 months
- Number of partners during the last 3 months
- Number of condomless sexual intercourse during the last month
- Side effects attributed to PrEP occurring during the last 3 months. Seven categories of side effects were identified : gastro-intestinal disorders, abdominal pain, headache, other pain, general alteration, dizziness, and others
- *Chlamydia trachomatis* infection: yes/no. In the case of an infection, the number of positive sites was looked at
- *Neisseria gonorrhea* infection: yes/no. In the case of an infection, the number of positive sites was looking at
- *Treponema pallidum* infection (yes/no)
- *Mycoplasma genitallum* infection (yes/no)
- Other STI
- Symptoms of STI (yes/no)
- Having a main partner within the last 3 months (yes/ no)
- HIV exposure accident: occurrence of HIV exposure accident because of PrEP misuse for example (yes/no)

Some participant took PrEP sometimes daily and sometimes on demand. To facilite the analysis, a man was classified as taking PrEP either daily or on-demand if he took PrEP that way in 3 quarters of his visits or more; otherwise, the regimen was called “mixed”. Women took PrEP daily (the on-demand regimen is not available for women).

D) Statistical analysis

The follow-up began at the date of the first PrEP prescription and ended either at the date of the end of the follow-up or on December 31st, 2022, if the person was still followed at the end of the study. In this study, participants may have had multiple dates of PrEP initiation and follow-up periods, including instances of PrEP discontinuation and re-initiation. However, for the the primary analysis, we considered only the data from the first follow-up.

Description of the variables

Quantitative variables were expressed as median and interquartile range (IQR), and categorial variables as frequency and percentages. We described the reasons for discontinuation with number and percentages. Except the category “no indication” that concerned the discontinuations proposed by the doctor, the other reasons were due to users’ decision.

Incidence of PrEP discontinuation

We calculated the length of follow-up for each PrEP user from his first prescription of PrEP to the end of his follow-up according to the status of each participant.We calculated the incidence rate of discontinuations by dividing the number of discontinuations by the total persons-years of follow-up for the whole cohort. The 95% CI were estimated with a Poisson model. We performed a Kaplan-Meier curve of PrEP discontinuations in censuring on the right the particiants LTFU or transfered.

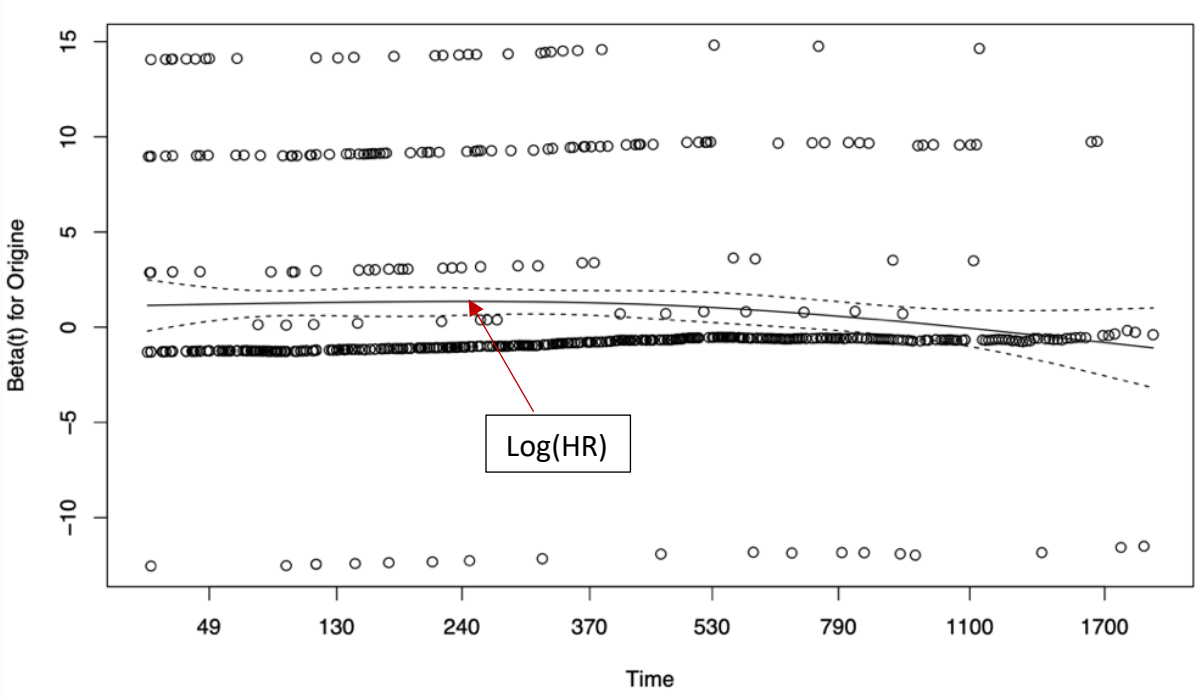
We calculated the incidence rate of PrEP discontinuations according to the time period: 2016-2019, 2020, and 2021-2022, to observe a possible impact of Covid-19 pandemic on PrEP discontinuations. We then compared these incidence rates by calculating the incidence rate ratio and testing its difference to zero.
In a sensitive analysis, we estimated this incidence rate with the hypothesis that all LTFU persons had stopped PrEP, and then with the hypothesis that half of them had stopped PrEP.

Factors associated with PrEP discontinuations

We used a Cox model to take into account the time of follow-up before discontinuation. This model was suitable because we assumed that censoring data were non-informative (i.e., being LTFU is not a predictor of discontinuation). To use this model, we assessed the assumption of proportional instantaneous hazards for each model with a graphical method (Figure 4). For each variable of interest, we performed a univariate Cox regression model; the association with the PrEP discontinuation was expressed with hazard ratio (HR) and IQR. When the P-value of the association was lower than 0.20, the variable was included into a multivariate Cox

proportional hazards model. A p-value lower than 0.05 was considered significant in the multivariate analysis.
Regarding sexuality and gender, only gender was integrated in these models, as they overlapped.

Figure 4: Evolution of the instantaneous risk ratio



Graphical representation of the instantaneous risk ratio (HR) over time. In this example, the line corresponding to the HR remains horizontal, indicating a constant HR over time. The hypothesis of proportional instantaneous hazard is respected.

3/ Article abstract

Incidence and factors associated with PrEP discontinuations in 3 PrEP centres in France

Objectives:
HIV Pre Exposure Prophylaxis (PrEP) is effective in preventing HIV. However, in PrEP users, most seroconversions occurred due to poor adherence or discontinuation of PrEP. Our objective was to estimate the incidence of PrEP discontinuations and describe the reasons and factors associated with such discontinuations.

Methods:
A retrospective cohort was constructed using data from 3 French hospital databases. PrEP users who had attended at least twice within a 6-month period between January 2016- and June 2022 were included and followed up until December 2022. The incidence was estimated by censoring PrEP users lost to follow up at the date of the last prescription plus 3 months. Factors associated with PrEP discontinuations were assessed using both univariate and multivariate Cox models.

