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MAJOR ARTICLE

# HIV Oral Pre-exposure Prophylaxis Effectiveness, Adherence, and Discontinuation in an Italian Multicentric Access Program: ItaPrEP Study

**Valentina Mazzotta,[1] Enrico Caruso,[2] Alessandro Tavelli,[3,4] Rozenn Esvan,[1] Simone Lanini,[5] Giulia Micheli,[1] Davide Moschese,[2] Anna De Bona,[6] Sandro Mattioli,[7] Daniele Calzavara,[2] Federico De Zottis,[1] Daniele Tesoro,[6] Lorenzo Badia,[7] Silvia Nozza,[8] Antonella Cingolani,[9] Alessandra Bianchi,[2] Rita Bellagamba,[1] Salvatore Cecere,[7] Alessandro Giacinta,[1] Nicoletta Frattini,[2] Alessandra Oliva,[1] Roberto Repossi,[2] Roberto Rossotti,[10] Marco Ridolfi,[11] Claudio Maria Mastroianni,[11] Carlo Torti,[9] Giulia Marchetti,[6] Antonella Castagna,[8] Antonella d'Arminio Monforte,[3] Massimo Cernuschi,[2] and Andrea Antinori[1]**

[1]HIV/AIDS Unit, Department of Clinical Infectious Diseases, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy, [2]Milano Checkpoint, Milano, Italy, [3]Icona Foundation, Milan, Italy, [4]National PhD Programme in One Health Approaches to Infectious Diseases and Life Science Research, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy, [5]Infectious Diseases Clinic, Department of Medicine (DAME), University of Udine, Udine, Italy, [6]Infectious Diseases Unit, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy, [7]PLUS aps (BLQ Checkpoint), Bologna, Italy, [8]Infectious Diseases Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, [9]Infectious Diseases Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Catholic University of the Sacred Heart, Rome, Italy, [10]Infectious Diseases Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy, and [11]Department of Public Health and Infectious Diseases, Sapienza University, Rome, Italy

***Background.*** Italian oral pre-exposure prophylaxis (PrEP) implementation faced challenges until the drug reimbursement approval in 2023. National real-life data on effectiveness are lacking. This study aimed to report incidence rates (IR) of HIV and other sexually transmitted infections (STIs), along with probabilities and predictors of poor adherence and PrEP discontinuation.

***Methods.*** Prospective national cohort study (ItaPrEP) on oral PrEP users (PrUs) in eight Italian centers (September 2017–November 2023) that could partially provide free drug supplies. IRs of HIV and STIs, and Kaplan–Meier estimated probabilities of poor adherence and discontinuation were evaluated. Mixed-effect logistic models with random intercept on the center were used to explore the association between risk factors and poor adherence and discontinuation.

***Results.*** About 1758 PrUs were included, 98% MSM; five HIV seroconversions were observed with an IR 0.187/100 person-year follow-up (PYFU; 95% CI: 0.061–0.436). IR/100 PYFU were 13.1 (95%CI:11.7–14.5) for syphilis, 23.8 (95% CI: 22–25.7) for chlamydia, and 24.2 (95% CI: 22.4–26.1) for gonorrhea. The 2-year probability of poor adherence and discontinuation was 57.9% (95% CI: 54.8–61.0) and 37.1% (95% CI: 34.3–40.1), respectively.

Chemsex and switching schedule were associated with poor adherence, unlike a high educational level. Age >40 years, free drug supplies, and laboratory monitoring were associated with a lower risk of discontinuation, while chemsex was associated with a higher risk.

***Conclusions.*** In this Italian oral PrEP program, the HIV incidence was lower than that observed in pivotal clinical trials in high-risk populations and close to that of observational real-life studies. Identifying fragile groups (youngest, low educational level, and chemsex users) and addressing barriers (free drugs and monitoring) are key to targeting strategies to improve oral PrEP implementation.

## INTRODUCTION

Despite a progressive decrease in the number of incident HIV infections, around 1.3 million new HIV infections were still diagnosed in 2023 worldwide [1].

HIV pre-exposure prophylaxis (PrEP) with antiretroviral drugs is one of the most effective approaches for preventing HIV in high-risk populations, and the 2025 UNAIDS target is to reach PrEP for 10 million people at substantial risk of HIV globally [1].

Currently, an oral combination of emtricitabine/tenofovir disoproxil (FTC/TDF) is the most used option for PrEP [2]. Data from randomized clinical trials have demonstrated its efficacy in preventing HIV infection in people at high risk, reaching 86% in men who have sex with men (MSM) [3–5]. In this population, protection against HIV infection was confirmed either with a daily schedule or with an *on-demand* schedule [6].

In countries where PrEP was extensively implemented, real-life data from big cohorts showed a consistent reduction in the number of new HIV infections [7–9]: the HIV incidence in high-risk MSM was reported around 1.1 cases per 1000 person-years in the PREVENIR cohort, and in the EPIC-NWS study, the

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Correspondence: Alessandro Tavelli, MSc, Icona Foundation, Via Antonio di Rudinì 8, 20142 Milan, Italy (alessandro.tavelli@icona.org); Valentina Mazzotta, PhD, Department of Clinical Infectious Diseases, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Via Portuense 292, 00149 Rome, Italy (valentina.mazzotta@inmi.it).