Results:
A total of 2,785 PrEP users were included, with 94% of men and 5% of transgender persons. The median age was 35 years. By December the 31st, 2022, 653 users had stopped PrEP (23% of the cohort), 20% were still on PrEP but followed in another center, 43% were still on PrEP and followed in the same center, and 14% were lost to follow-up. The incidence rate was 10.8 PrEP discontinuations for 100 persons-years (PY).
The main causes of discontinuation were having a stable relationship with a partner (32% of cases), and not judging the treatment useful anymore (12%). Poor tolerance led to a PrEP discontinuation in 42 cases (6%). Individuals who discontinued treatment were younger (<29, HR=1.45 (1.17-1.80), more likely to be women (HR=2.44 (1.50-3.96)), or sex workers (HR=1.53 (0.96-2.44)). They were more likely to report during the last year, PrEP side effects (HR=2.25 (1.83-2.77)) or ≥2 sexually transmitted infections (HR=1.87 (1.53-2.27)).

Conclusion:
The incidence of PrEP discontinuations was lower than the one estimated in a cohort of PrEP users in Paris over the same period (PREVENIR study, 17.6/ 100PY). Despite the reasons provided for discontinuation, the users who had stopped the PrEP were still at a high risk of exposure to HIV.

4/ Article

A) Background

HIV pre-exposure prophylaxis (PrEP) is a medication taken before a potential exposure to HIV to prevent infection. Its effectiveness was first demonstrated in the iPrEx trial of 2010 for men who have sex with men (MSM) (8), and later for heterosexual men and women (24) and men who inject drugs (25). These findings were further confirmed in a real world setting through the PROUD study (10) in 2016, and many times thereafter (11)(12). PrEP with the oral daily combination of tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC) was approved by the FDA in 2012 (26), and by the WHO in 2014. It has been recommended in France since 2016 for individuals at risk of HIV infection, particularly MSM with unprotected anal sex, heterosexual persons with multiple partners, people who inject drugs, and other persons exposed to HIV. It is now clearly admitted that PrEP should be used in association with other prevention measures of HIV to reduce the burden of this disease. Today, it is prescribed either daily or in an on-demand regimen (27), this second option having been prouved to be effective only for MSM.

The efficacy of this treatment is largely dependent on its adherence; the predicted efficacy in iPrEx increased from 44% to over 90% when the drug was detected in blood (9). A meta-analysis of 29 studies in 2019 emphasized the role of adherence in reducing the risk of HIV infection (11). However, two studies did not demonstrate PrEP efficacy : the VOICE (28) (Vaginal and Oral Interventions to Control the Epidemic) and the FEM-PrEP (29) (Preexposure Prophylaxis Trial for HIV Prevention Among African Women) studies; there are arguments today suggesting that this lack of effectiveness was due to poor adherence (30). Furthermore, most PrEP failures are actually failure after treatment discontinuation or misuse; in a Canadian cohort (31), no seroconversion were reported among PrEP users but three occurred after discontinuation. Similarly, in the French PREVENIR study, 6 seroconversions were described ; all of their occurred after PrEP discontinuation for several weeks (16).

The proportion of discontinuations among PrEP users seems quite important but is difficult to estimate because of the significant number of individuals lost to follow up (LTFU). While PrEP retention rates were relatively high (69–92%) in clinical trials, they have been estimated at only 15–62% in non-research settings in US (32). A recent meta-analysis incuding 44,000 individuals from 20 countries worldwild found 39.5% of PrEP discontinuation in real-world implementation studies (33), higher than in clinical trials. In the French PREVENIR cohort (16), with 3000 PrEP users and a 3-year follow-up, the incidence of study discontinuations was about 17.6 for 100 persons-years. However, these numbers included PrEP discontinuation and people missing the last visits for other reasons. Since 2017, PrEP follow-up is possible through general practitionners, and since June 2021, PrEP initiation is available through general practitioners, so individuals who do not return to the hospital for their PrEP prescription may actually be receiving care in another center or from their local doctor. Additionally, with the introduction of the on-demand regimen, some PrEP users may use it only occasionally, thus they might have drug supply for more than three months, and attend healthcare providers only once or twice a year, although it is not recommended.

There are many causes of PrEP discontinuation. This treatment can lead to gastro-intestinal disorders (diarrhea, nausea, vomiting) and abdominal pain (27) (34), or, less frequently, it may cause a decrease in bone mineral density and renal insufficiency (15) (35). However, these side effects are often temporary (36), and if it is a classical cause of PrEP discontinuation, it is not the main one (37). In an analysis on FEM-PrEP population, including 2,000 PrEP users in 3 centers in Africa, Corneli et al. found a positive association between adherence and perceived risk of HIV (38); changes in HIV risk behavior are often a key reason for PrEP discontinuation (39). Other reasons include the challenges in medication adherence or the pill burden (33) and stigma (40).

Factors associated with discontinuation have been examined in an Austrian cohort (41), in which a younger age and female gender were associated with PrEP discontinuation. Similar results were found in others studies (39) (42) (43). However, it remains unclear if other characteristics of PrEP users, such as ethnical origin, substance misuse, or sexual orientation, are also related to PrEP discontinuation.

The objectives of this study were to estimate the incidence rate of PrEP discontinuations in 3 French PrEP centers, describe the reasons for discontinuing, and evaluate the characteristics of people who discontinued PrEP.

B) Material and methods

We conducted a multicentric, retrospective cohort from hospital databases, which included 3 hospital PrEP centers, 2 in Paris (Bichat and Tenon hospitals) and the hospital center of Tourcoing (in the Northern France). At these centers, PrEP was prescribed as a fixed dose combination of 245 mg of Tenofovir DF and 200 mg of Emtricitabine per pill, for 3 months. Theoretically, PrEP users were seen one month after PrEP initiation, to rule out a potential undiagnosed primary infection at initiation and ensure that there was a good tolerance to the treatment, and every 3 months thereafter. PrEP could be taken on a daily basis or discontinuously (only for MSM) (27). Every PrEP user who had not attended for ≥6 months and without notion of discontinuation or transfer/referral to another center or to a general practitioner was reached out to by phone and e-mail as part of the care. Some of the data in our study were made available thanks to these calls.

Study population

All PrEP users who received their first prescription of PrEP between January 1st, 2016, and June 30th, 2022, and who had attended at least two PrEP visits within 6 months, were included in the study. The follow-up began on the date of the first prescription and ended either on the date of the end of follow-up or on December 31st, 2022, for those still followed up at the end of the study.

Outcome

A treatment discontinuation was defined by 3 months treatment-free.