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HIV incidence was 92% less than the expected in the absence of PrEP [10, 11].

PrEP implementation in Italy faced challenges: at the time of its authorization in 2017, PrEP could be purchased in pharmacies at a cost of around 60 euros per 30 FTC/TDF tablets by a prescription from an infectious disease specialist [12]. PrEP reimbursement by the Regional Health System in Italy was only approved in May 2023, linked to three-month clinical visits and screening for HIV and sexually transmitted infections (STIs) [13]. However, whereas HIV screening is free of charge in Italy, STI monitoring is only free in some regions, with the cost of STI monitoring and medical visits every 3 months being around 50 euros.

In this context of difficult access and cost barriers, and with a fragmented health data system in Italy, no institutional national data platform is still available on PrEP access, user's characteristics, PrEP program effectiveness, and PrEP adherence and persistence [14].

Here, we report data from the largest multicenter Italian national cohort (ItaPrEP) with the aim of describing the incidence of HIV and other STIs, together with rates and predictors of poor adherence and discontinuation.

## METHODS

### Study Design and Population

Since 2017, the National Institute for Infectious Disease Lazzaro Spallanzani IRCCS in Rome and the Italian Society of Infectious Diseases (SIMIT) promoted the first Italian PrEP network (ItaPrEP) across the main towns providing PrEP in Italy (Rome, Milan, and Bologna).

ItaPrEP was a multicenter prospective cohort study on people taking PrEP in 8 Italian sites from 2017 to 2023 (before the national reimbursement). Two out of eight centers were community-based.

Through donations from pharma companies, the ItaPrEP program partially provided a free drug supply to users, according to availability. STI monitoring was free of charge only for users residing in regions that approved reimbursement (particularly in Milan and Bologna).

All adults (age $\geq$ 18 years), HIV-negative, willing to take oral PrEP, and meeting the Italian Drug Agency (AIFA) criteria for oral FTC/TDF prescription were included [12]. All the participants provided written informed consent and were asked to attend the clinic every 3 months, according to AIFA recommendations [12].

After the acquisition of consent, sociodemographic features, medical history, including comedication, behavioral data exploring the use of recreational drugs, HIV exposure, and risk perception were collected.

Data on the mode of taking oral PrEP (daily, on-demand, or switching between the two) and the eventual free supply of the drug were recorded. Monitoring consisted of a 3-month screening for HIV (fourth-generation HIV assay), HCV serology, treponemic and non-treponemic tests for *T. pallidum* screening, nucleic acid amplification tests for detection of *C. trachomatis* and *N. gonorrhoeae* in pharyngeal, rectal, vaginal swabs, and spot urine, as appropriate.

At each evaluation, participants completed a questionnaire about adherence and risk behaviors. Poor adherence was defined as an incorrect intake of the 2:1:1 scheme for on-demand PrEP and a temporary stop (more than three consecutive days) for daily PrEP or reported sex without PrEP and without a condom in the behavioral questionnaire. Oral PrEP discontinuation was defined as a definitive stop or loss to follow-up for at least 1 year. For those who are lost and re-engaged around the COVID-19 lockdown period (March–August 2020), an additional 5 months of loss are considered in the definition of PrEP discontinuation.

### Outcomes

The primary outcome was to assess incidence rates (IRs) for HIV, STIs, and HCV, expressed as the number of new events over 100 person-year follow-up (PYFU) on PrEP. The secondary outcomes were to evaluate the proportion of PrEP users experiencing adverse events to oral PrEP, to investigate the probability of poor adherence to oral PrEP and discontinuation, and to evaluate the factors associated with them.

### Statistical Analysis

Baseline demographic, clinical, and behavioral characteristics were reported as absolute and relative frequencies for categorical variables and median and interquartile range (IQR) for continuous ones.

The incidence of HIV and the other STIs (gonorrha, chlamydia, and syphilis) was calculated as the number of new events for each infection divided by the total time at risk. The 95% CIs were calculated using a Poisson distribution, and the results were reported per 100 patient-year follow-up (PYFU). Each patient was considered at risk of new gonorrhea, chlamydia, or syphilis at every control visit. The incidence of HCV seroconversion was calculated as the number of users with a positive HCV serology among those with negative HCV-Ab at PrEP initiation, divided by the follow-up time at risk. For HCV seroconversion, the time at risk was censored at the date of the first HCV-Ab positive or last one available if negative. Kaplan–Meier curves were used to estimate the cumulative 1–, 2–, 3–, and 4-year probabilities of PrEP discontinuation and poor adherence. Follow-up accrued from the day of oral PrEP initiation till the first occurrence of the event or the date of the last available PrEP visit, whichever occurs first.

Unadjusted and adjusted mixed-effect logistic models with a random intercept at the center were used to explore the association between selected risk factors and outcomes. The strength of the association between risk factors and outcomes was

expressed as the odds ratio (OR) and adjusted odds ratio (AOR), with a relative 95% confidence interval (95%CI). The factors associated in the unadjusted analysis with a *P*-value < .1 were retained for the adjusted model, together with age, which was included *a priori* in the multivariable model. The variable "number of criteria for starting PrEP" was not retained in the final model due to collinearity with the variable chemsex use at enrolment. Proportion of PrEP users who experienced an adverse event to oral PrEP at least once during the follow-up was also reported, together with the list of main toxicities reported, and the proportion of discontinuation—temporary or definitive—due to adverse events. All statistical analyses were performed using Stata v 18. All *P*-values presented are two-sided, and a *P*-value <.05 indicates conventional statistical significance.