Each PrEP user had one of these status at the end of his follow-up:

- "Followed-up" if he was still followed at the same hospital center on December 31st, 2022. Anyone with a last visit on July 1st, 2022, or after, and without notion of discontinuation or transfer/referral, was considered as followed up on December 31st, 2022 (because a six-month interval between two visits was typical).
- "PrEP discontinuation" if a stop of 3 months or more of the treatment was mentioned in any visit of the PrEP user. The date of discontinuation was also the date of end of follow-up.
- "Transfer" if the last visit of the PrEP user mentioned that they would continue their follow-up with a general practitioner or at another hospital center. The date of the last visit was then considered the end of their follow-up.
- "Lost to follow-up" (LTFU) if the last visit of the PrEP user took place before July 1st, 2022, and without mention in the database of a transfer/referral or a discontinuation of treatment. In this case, 3 months were added to the date of the last visit because 3 months of treatment were prescribed at that last visit.

For the main analysis, each individual was eligible for follow up only once. In the case of a restart of the treatment after a previous discontinuation, it was not considered for the calculation of the incidence, the description of reasons for discontinuation, and the comparison of characteristics between those who discontinued PrEP and those who did not. The stops and restarts were the subject of a secondary analysis.

Variables of interest

General characteristics of PrEP users

Age was divided in 4 categories based on the median and quartiles. Gender distinguished men, women, and transgender persons. Sexuality was classified as either heterosexual or MSM+, which means men who have sex with men and transgender women who have sex with men. Because of the collinearity with the gender, we excluded sexuality from the univariate and multivariate analyses. Countries of birth were grouped into 6 geographic regions of birth.

PrEP usage data

The PrEP use regimen was collected at each visit; if a patient had taken PrEP daily during at least 75% of his follow-up, he was classified as a daily user, if he had taken it on-demand for at least 75% of the time, he was classified as an on-demand user, and in other cases he was classified as mixed user. The date of each visit was documented to estimate the time interval between two visits. The occurrence of side effects or sexual exposure accident were also noted, as well as the nature of side effects described by the PrEP user.

Data of HIV exposure

Recreative drug use included the use of Cocaine, amphetamines and methamphetamines, GHB/ GBL, ecstasy, LSD, ketamine, heroin, and cathinones. The practice of slam and sex working was collected. The presence of Sexually Transmitted Infections (STI) was noted at each visit.

C) Statistical analysis

Calculation of incidence

We calculated the duration of treatment for each PrEP user, starting from their first prescription of PrEP until the end of their follow-up. We calculated the total person-years of follow-up for the whole cohort, the number of discontinuations, and the incidence rate of discontinuation. We calculated the incidence rate of discontinuation according to period before (2016-2019)/ after (2021-2022)/ or during (2020) Covid19 pandemic containment, and compared these incidence rates by computing the incidence rate ratio and testing its difference to zero. The confidence intervals of the incidence rates were estimated using Poisson models.

In a sensitivity analysis, we calculated this incidence rate under 2 hypotheses about LTFU people: the first hypothesis assumed that all LTFU individuals had stopped taking PrEP, and the second hypothesis assumed that half of them had stopped PrEP.

Description of reasons for discontinuation

Reasons for discontinuation were grouped into categories and described with the numbers and percentages. In cases where the discontinuation was advised by the doctor due to the absence of indication for PrEP, it fell under the category “No indication”.

Evaluation of factors associated with PrEP discontinuation

For the univariate analysis, we studied the association between PrEP discontinuation and the other variables using univariate cox model. When the p value was less than 0.20, the variables were included in the multivariate cox model.

Software

All analyses were performed on R, version 4.2.1.

Ethics

All individuals had signed a written informed consent form for the computerized processing of medical data in the care monitoring software. An individual informed consent was not required for this anonymized register-based study, but an information note with the possibility of opposition was available in each hospital center. The study was in the conformity with the CNIL Reference Methodology 004.

D) Results

Characteristics of enrolled PrEP users

Between January 1st, 2016, and June 30th, 2022, a total of 2,785 PrEP users were included in the 3 hospital centers, with 2,608 men (93.6%), and 126 transgender persons (4.5%). The median age at PrEP initiation was 35 [29;43] years old; 380 individuals (13.4%) reported having

a main partner at the first consultation. Characteristics of PrEP users are presented in the Table 1 and the Figure S1.

Table 1: Characteristics of the participants at baseline

Baseline characteristics	**2,785 PrEP users - Number (%)**
Center	
Bichat	1011 (36.3)
Tenon	859 (30.8)
Tourcoing	915 (32.9)
Gender	
Men	2608 (93.6)
Women	51 (1.8)
Transgender MtF	121 (4.3)
Transgender FtM	5 (0.2)
Sexuallity	
MSM+	2694 (96.7)
Heterosexuals	89 (3.2)
Missing	2 (0.1)
Age (years)	
Median (IQR)	35 (29-43)
< 29 years	621 (22.3)
29-35 years	564 (20.3)
35-43 years	917 (32.9)
> 43 years	683 (24.5)
Origin	
France	1797 (64.5)
Sub-Saharan Africa	92 (3.3)
Latin America and Caribbean	239 (8.6)
Eastern Europe and Asia	60 (2.2)
Middle East and North Africa	111 (4.0)
Western countries	117 (4.2)
Missing	369 (13.3)
Potential HIV exposure	
Sex worker	157 (5.6)
Recreative drug use	728 (26.1)
Slam	70 (2.5)
Stable Relationship at initiation	380 (13.4)

Overall, there were 21,401 follow-up visits among the 2,785 individuals. After removing the first visit, the median time between 2 visits was 95 days (88-112), which is close to the theorical 90 days. 1,094 individuals (39.3%) used PrEP on a daily basis, 1,221 (43.8%) on-demand, and 470 (16.9%) in mixed regimen. During follow-up, 769 (27.6%) PrEP users had at least one side effect attributed to the treatment and 374 (13.4%) had a side effect during their

last year of follow-up. The main side effects described were gastro-intestinal disorders (72.4% of cases) and abdominal pain (17.8%) (Table S1). 756 PrEP users (27.2%) had symptoms of STI at least once during follow-up, 955 (34.3%) had at least 2 STIs, and 414 (14.9%) had at least 2 STI during the last year of follow-up.

Estimation of PrEP discontinuation incidence and reasons for disconstinuing PrEP

At the end of the study, 653 (23.5%) PrEP users had stopped the treatment, 1187 (42.6%) were still followed in the same center, 555 (19.9%) were followed elsewhere including 283 (10.2%) by a general practitioner, and 390 (14.0%) were LTFU (Figure 5). The median time of follow-up per person was 19.1 months (IQR=7.6-39.7), with a total of 6,070 person-years (PY) of follow-up. The median time of follow-up for the PrEP users who stopped the treatment was 9.4 (4.1-19.7) months. The incidence rate of PrEP discontinuations was 10.76 [9.93; 11.59] for 100 PY (in Figure 6, Kaplan Meier curve of first discontinuations).