#### Patient Consent Statement

The protocol and its amendments were approved by the Ethical Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani (Approval number 57/2018). All patients signed a consent form for study participation and data processing in accordance with the ethical standards of the Committee on Human Experimentation and the Helsinki Declaration.

#### Role of Funding Source

The study was funded by the Italian Ministry of Health, "Ricerca Corrente, Linea 2, Project 4". The partial free supply of FTC&TDF during the study was provided with unconditional support from Gilead Sciences and Viatris.

## RESULTS

Participants' selection flow chart is detailed in Figure 1.

Among the 1758 participants with at least one follow-up visit after enrolment, the large majority (1731, 98.5%) identified as men, 14 (0.8%) as female, and 13 (0.7%) as transgender women (TGW). MSM were the most numerous group (1599, 91.2%), followed by bisexual (114, 6.5%) and heterosexual (35, 2%) individuals. The majority were Italian-born (1450, 82.5%), with a university (1071, 60.9%) or a high school degree (487, 27.7%). The median age was 36 years (IQR: 31–44), and only 87 (4.9%) were younger than 25. 1370 (87.4%) were employed, and only 44 (3%) were sex workers. The main criteria for starting PrEP were reporting inconsistent use of condoms (1216, 73.5%), previous STIs (445, 29%), chemsex use (274, 17.8%), or previous use of post-exposure prophylaxis (PEP; 232, 15%). 12 (0.7%) were HCV-Ab positive at first screening.

655 (37.3%) participants always took PrEP daily, 619 (35.2%) were always on-demand, and 464 (26.4%) switched over the study period (Figure 2).

790 (44.9%) people benefited from the free drug supply at least once, and 1218 (69.3%) did not pay for STI monitoring. Characteristics of the study population are reported in Table 1.

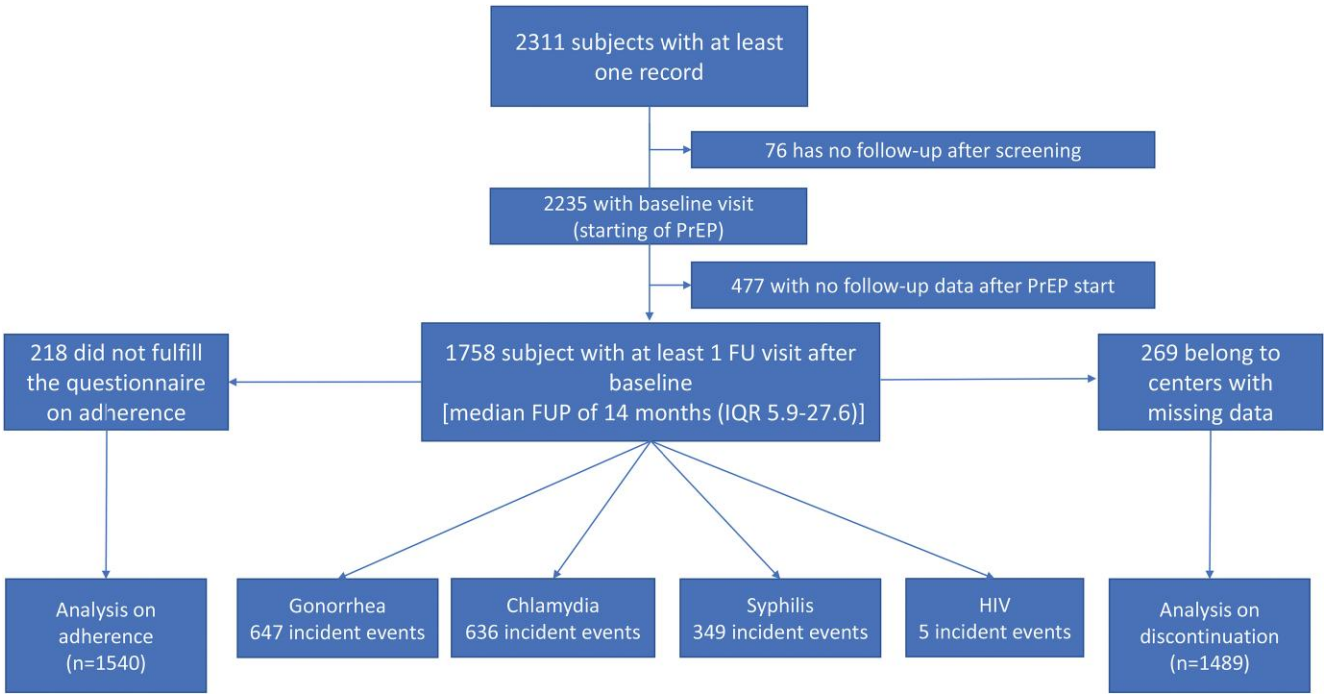



**Figure 1.** Oral PrEP users selection study flowchart.

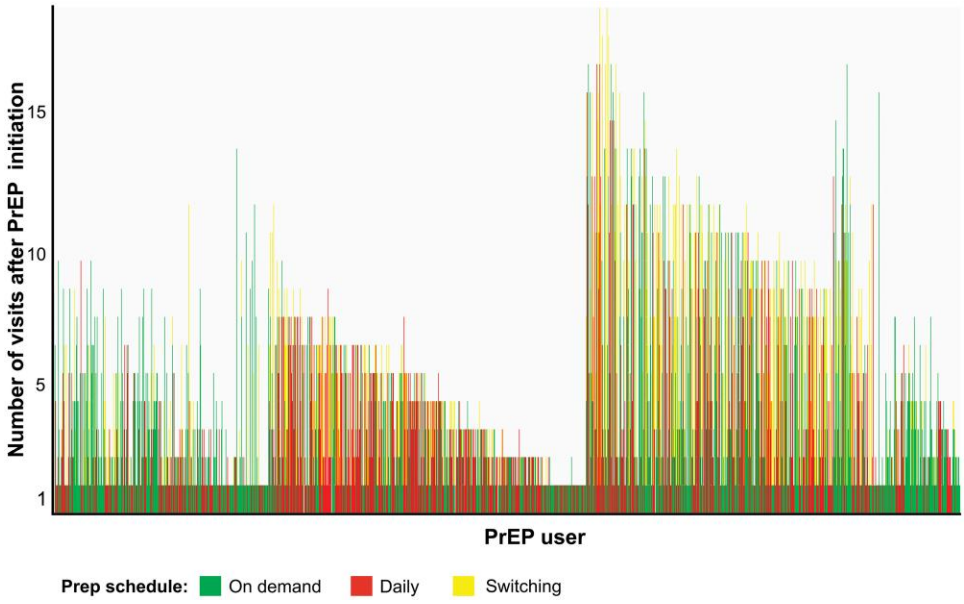



**Figure 2.** Oral PrEP schedule of assumption matrix.

#### HIV and STI Incidence

Five HIV seroconversions were observed over 2673 PYFU (IR 0.187/100 PYFU [95% CI 0.061–0.436]). All seroconversions occurred in people reporting poor adherence. The genotypic resistance test at HIV diagnosis was available for three of the five patients: M184V was identified in two patients. No other resistance-associated mutations were detected.

Incidence rates over 100 PYFU for STIs were 13.1 (95% CI: 11.7–14.5) for syphilis, 23.8 (95% CI: 22–25.7) for *Chlamydia trachomatis*, and 24.2 (95% CI: 22.4–26.1) for gonorrhea infection with a risk of subsequent events of 2.66 (95% CI: 2.11–3.34), 1.67 (95% CI: 1.42–1.96) and 1.70 times (95% CI: 1.45–1.99), respectively.

Nine incident cases of HCV seroconversions during PrEP occurred in those with HCV-Ab negative at baseline, with an incidence rate of 0.37 × 100 PYFU (95%CI 0.17–0.72).

#### Analysis on Oral PrEP Adherence

About 1540 participants fulfilled the questionnaire on adherence and were included in this specific subanalysis. Incidence rate of poor adherence was 44/100PYFU (95% CI: 40.8–47.2). The cumulative probability of poor adherence was 40.2% (95%CI: 37.5–43) at 1 year, 57.9% (95% CI: 54.8–61.0) at 2 years, 67.4% (95% CI: 63.9–70.9) at 3 years and 75.4% (95% CI: 70.9–79.6) at 4 years (Figure 3*A*). In the multivariable logistic model, chemsex users (AOR: 1.56; 95% CI: 1.11–2.18, $P = .01$) and those who switched schedules (AOR: 3.21; 95% CI: 2.38–4.33; $P < .001$) were more likely to be poorly adherent, unlike PrEP users with a high educational level (AOR, 0.70; 95% CI: 0.54–0.91; $P = .007$) (Table 2).

#### Analysis on Discontinuation

About 1489 participants had complete records for this analysis and were included. 477 discontinuations occurred with an incidence rate of discontinuation of 22.1/100PYFU (95% CI: 20.2–24.2). The cumulative probability of discontinuation was 24.8% (95% CI: 22.5–27.2) at 1 year, 37.1% (95% CI: 34.3–40.1) at 2 years, 44.3% (95% CI: 40.9–47.9) at 3 years, and 50.5% (95% CI: 46–55.2) at 4 years (Figure 3*B*). A temporary discontinuation occurred in 106/1489 users (7.1%), who returned to the PrEP program after 12 months of interruption, while the other 371 (24.9%) were definitively discontinued from PrEP. In the multivariable logistic model, participants older than 40 years old (AOR 0.68; 95%CI 0.53–0.86; $P = .002$) were more unlikely to discontinue the PrEP program as well as those who received free drug supply (AOR: 0.73; 95% CI: 0.54–0.99; $P = .045$) and who did not pay for laboratory monitoring (AOR: 0.40; 95% CI: 0.29–0.53; $P < .001$). Chemsex habit was associated with a higher risk of discontinuation (AOR: 1.80; 95% CI: 1.30–2.48; $P < .001$) (Table 2B).