Figure 5: Status of the PrEP users followed in 3 PrEP centers in France at the endpoint date of the study (2022-12-31)

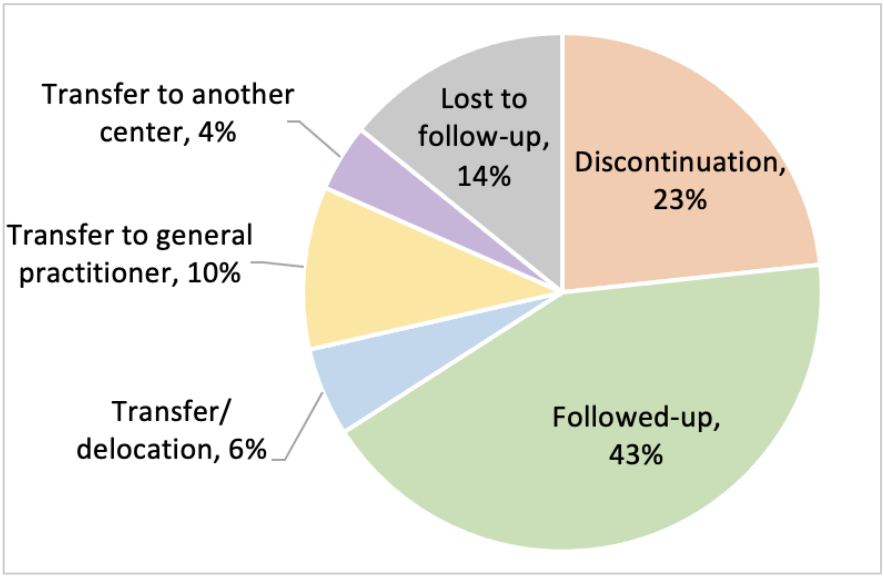
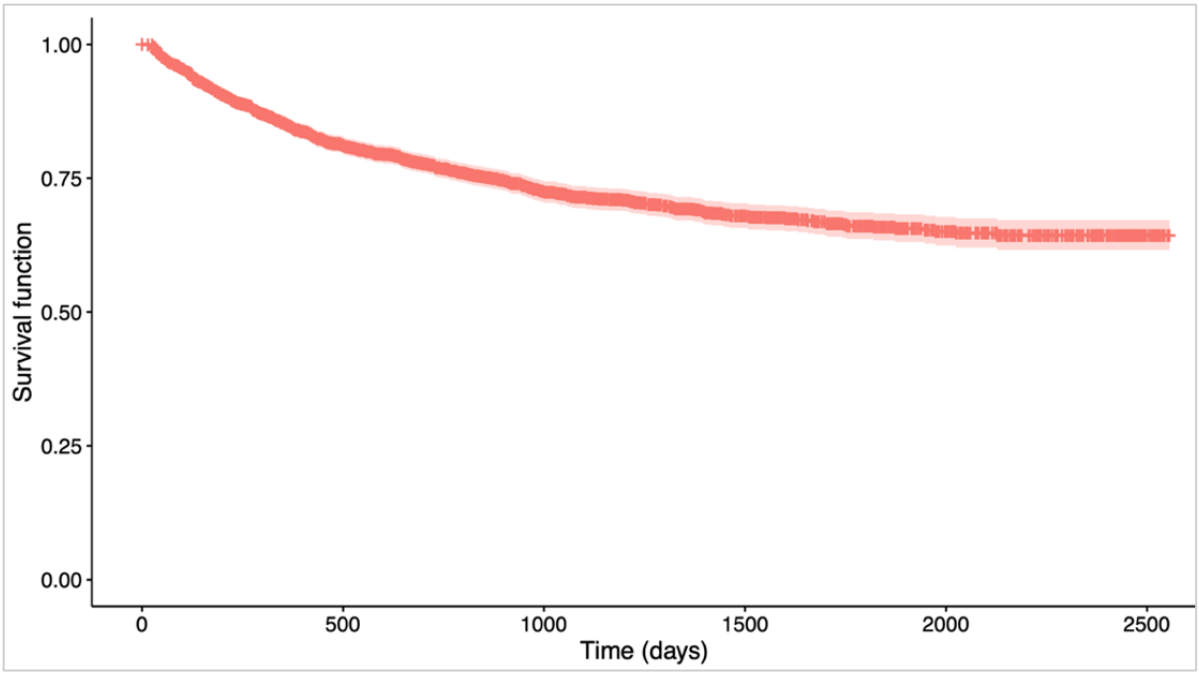
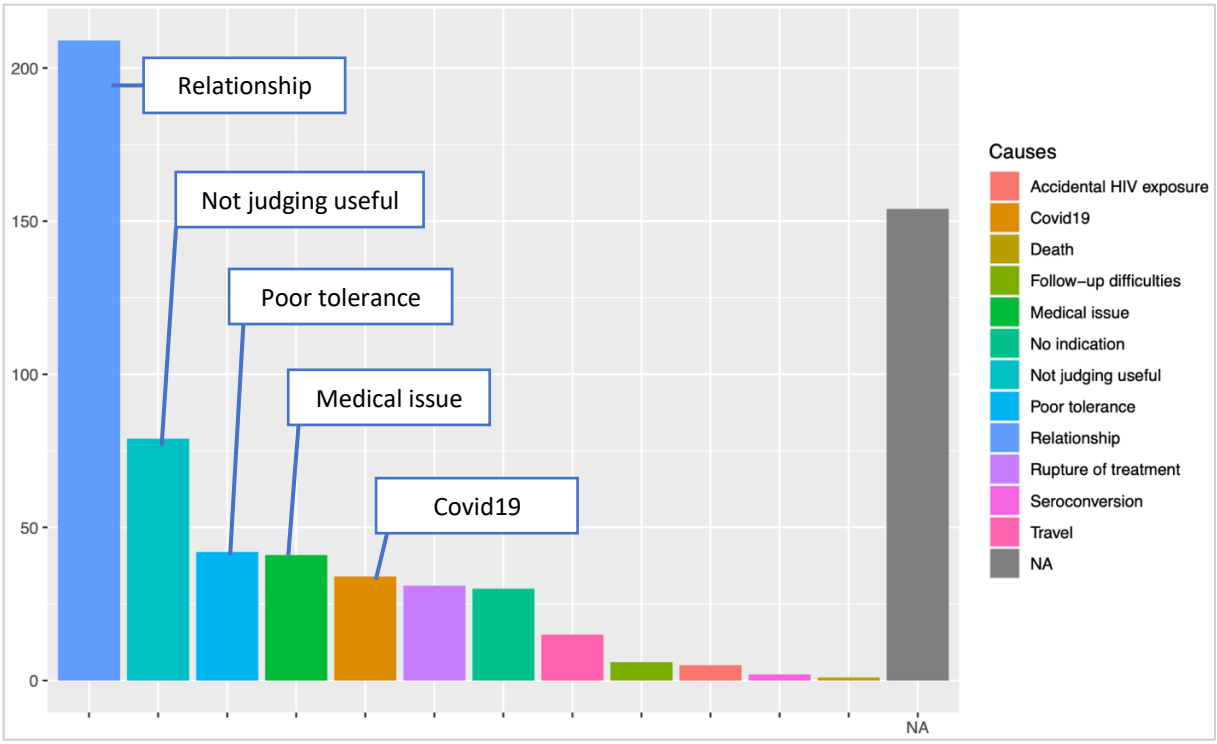


Figure 6: Kaplan Meier curve of PrEP discontinuation



The reasons given for PrEP discontinuations are presented in the Figure 7 and Table S2. The two main causes were having an exclusive stable partner (n=208, 32.2%) and not judging PrEP useful anymore (N=79, 12.2%). Poor tolerance led to PrEP discontinuation in 42 cases (6.5%). Two seroconversions occurred during follow-up, the first one in a non-adherent user and the second one after several weeks of PrEP discontinuation (Table S3). We do not know what was the reason for this discontinuation. Both discontinuations occurred more than a year after starting PrEP.