#### Side Effects

About 1526 participants fulfilled the questionnaire on side effects of PrEP and were included in this specific subanalysis. Overall, 365 users (23.9%) reported at least one side effect of PrEP. The most frequently reported side effect was gastrointestinal intolerance (diarrhea/nausea) ($n = 237$ users, 15.5%), followed by fatigue ($n = 53$ users, 3.5%), headache ($n = 49$ users, 3.2%), sleep difficulty ($n = 19$, 1.2%), and rash ($n = 1$, 0.7%); 76/1526 (5.0%) had a temporary

**Table 1. Main Characteristics of Study Participants**

| Total Of Participants | *N* = 1758 |
|---|---|
| Gender, *n* (%) | |
| Male | 1731 (98·5%) |
| Female | 14 (0·8%) |
| Transgender (MtF) | 13 (0·7%) |
| Age, y, median [IQR] | 36·0 [31·0 44·0] |
| Class of age, *n* (%) | |
| < 25 | 87 (4·9%) |
| 25–39 | 1050 (59·7%) |
| > 40 | 621 (35·3%) |
| Nation of birth, Italy, n (%) | |
| No | 300 (17·1%) |
| Yes | 1450 (82·5%) |
| Unknown | 8 (0·4%) |
| Sexual orientation, *n* (%) | |
| MSM | 1599 (91·0%) |
| Heterosexual | 35 (2·0%) |
| Bisexual | 114 (6·5%) |
| Other | 6 (0·3%) |
| Unknown | 4 (0·2%) |
| Level of education, n (%) | |
| Primary school | 5 (0·3%) |
| Junior high school | 49 (2·8%) |
| High school | 487 (27·7%) |
| University | 1071 (60·9%) |
| Unknown | 146 (8·3%) |
| Job status, *n* (%) | |
| Employed | 1370 (77·9%) |
| Unemployed | 168 (9·6%) |
| Student | 29 (1·6%) |
| Unknown | 191 (10·9%) |
| Sex worker, *n* (%) | |
| No | 1438 (81·8%) |
| Yes | 44 (2·5%) |
| Unknown | 276 (15·7%) |
| Criteria for starting PrEP, *n* (%) | |
| Inconsistent use of condom | 1216 (73·5%) |
| Previous STI | 445 (29·0%) |
| Previous PEP | 232 (15·0%) |
| Chemsex use | 274 (17·8%) |
| Number of high-risk defining criteria, *n* (%) | |
| 0 | 295 (16·8%) |
| 1 | 786 (44·7%) |
| 2 | 440 (25·0%) |
| 3 | 130 (7·4%) |
| 4 | 28 (1·6%) |
| Unknown | 79 (4.5%) |
| Mode of PrEP administration, *n* (%) | |
| Always daily | 655 (37·3%) |
| Always on demand | 619 (35·2%) |
| Switching | 464 (26·4%) |
| Unknown | 20 (1·1%) |
| Free supply, *n* (%) | |
| Never | 968 (55·1%) |
| Always/sometimes | 790 (44·9%) |
| Free laboratory monitoring, *n* (%) | |
| No | 540 (30·7%) |
| Yes | 1218 (69·3%) |
| Total follow-up, m, median [IQR] | 14·0 [5·9 27·6] |

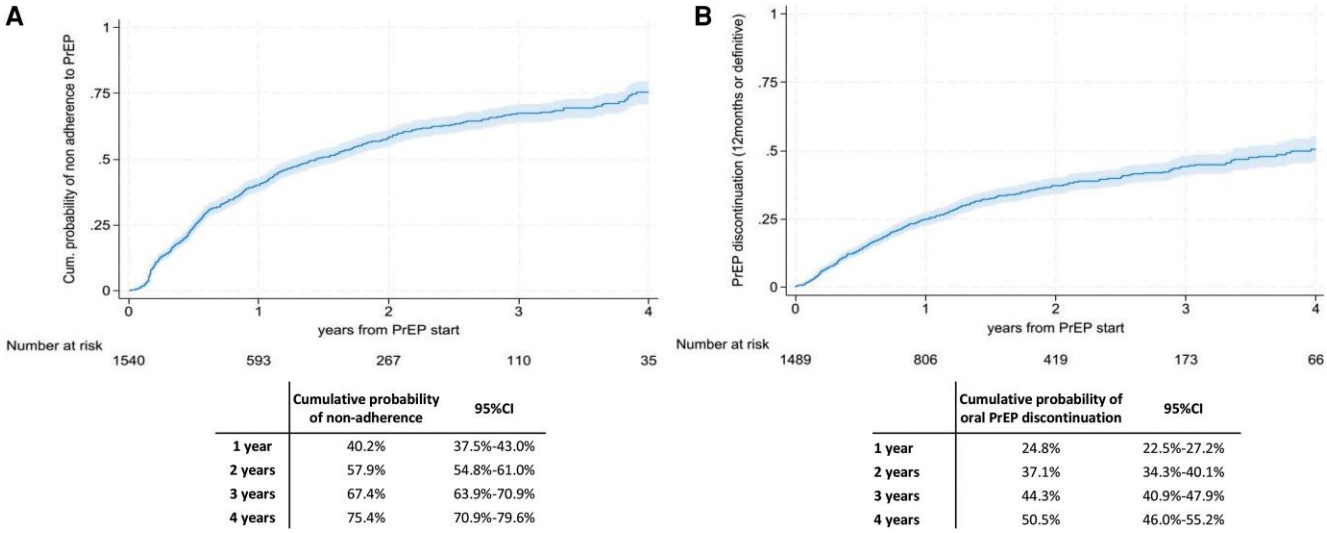
discontinuation of PrEP due to adverse events, and only one user (0.06%) permanently interrupted PrEP for an adverse event (skin rash).

## DISCUSSION

Our findings from the ItaPrEP program support the evidence of the effectiveness of PrEP in real-life applications in Italy. Although conducted in the period before reimbursability and therefore in a context of high barriers to access, including economic, the present analysis showed an HIV seroconversion incidence of 0.187 per 100 person-years, significantly lower than in the control arms of the main randomized clinical trials with the same high-risk population. Indeed, in the IPERGAY study, enrolling MSM, the reported incidence of HIV infections in the placebo group was 6.60 per 100 person-years, and in the EPIC-NSW cohort, an incidence of 2 per 100 person-years was observed in high-risk MSM without PrEP [6, 10]. Moreover, the background incidence observed in the lenacapavir PrEP randomized trial enrolling men and gender-diverse persons was 2.37 per 100 person-years [15]. Accordingly, with this range of incident infections during unprotected sex among MSM, the relative risk reduction estimated in the present study ranged from 91.0% to 97.2%.

Moreover, the HIV incidence observed in the present study was also lower than the 0.77 per 100 person-years reported in a large pooled analysis of global PrEP studies with FTC/TDF [16], and close to that estimated in a large reference population study in France [11], confirming the consistent effectiveness of oral PrEP strategy also in Italian setting, even before country reimbursability of oral drugs.

Regarding STIs risk, the observed incidence rate of STIs during the observation period was high, in line with previous reports [17] and consistent with a study population mainly including MSM. Accordingly, we observed a syphilis incidence of 13.1/100 PYFU, mirroring the global increasing reported incidence among MSM [18, 19]. This significant STI burden in MSM PrEP users underlines the importance of an integrated STI service in PrEP delivery programs and, from another perspective, confirms that the target population of the PrEP program is the right one. Moreover, the high risk of subsequent STIs revealed the high-risk behavior of PrEP users and the risk compensation already described in people using PrEP [4, 20].




| | Cumulative probability of non-adherence | 95%CI |
|---|---|---|
| 1 year | 40.2% | 37.5%-43.0% |
| 2 years | 57.9% | 54.8%-61.0% |
| 3 years | 67.4% | 63.9%-70.9% |
| 4 years | 75.4% | 70.9%-79.6% |

| | Cumulative probability of oral PrEP discontinuation | 95%CI |
|---|---|---|
| 1 year | 24.8% | 22.5%-27.2% |
| 2 years | 37.1% | 34.3%-40.1% |
| 3 years | 44.3% | 40.9%-47.9% |
| 4 years | 50.5% | 46.0%-55.2% |

**Figure 3.** Kaplan–Meier curves showing the cumulative probability of poor adherence (*A*) and oral PrEP discontinuation (*B*).

Conversely, the incidence of HCV infection was low among PrEP users in Italy, with a rate of 0.37 per 100 PYFU. This incidence is considerably lower than the estimates of the early PrEP projects like the French IPERGAY Study (1.4 HCV per 100 PYFI) or the UK PROUD Study (2.1 HCV per 100 PYFU), and similar to the recently published data from Dutch national PrEP program (0.37 HCV per 100PYFU) or the incidence from HIV population in Italy reported by the Icona cohort (0.48 HCV per 100PYFU) [21–24]. This result reflects the different behaviors of chemsex practice in different countries, which very rarely include injection of drugs ("slamming") in Italy, and on the other hand, it is the effect of the reduced HCV circulation in recent years in Italy after the extensive use of direct antiviral agents for HCV started in 2014 [25].

People who accessed the ItaPrEP program for HIV prevention were almost all Italian MSM with a high educational level and a steady job. Understanding which populations should be prioritized for PrEP at the policy level is an important step in determining the extent of PrEP deployment in Italy and identifying gaps in program implementation.

We observed a remarkably poor self-reported adherence to oral PrEP, with a significant decline over time, with a probability of poor adherence at 2 years reaching 67%. Previous reports demonstrated that poor adherence was associated with a longer time on oral PrEP [26]. Because optimal adherence is crucial for PrEP efficacy and early adherence is predictive of sustained adherence, prompt identification of subgroups who need specific support for adherence will be crucial to improve effectiveness [27–29].