Figure 7: Reasons given by participants for discontinuing PrEP (N=653)



NA = not available

Sensitive analyses

We calculated the incidence rate of discontinuation assuming that all LTFU individuals had stopped PrEP. The number of discontinuations was 1042, and the incidence rate was 17.19 for 100 PY (16.14-18.23). Considering that half of LTFU were PrEP discontinuations, the incidence rate of discontinuation was 13.97 for 100 PY (13.03-14.92).

Incidence according to periods

The Covid-19 pandemic was the fifth reason for PrEP discontinuations (N = 34, 5.2%). Indeed, during the 2020 lockdow individuals could experience difficulties accessing PrEP consultations (Table S4). The incidence rate of PrEP discontinuations was higher in 2020, i.e. the year the most impacted by the lockdowns (13.93/100PY (11.74-16.13), than in 2016-2019 (11.12/100PY (9.80-12.44), p=0.03) and in 2021-2022 (9.38/100PY (8.16-10.61), p<0.001).

Individuals restarting PrEP after a first discontinuation

Among the 653 PrEP discontinuations, 162 (24.8%) led to a restart after a period of at least 3 months without treatment. Some causes of discontinuation appeared to be more predominant for transient stops than definitive ones: a medical issue (17.8% of transient stops versus 5.0% of definitive stops), the Covid-19 pandemic (9.6% versus 5.8%), travels (5.9% versus 1.9%) and a lack of treatment supply (8.2% versus 5.5%). Conversely, being in a stable relationship with a partner led more often to a definitive stop than a transient one (45.7% versus 31.9%) (Table S5).

Comparison of early and late discontinuations

We looked at the causes of discontinuation according to the time between initiation and discontinuation of PrEP (less or more than a year). 384 (58.8%) discontinuations occurred before a year of follow-up, and 269 (41.2%) after. A poor tolerance to the medication seemed to lead to an early discontinuation of PrEP (Table 2 and Figure S2).

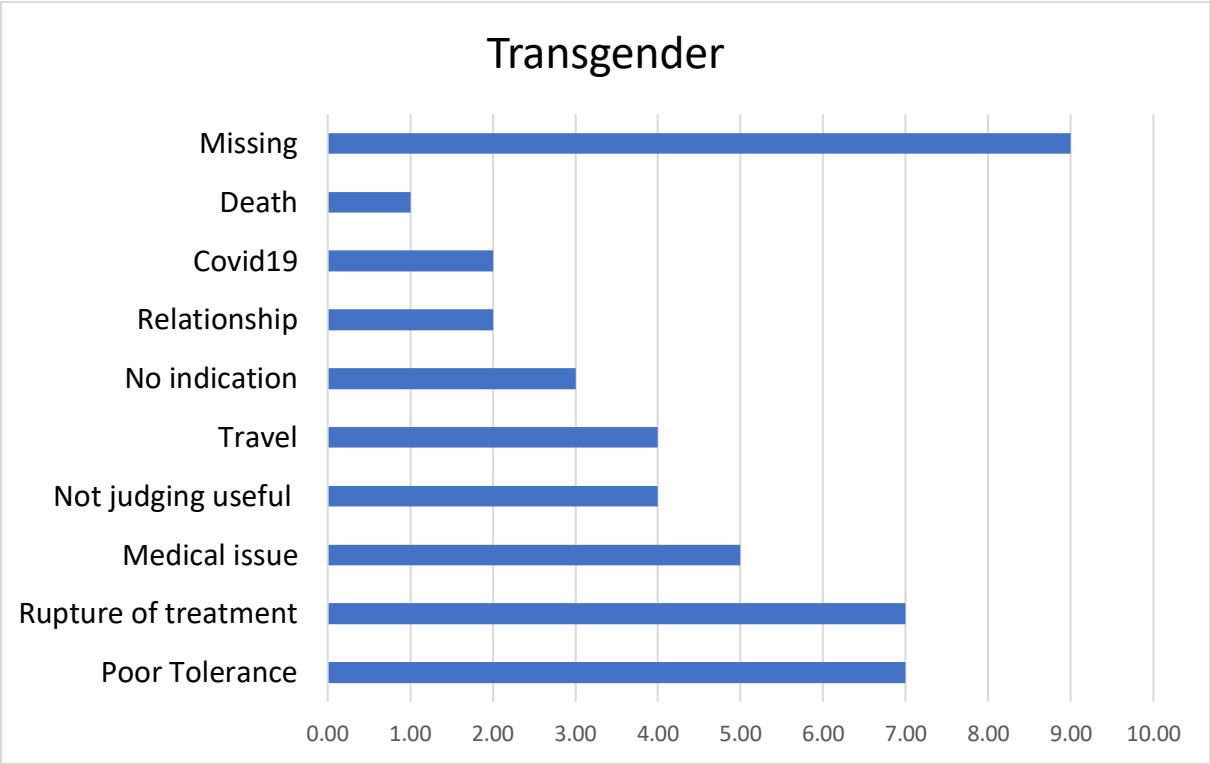
Table 2: Comparison of early and late discontinuations

Causes of discontinuation	Stop ≤ 1 year – Number (%)	Stop > 1 years – Number (%)
Not judging useful	50 (17.9)	31 (14.2)
Covid-19 pandemic	13 (4.7)	21 (9.6)
Stable Relationship with a partner	110 (39.4)	99 (45.2)
Poor tolerance	33 (11.8)	9 (4.1)
No indication	14 (5.0)	16 (7.3)
Medical issue	19 (6.8)	23 (10.5)
Rupture of treatment	22 (7.9)	9 (4.1)
Other	18 (6.5)	11 (5.0)
NA	105	50
Total	384	269

Transgender people

In our cohort, 126 (4.5%) individuals were transgender, essentially MtF (121, 96.0%). They came from Latin America and the Caribeean for 81.0% of them (N=102) and had a median age of 32 (29-39) years old at PrEP initiation. Among them, 102 (81.0%) were sex workers; in other words, 65.0% of all sex workers in the cohort were transgender people. At the endpoint of the study, 44 (34.9%) had stopped the PrEP, 58 (46.0%) were still followed in their center, 22 (17.5%) were LTFU, and 2 (1.6%) were followed in another center or by a general practitioner. Their median length of follow-up was 12.5 months (6.5-34.2). The incidence rate of PrEP discontinuation was 18.81/100PY (13.252-24.368). The main reasons for discontinuing were poor tolerance (N= 7, 15.9%) and lack of treatment supply (N = 7, 15.9%) (Figure 8).