Our model analysis showed that chemsex users and those switching autonomously between different schedules were at high risk of poor adherence. Data on the association between chemsex use and PrEP adherence are conflicting and reflect the complex interplay between chemsex use, risk perception, and risk compensation. Some studies reported an association between chemsex use and missed doses, especially on the same day of the chemsex session [30–32]. On the other hand, this association was not found in other studies that explained the result by associating it with chemsex users' increased perception of risk [26, 33, 34]. However, adherence support strategies have been reported to be needed during intense chemsex sessions, including restriction of the intensity of chemsex or external reminders [35]. Anyway, this group of MSM needs detailed and comprehensive counselling about the concomitant use of PrEP and substances, and to be informed about the risk of missing doses and losing effectiveness. Similarly, switching from a daily to an on-demand schedule has been commonly described [11, 36]. Although the PrEP assumption must be linked with HIV exposure that could change over time, the management of the switch could be challenging, and targeted counselling on adherence is needed [37]. As expected, a high educational level was found to be protective against poor adherence [38], probably due to a better ability to recognize sexual exposure at risk, to understand dose management, including discontinuation and restart, and thus maximizing the benefit of PrEP [39].

Discontinuation in our cohort was around 25% at 1 year, with a progressive increase over time. This finding is consistent with that reported in other cohorts of high-income countries, including mainly MSM [19, 40, 41]. Notably, the increasing probability of discontinuation over time is worrying in terms of affecting the effectiveness of PrEP. HIV seroconversion frequently occurs early after discontinuation,

**Table 2. Odds Ratio (OR) and Adjusted Odds Ratio (aOR) of Poor adherence to Oral PrEP (A) and Oral PrEP Discontinuation (B) From Mixed Logistic Regression Model**

| | | Unadjusted Model | | | Adjusted Model | | |
|---|---|---|---|---|---|---|---|
| (A) | | OR | 95%CI | *P*-value | aOR[a] | 95%CI | *P*-value |
| Age, y | <40 | ref | | … | ref | … | … |
| | ≥40 | 0·89 | 0·71–1·11 | 0·285 | 0·88 | 0·69–1·12 | 0·294 |
| Nation of birth | Italy | 1·09 | 0·83–1·43 | 0·545 | … | … | … |
| | Other | ref | | … | … | … | … |
| Ethnicity | Non-Caucasian | ref | | … | … | … | … |
| | Caucasian | 0·95 | 0·68–1·31 | 0·745 | … | … | … |
| | Unknown | 0·76 | 0·43–1·33 | 0·335 | … | … | … |
| Education | Elementary, Middle/High School | ref | | … | ref | … | … |
| | University | 0·77 | 0·61–0·97 | 0·026 | 0·70 | 0·54–0·91 | 0·007 |
| | Unknown | 0·66 | 0·39–1·11 | 0·116 | 0·66 | 0·36–1·2 | 0·171 |
| Sexual role | Insertive sexual intercourses | ref | | … | … | … | … |
| | Receptive sexual intercourses | 0·81 | 0·56–1·18 | 0·271 | … | … | … |
| | Both | 1·07 | 0·8–1·43 | 0·641 | … | … | … |
| | Unknown | 0·95 | 0·67–1·34 | 0·774 | … | … | … |
| N. Partner in life | <30 | ref | | … | … | … | … |
| | ≥30 | 1·16 | 0·87–1·56 | 0·316 | … | … | … |
| | Unknown | 0·92 | 0·6–1·41 | 0·687 | … | … | … |
| Mode oral PrEP administration | Always daily | ref | | … | ref | … | … |
| | Always on-demand | 0·90 | 0·7–1·17 | 0·43 | 0·93 | 0·7–1·22 | 0·591 |
| | Switching | 2·70 | 2·05–3·55 | <.001 | 3·21 | 2·38–4·33 | <.001 |
| Chemsex at enrolment | Never | ref | | … | ref | … | … |
| | Sometimes | 1·54 | 1·11–2·13 | 0·009 | 1·56 | 1·11–2·18 | 0·01 |
| N. criteria PrEP initiation | Per 1 more | 1·47 | 1·29–1·68 | <.001 | … | … | … |
| Free laboratory monitoring | No | ref | | … | … | … | … |
| | Yes | 3·468 | 0·66–18·09 | 0·14 | … | … | … |
| Free laboratory monitoring and drug supply | Free lab monitoring and free PrEP supply ≥80% times | ref | | … | … | … | … |
| | Free lab monitoring and free PrEP supply never or <80% times | 1·458 | 0·68–3·11 | 0·328 | … | … | … |
| | Paid lab monitoring and free PrEP supply ≥80% times | 0·425 | 0·07–2·57 | 0·351 | … | … | … |
| | Paid lab monitoring and free PrEP supply never or <80% times | 0·257 | 0·04–1·74 | 0·164 | … | … | … |

| | | Unadjusted model | | | Adjusted model | | |
|---|---|---|---|---|---|---|---|
| (B) | | OR | 95%CI | *P*-value | aOR[a] | 95%CI | *P*-value |
| Age, years | <40 | ref | | … | ref | … | … |
| | ≥40 | 0·68 | 0·54–0·87 | 0·002 | 0·68 | 0·53–0·86 | 0·002 |
| Nation of birth | Italy | 0·98 | 0·73–1·31 | 0·892 | … | … | … |
| | Other | ref | | … | … | … | … |
| Ethnicity | Non-Caucasian | ref | | … | … | … | … |
| | Caucasian | 1·25 | 0·86–1·81 | 0·246 | … | … | … |
| | Unknown | 2·86 | 1·68–4·85 | <.001 | … | … | … |
| Education | Elementary, Middle/High School | ref | | … | … | … | … |
| | University | 0·82 | 0·64–1·05 | 0·121 | … | … | … |
| | Unknown | 1·21 | 0·78–1·86 | 0·396 | … | … | … |
| Sexual role | Insertive sexual intercourses | ref | | … | … | … | … |
| | Receptive sexual intercourses | 0·80 | 0·53–1·2 | 0·285 | … | … | … |
| | Both | 0·98 | 0·72–1·32 | 0·89 | … | … | … |
| N. Partner in life | <30 | ref | | … | … | … | … |
| | ≥30 | 1·26 | 0·89–1·77 | 0·188 | … | … | … |
| | Unknown | 3·81 | 2·46–5·9 | <.001 | … | … | … |
| Mode oral PrEP administration | Always daily | ref | | … | ref | … | … |
| | Always on-demand | 1·12 | 0·86–1·45 | 0·396 | 1·09 | 0·83–1·43 | 0·556 |
| | Switching | 0·75 | 0·56–1·01 | 0·059 | 0·80 | 0·59–1·08 | 0·138 |
| Chemsex at enrolment | Never | ref | | … | ref | … | … |

**Table 2. Continued**

| | | Unadjusted model | | | Adjusted model | | |
|---|---|---|---|---|---|---|---|
| (B) | | OR | 95%CI | *P*-value | aOR[a] | 95%CI | *P*-value |
| | Sometimes | 1·77 | 1·29–2·43 | <.001 | 1·80 | 1·3–2·48 | <.001 |
| Free laboratory monitoring | No | ref | | … | ref | … | … |
| | Yes | 0·756 | 0·57–0·99 | 0·045 | 0·73 | 0·54–0·99 | 0·045 |
| Free drug supply | No | ref | | … | ref | … | … |
| | Yes | 0·432 | 0·34–0·54 | <.001 | 0·39 | 0·29–0·53 | <.001 |

[a]Adjusted for the factors shown in table.

and the identification of factors that undermine PrEP persistence remains crucial [42]. Moreover, our study showed that chemsex users are at high risk of discontinuation, as previously described [43, 44]: this, together with the reported poor adherence, should not be a reason not to prescribe PrEP but, on the contrary, should stimulate the clinicians to strengthen counselling [45].

The cost of medication and monitoring was described as a barrier to access and persistence of PrEP, and our cohort of mixed fee-for-service situations confirmed this finding [44]. After the reimbursement, PrEP access increased rapidly, and a new multicentric cohort was being built in Italy: an initial survey showed around 9000 people currently on oral PrEP across 57 centers in Italy; of those, more than 4000 started oral prophylaxis after the reimbursement regulatory decision [46]. Costs probably selected the ItaPrEP population that included low percentages of very young people, women (cis and trans), people without employment, migrants, and sex workers. In general, PrEP roll-out in Italy has been slow and challenging, and efforts are needed to fund PrEP uptake and STI monitoring to expand access to key populations at high risk of HIV who are today substantially excluded from prevention programs.

In this study, we have several limitations to disclose. First of all, the observational nature of the study, which by its nature is prone to residual and unmeasured confounding. Users who choose not to complete the study questionnaire might differ systematically from those who completed it, potentially introducing a bias and skewing the results.

Self-reported adherence could hide recall and social-desirability bias and potentially underestimate the magnitude of adherence issues during prep. The definitions of adherence and discontinuation are not universal, but we have tried to reproduce those already used in large cohorts. The relatively high incidence of STIs observed on PrEP may raise concerns about potential risk compensation. However, we cannot confirm this hypothesis, as no longitudinal data on STI incidence or sexual behaviors before PrEP were collected, and assessing behavioral changes over time was not among the objectives of this study. Further research is needed to explore this issue.

Moreover, we cannot provide evidence of users transferring to other centers, not part of the ItaPrEP study, resulting in an overestimation of the discontinuation of the PrEP program. Conversely, the number of seroconversions might be underestimated, as some cases may occur outside the centers involved in ItaPrEP and are therefore not directly under our observation. The participating sites of this study were highly motivated PrEP centers that were competent in managing PrEP; their results in PrEP delivery might not be generalizable to other clinical settings in Italy.

Finally, we think that this cohort is under-representative of non-MSM individuals at risk of HIV acquisition, reflecting under-representation at the participating centers, underlining the need to expand access to other key populations. Further PrEP studies in Italy, including a large sample size, will be needed.

## CONCLUSIONS

The ItaPrEP program, before reimbursability in Italy, showed high real-life effectiveness of oral PrEP with FTC/TDF, with a low HIV seroconversion incidence in the high-risk population of MSM. The PrEP program was a helpful tool not only for the prevention of HIV infection but also for monitoring and treating other sexually transmitted diseases. Support for special populations such as young people, people with low educational level, and chemsex users, improving counselling on how to take PrEP, and addressing barriers such as costs of drugs and STI monitoring are key to targeting strategies for improving PrEP adherence, decreasing discontinuation, and extending the implementation of this prevention strategy.

### Notes

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***Data availability.*** The datasets generated during the current study are not publicly available because they contain sensitive data that must be treated under data protection laws and regulations. Appropriate data sharing agreement can be arranged after a reasonable request to the corresponding author.

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