Figure 8: Reasons for discontinuation among transgender persons



Factors associated with PreP discontinuations

Table 3 represents the results of univariate and multivariate cox regression models. In the univariate analysis, we found an excess risk of discontinuations for people born in sub-Saharan Africa and in Latin America and the Caribbean when compared to French people, for women and transgender persons than men, for sex workers, and for yound people (<29 years). During the last year of follow up, people who had at least 2 STIs or a PrEP side effect were more at risk of discontinuation. Individuals with recreative drug use had a reduced risk of PrEP discontinuation, as well as people in a relationship at the initiation of PrEP. Individuals who had symptoms of STI at least once during the follow up stopped the treatment less often. On-demand and mixed regimen decreased the risk of discontinuation in comparison with daily PrEP. Risk of discontinuation varied according to the centers, with less discontinuation in Tenon and Tourcoing hospitals in comparison to Bichat hospital.

Table 3: Factors associated with PrEP discontinuations in a cohort of PrEP users in 3 centers in France (n=), resulst of theunivariate and multivariate Cox models

Variables	Discontinuation (%)	Unadjusted HR (IQR)	P-value	Adjusted HR (IQR)	P-value
Centre					
Bichat	293 (29.0)	Reference	Ref	Ref	Ref
Tenon	193 (22.5)	0.59 (0.49-0.71)	< 0.0001	0.88 (0.71-1.08)	0.210
Tourcoing	167 (18.3)	0.56 (0.46-0.68)	< 0.0001	0.79 (0.62-1.01)	0.060
Gender					
Cis Men	588 (22.6)	Ref	Ref	Ref	Ref

Cis Women	21 (41.2)	3.32 (2.15-5.14)	< 0.0001	2.44 (1.50-3.96)	< 0.001
Transgender	44 (34.9)	1.74 (1.28-2.36)	< 0.001	0.74 (0.44-1.24)	0.258
Age					
< 29 years	182 (29.3)	1.70 (1.39-2.09)	< 0.0001	1.45 (1.17-1.80)	< 0.001
29-35 years	142 (25.2)	1.23 (0.99-1.53)	0.059	1.17 (0.93-1.47)	0.186
35-43 years	199 (21.7)	Ref	Ref	Ref	Ref
> 43 years	120 (19.0)	0.81 (0.65-1.01)	0.062	0.80 (0.63-1.02)	0.066
Region of birth					
France	425 (23.7)	Reference	Ref	Ref	
Sub-Saharan Africa	28 (30.4)	1.79 (1.22-2.62)	0.003	1.11 (0.74-1.66)	0.612
Latin America and Caribbean	76 (31.8)	1.47 (1.15-1.88)	0.002	0.94 (0.65-1.34)	0.715
Eastern Europe and Asia	15 (25.0)	1.05 (0.63-1.75)	0.861	0.87 (0.51-1.46)	0.590
Middle East and North Africa	28 (25.2)	1.17 (0.79-1.71)	0.433	0.90 (0.61-1.33)	0.611
Western countries	19 (16.2)	0.64 (0.41-1.02)	0.061	0.63 (0.40-1.01)	0.053
Regimen					
Daily	280 (25.6)	Ref	Ref	Ref	Ref
On-demand	266 (21.8)	0.81 (0.69-0.96)	0.015	1.00 (0.82-1.21)	0.992
Mixed	107 (22.8)	0.74 (0.59-0.93)	0.009	0.82 (0.64-1.05)	0.110
Other					
Sex worker	58 (36.9)	1.85 (1.41-2.42)	< 0.0001	1.53 (0.96-2.44)	0.072
Recreative drug use	161 (22.1)	0.79 (0.66-0.95)	0.011	0.85 (0.70-1.03)	0.103
Slam	13 (18.6)	0.62 (0.36-1.08)	0.090		
Side effects (last year)	138 (36.9)	2.54 (2.10-3.07)	< 0.0001	2.25 (1.83-2.77)	< 0.0001
Symptoms of STI	152 (20.1)	0.56 (0.46-0.67)	< 0.0001	0.54 (0.44-0.66)	< 0.0001
≥ 2 STI (last year)	151 (36.5)	1.78 (1.48-2.13)	< 0.0001	1.87 (1.53-2.27)	< 0.0001
Stable Relationship at initiation	80 (21.2)	0.78 (0.62-0.98)	0.036	0.77 (0.60-0.99)	0.042
Stable Relationship during follow-up	119 (24.9)	0.81 (0.66-0.99)	0.039	0.90 (0.72-1.12)	0.334
HIV exposure accident	23 (25.3)	0.85 (0.56-1.28)	0.434		

A multivariate cox model was performed with adjustment under all significant variables quoted before. After the adjustment, there was an increased risk of discontinuation for young people (<29 years, HR=1.45 (1.17-1.80)), women (H= 2.44 (1.50-3.96)), and for individuals who had a side effect (HR 2.25 (1.83-2.77)) or at least 2 STIs (HR 1.87 (1.53-2.27)) during the last year of follow-up. There was no association with transsexual genders or PrEP regimen anymore. Additionally, we found a reduced risk of stopping PrEP for people who reported a steady partner at PrEP initiation (HR 0.77 (0.60-0.99)) or who had had symptoms os STI (HR 0.54 (0.44-0.66)). Although not statistically significant, it appeared that there were fewer

discontinuations among PrEP users followed at Tourcoing and those from Western countries, as well as among older PrEP users (above 43 years old). Conversely, sex work seemed to be associated with a higher rate of PrEP discontinuations.

E) Discussion

In this cohort of PrEP users from 3 hospital PrEP centers in France, we observed an incidence rate of PrEP discontinuations of 10.8 for 100 PY. There were multiple reasons for discontinuation, the most prevalent one was being in a stable relationship. The factors associated with PrEP discontinuations in the multivariate analysis were female gender, young age, having 2 STI or more in the last year of follow-up or having side effects in the last year of follow-up.

Our sample was representative of the population of PrEP users in France, with a median age of 35 years old and a majority of men who have sex with men. This aligns with findings from healthcare reimbursementdata, including almost 10,000 PrEP users, with a median age of 36 years and 98.8% of men (44). Similar demographic characteristics were observed in cohorts conducted in Belgium (45) and in Canada (31).

The incidence rate in our study was much lower than the one found in the French PREVENIR study (17.6 for 100 PY), a prospective cohort following 3,000 Parisan PrEP users during 3 years (16). The disparity could be attributed to the differing definitions of PrEP discontinuation used in that study. In our study, we only counted the proved discontinuations, without the LTFU people, whereas in the PREVENIR study, Molina et al. defined PrEP discontinuation as stopping PrEP or missing the 2 last follow up visits, thus including all LTFU people. When we applied the same definition, we found an incidence rate approaching the one of PREVENIR (17.2 (16.1-18.3) for 100 PY). However, the most accurate definition is probably in between, with approximately half of the LTFU having discontinued the PrEP, and half continuing it (our second hypothesis in the calculation of incidence).
In the Austrian study of Chidwick et al. the definition of a PrEP discontinuation was close to ours, and they found 19.2% of PrEP discontinuation, lower than our rate of 23.5%. But this study included PrEP users followed in primary care by general practitioner (46). Conversely, in the study of Serota et al. among young black men who have sex with men in the US, the discontinuation was defined by only 14 days or more without treatment, leading to 69% of first discontinuations (21). But it was a prospective, interventional study facilitating the accuracy of the data; moreover, with the on-demand regimen available in France, allowing occasional use of PrEP relative to risk behavior, this definition would not be adapted.
Furthermore, in our study, the results were likely influenced by the Covid-19 pandemic, particularly the lockdown mesures in 2020, with a lower rate of PrEP prescription in 2020, a higher rate of discontinuation, and a higher rate of restarting after discontinuation. However, most of these discontinuations were probably justified by a significant reduction in risky behavior, as assessed by the ERAS investigation (47).

Most of the reasons for discontinuing PrEP were relative to an absence of indication (being in an exclusive relationship or not having an indication according to the doctor), but some were not. Particularly, the second most common cause for discontinuation was “not judging PrEP

useful for themselves anymore", as reported by the PrEP users, and without seeking medical advices in most cases. In a meta-analysis of 2022 (33), the most frequent reasons for stopping the PrEP were the low perceived risk of HIV infection and experiencing side-effects. Additionally, in a qualitative study in Kenya, where 46 participants were asked why they discontinued PrEP, most of them emphasized that the decision to discontinue was made independently and without consulting their clinician (48). But we could wonder the rate of misevaluation of risk by PrEP users. While it is understandable for PrEP users to evaluate their own risk of HIV exposure and need for PrEP, such decisions should be taken with the care provider after reassessing together HIV exposure risk.
Some of the reasons for discontinuations were related to treatment interruptions and difficulties with follow-up. In our cohort there were 126 transgender persons, a population disproportionally affected by HIV infection. They had different characteristics compared to cis men and women, with higher exposure to precarity (such as immigration and sex working) leading to an increased risk of contracting HIV. Their reasons for PrEP discontinuation were also distinct, with a poor tolerance and the lack of treatment supply in first positions, although the small sample available. These people may face more barriers in accessing treatment and healthcare facilities and thus need particular attention to prevent them from being LTFU (49) (50). In contrast to other studies, transgender persons did not show an excess risk of PrEP discontinuation in multivariate analysis, when adjusted on the PrEP centre, country of birth, and sex work. However, the proportion of discontinuations among this subpopulation was higher, and their median time of follow-up per person was lower. We can hypothesize that the adjustment on sex working, which constitutes a significant proportion of this subpopulation, masked this association.

Research is making progress in that direction with the development of numerous apps (51), pharmacist-managed PrEP clinic intervention (52), teleconsultations (53), and new PrEP formulations. Long-acting Cabotegravir consists of a single 600 mg intramuscular injection given at 2-month intervals after an initial two injections 1 month apart; its efficacy was demonstrated in the HPTN 083 and HPTN 084 trials (54). It was approved by the US Food and Drug Administration in December 2021 (55), and had a favorable opinion from the European Medicines Agency in July 2023. Multiple studies are underway with subcutaneous injections of Lenacapavir every 6 months (56). These new formulations should increase users' adherence and promote PrEP persistence for people who do not feel comfortable with oral PrEP, who face adherence challenges, or who perceive oral PrEP as too burdensome.

Young age and female gender were found to be two risk factors of PrEP discontinuations in agreement with orther studies (33). In addition to the preexisting literature, we found that experiencing side effects and having two or more STIs during the last year of follow-up were associated with an increased risk of discontinuation. That is an issue because these individuals are potentially still at risk of HIV infection, the presence of STIs reflecting their sexual behavior and may remain particularly exposed to HIV after discontinuing PrEP.
On the contrary, we identified being in a relationship at the initiation of the PrEP as a protective factor, maybe reflecting a lower risky behavior.
We did not find excess risk depending on the regimen of PrEP, which is in line with the comparable efficacy already described (27), neither in case of substance use disorder.

One significant concern with PrEP users is the number of LTFU people. Despite actively reaching-out to individuals who have not attended the hospital centres for 6 months, almost 15% of PrEP users were classified as LTFU in our study. Some of them may have discontinued PrEP or sought follow-up elsewhere, but others may have faced barriers accessing PrEP or being misinformed regarding PrEP. That is why it is important in our practice to minimize this number as much as possible. In an interventional study conducted in San Francisco, authors contacted LTFU people with SMS to inquire about their status with regards to PrEP. Among the 846 LTFU PrEP users, only 130 (15.4%) agreed to participate and answered the survey; among them, 42 (32.3%) were still on PrEP while 88 (67.7%) were not (57). In another study in New York City (58) authors were able to reach out to 88/ 634 LTFU persons (12%); among them, 55 (64%) had stopped taking PrEP at the time of the survey and 31 (36%) reported actively taking PrEP, in keeping with the proportions reported in the previous study. These findings underscore the challenges in recontacting LTFU individuals and align with our second hypothesis concerning LTFU people. Besides, we could wonder if LTFU people who can be contacted have the same characteristics than LTFU who cannot.

Limits and strengths

The main limitation of this study is its retrospective nature, resulting in more missing values regarding the status of PrEP users, causes of discontinuation, and other potentially important factors. We did not have access to the evaluation of HIV risk behavior of the PrEP users performed at each visit (number of unprotected sexual intercourse, number of partners) that may help to interprete reasons for disconstinuing PrEP. Very few socio-economic data were available, mainly the educational level that often associated with a poorer access to healthcare facilities and poorer adherence. Moreover, due to the limited sample size of only 126 transgender individuals and 51 cisgender women, we encountered insufficient statistical power to thoroughly study these two populations, which appear to be at higher risk but are represented by too few cases.

Nevertheless, it is a powerful cohort with a large sample size and long follow-up period, providing valuable evaluation of PrEP discontinuations. Our sample was representative of French PrEP users, as it included two Parisian hospital centers and a peripheral hospital center, effectively mitigating selection bias..

F) Conclusion

In our cohort, the incidence rate of PrEP discontinuation was 10.8 per 100 PY, with probable underestimation due to censoring on LTFU individuals. A significant number of individuals stopped the treatment on their own, without seeking for medical recommendation, and remained at risk of HIV infection. The critical challenge is to ensure they continued engagement in the healthcare system to prevent post-discontinuation seroconversion and enable prompt HIV diagnosis if needed. These data would merit a confirmation in a prospective study.

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6/ Annex

A) Tables

Table S1: Nature of side effects

Side effects	Number (%)
Digestive disorders	889 (72.4)
Abdominal pain	219 (17.8)
General alteration	121 (9.9)
Headache	85 (6.9)
Dizziness	25 (2.0)
Other pain	19 (1.6)
Other	109 (8.9)
Total	1228

Table S2: Causes of discontinuation

Cause of discontinuation	Number (%)
HIV exposure accident	5 (0.8)
Not judging useful	81 (12.4)
Covid19	34 (5.2)
Relationship	209 (32.0)
Death	1 (0.2)
Follow-up difficulties	6 (0.9)
Poor tolerance	42 (6.4)
No indication	30 (4.6)
Medical issue	42 (6.4)
Rupture of treatment	31 (4.8)
Seroconversion	2 (0.3)
Travel	15 (2.3)
Missing	155 (23.7)
Total	653

Table S3: Seroconversions

Variables	PrEP user 1	PrEP user 2
Origin	France	France
Sex and sexuallity	HSH	HSH
Age (years)	42	38

Sex worker	No	No
Drug use	No	Yes
Slam	No	No
Relationship	Yes	No
Follow-up (days)	641	1873
Side effects	No	No
STI	0	4
Regimen	Mixed	On-demand

Table S4: Number of prescriptions per year

Year of prescription	**Number (%)**
2016	391 (14.0)
2017	354 (12.7)
2018	422 (15.2)
2019	588 (21.1)
2020	374 (13.4)
2021	449 (16.1)
2022 (6 months)	207 (7.4)
Total	2785

Table S5: Causes of temporary versus definitive discontinuations

Modalités	**Temporary stops – Number (%)**	**Definitive stops – Number (%)**
Accidental HIV exposure	0	5 (1.4)
Not judging useful	18 (13.3)	63 (17.4)
Covid19	13 (9.6)	21 (5.8)
Relationship	43 (31.9)	166 (45.7)
Death	0	1 (0.3)
Follow-up difficulties	0	6 (1.7)
Poor tolerance	9 (6.7)	33 (9.1)
No indication	9 (6.7)	21 (5.8)
Medical issue	24 (17.8)	18 (5.0)
Rupture of treatment	11 (8.2)	20 (5.5)
Seroconversion	0	2 (0.6)
Travel	8 (5.9)	7 (1.9)
Missing	27	128

Total	162	491

B) Figures

Figure S1: Origin of PrEP users

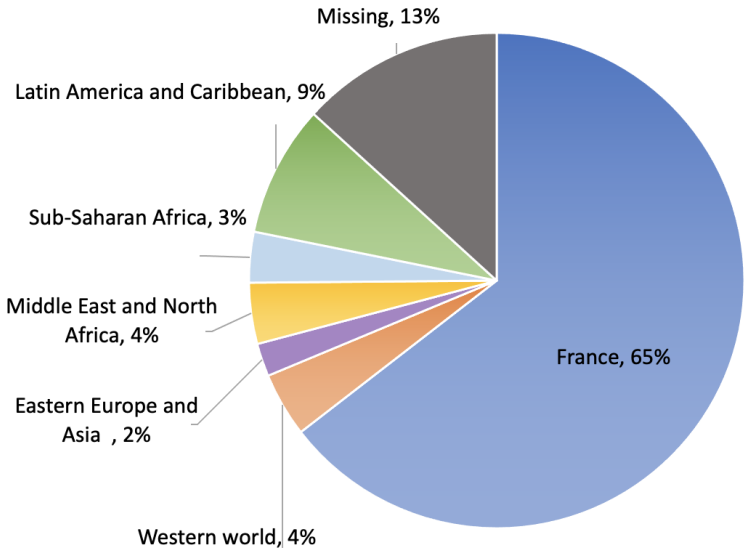
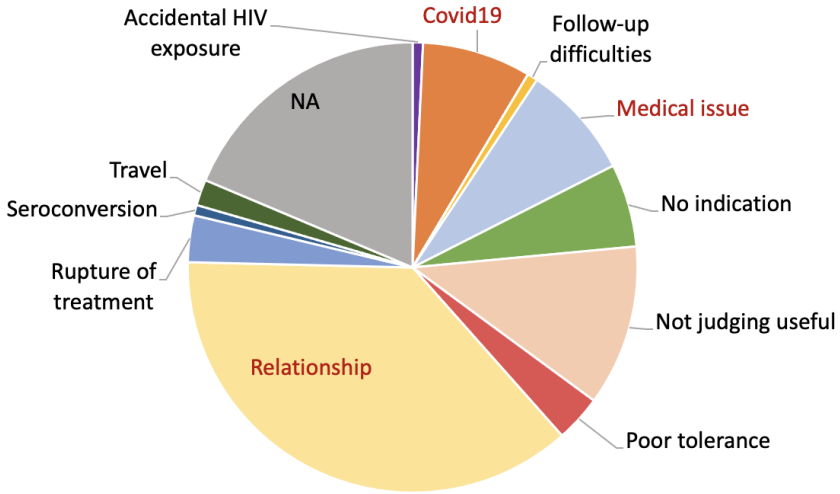
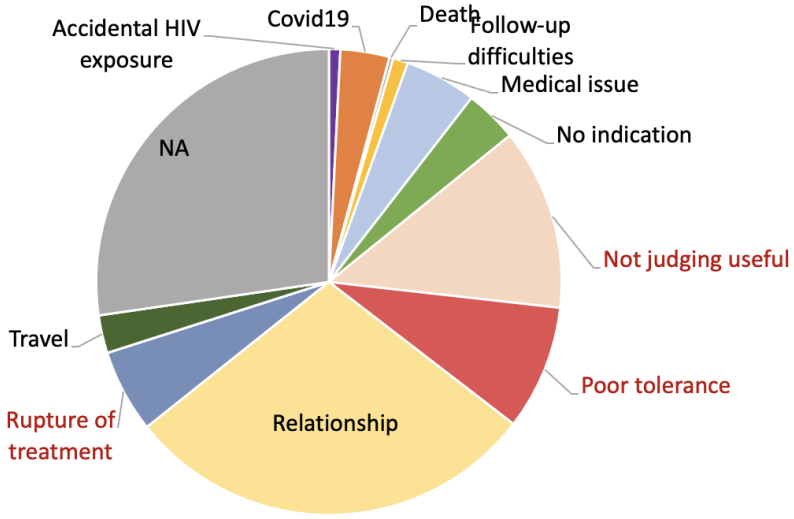


Figure S2: Causes of early and tardive discontinuations

a- Early discontinuations



b- Tardive discontinuations



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