

Real-world effectiveness of pre-exposure prophylaxis in men at high risk of HIV infection in France: a nested case-control study



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Summary

Background Pre-exposure prophylaxis (PrEP) has shown high efficacy in clinical trials, but few observational studies have confirmed its effectiveness when prescribed in real life to users with diverse profiles. This study aimed to assess real-world PrEP effectiveness.

Methods We did a matched, nested case-control study among adult men at high risk of HIV infection between Jan 1, 2016, and June 30, 2020, using data from the French national health data system. Men who were newly diagnosed with HIV infection up to Dec 31, 2020, were individually matched with up to five controls for age, socioeconomic status, place of residence, calendar year, and follow-up duration. PrEP use was characterised on the basis of tenofovir disoproxil fumarate plus emtricitabine dispensing over time. Conditional logistic regression was used to calculate the adjusted odds ratios (ORs) of PrEP use associated with HIV infection. PrEP effectiveness (computed as 1-adjusted OR), was estimated overall, by mode of PrEP use, and by individuals' sociodemographic characteristics.

Findings Among a total of 46 706 individuals, 256 patients with HIV infection were identified and matched with 1213 controls. PrEP users accounted for 29% of cases and 49% of controls. PrEP effectiveness was 60% (95% CI 46 to 71) overall, reaching 93% (84 to 97) for a high amount of PrEP consumption, and 86% (78 to 92) if excluding periods after PrEP discontinuation. PrEP effectiveness was significantly reduced in people younger than 30 years (26% [-21 to 54]) and in those who were socioeconomically deprived (-64% [-392 to 45]), both of which groups showed low amounts of PrEP consumption and high rates of PrEP discontinuation.

Interpretation PrEP effectiveness appears to be lower in real-world conditions than is reported in clinical trials. Strengthening efforts to improve the monitoring of PrEP compliance will be essential to ensure PrEP effectiveness, especially among young and socioeconomically deprived recipients.

Funding None.

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Introduction

Pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate plus emtricitabine has proved to be a highly effective means of HIV prevention in randomised clinical trials (RCTs), with reported efficacy in preventing HIV infection of up to 92% (among patients with a detectable drug concentration) in iPrEx,¹ 86% in PROUD,² and 86% in IPERGAY.^{3,4} On the basis of these figures, PrEP use has been increasingly encouraged for populations at high risk in many countries worldwide.⁵

Although RCTs are important to show the efficacy of a drug, the degree of efficacy that they report can differ from that obtained once the drug is widely prescribed in real life to users with diverse profiles, in accordance with various schemes of care and monitoring, and for extended periods of time. Until now, few observational studies have assessed PrEP effectiveness in a real-world setting; most of those that have were ecological studies that reported population-level HIV incidence in settings

in which PrEP was implemented, but without any comparison group, which hindered the evaluation of effectiveness.⁶⁻¹² The only comparative studies available were done in specific populations or health-care settings (eg, sexually transmitted infection [STI] clinics^{13,14}), and thus provided measures of PrEP effectiveness that did not account for the diversity that exists in the real world, both among individuals' profiles and in the care management of PrEP users.

In France, since January, 2016, oral PrEP with tenofovir disoproxil fumarate plus emtricitabine has been authorised and reimbursed specifically for use in adults at high risk of HIV infection. As of June 30, 2020, a total of 32 042 people had initiated PrEP, who were mostly men who have sex with men (MSM) and who lived in large urban areas.¹⁵ The recommended regimen is either daily or on-demand PrEP. Among more than 3000 MSM at high-risk in the ANRS-Prevenir study¹⁶ done in the Paris area, approximately half opted for an on-demand

Lancet Public Health 2022;

7: e529-36

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Research in context

Evidence before this study

Pre-exposure prophylaxis (PrEP) has proved to be a highly effective means of HIV prevention in randomised clinical trials (RCTs), with remarkable reported efficacy in preventing HIV infection, reaching up to 92% in iPrEx in individuals with a detectable drug concentration, 86% in PROUD, and 86% in IPERGAY. As a consequence, WHO and national health authorities across the world have increasingly recommended PrEP as a major tool in the HIV-prevention arsenal. Although RCTs are essential to show the efficacy of a drug, the degree of efficacy that they report might differ from the degree obtained once the drug is widely prescribed in common practice—to users with diverse profiles, in accordance with various schemes of care and monitoring, and for extended periods of time. We searched PubMed for studies published in French or English from database inception to Sept 1, 2021, and found 11 observational studies assessing PrEP effectiveness in the real world. Most of the studies were ecological and reported population-level HIV incidence in settings in which PrEP was implemented, but the absence of comparative study groups hindered the evaluation of effectiveness. The only comparative studies available were done in specific subpopulations or health-care settings, such as sexually transmitted infections clinics, and thus provided measures of PrEP effectiveness that

did not account for the diversity in both individuals' profiles and care management of PrEP users in the real world.

Added value of this study

We found that PrEP use was associated with an overall 60% reduction in the risk of HIV infection, reaching 93% for a high amount of PrEP consumption, and 86% if excluding periods after PrEP discontinuation. PrEP effectiveness appeared to be reduced in individuals who were younger than 30 years and who were socioeconomically deprived, both of which groups showed low amounts of PrEP consumption and high rates of PrEP discontinuation. Thus, our findings suggest that PrEP effectiveness is substantially lower in real-world conditions than is reported in clinical trials, as a result of frequent suboptimal PrEP consumption and interruptions of treatment supply.

Implications of all the available evidence

These findings, by providing new insights on the degree and determinants of PrEP effectiveness in the real world, are important in the current context of worldwide PrEP scale up. Strengthening efforts such as enhanced counselling or SMS-based support to improve the monitoring of PrEP compliance will be essential to ensure PrEP effectiveness, especially among young and socioeconomically deprived recipients.

regimen. Regardless of the regimen, PrEP care includes quarterly HIV and STI screenings and the promotion of condom use. PrEP initiation was initially restricted to specialised hospital practitioners, but was extended to all prescribers on June 1, 2021, to further expand PrEP use and to diversify recipient profiles. In the context of this scale up, the present study aimed to assess the degree and determinants of PrEP effectiveness in the real world in France.

Methods

Study design and data source

We did a matched case-control study nested among adult men at high risk of sexually acquired HIV infection in France, using data from the French National Health Data System (SNDS). The SNDS covers almost all (>99%) of the French population of 67 million residents. Each person is identified by a unique and anonymous SNDS number. Since 2006, the SNDS has recorded comprehensive information for outpatients (reimbursed drugs and procedures) and inpatients (expensive drugs dispensed and procedures done during hospital stays, with discharge diagnoses coded according to the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision [ICD-10]¹⁷). The SNDS also contains sociodemographic information on sex, age, place of residence, receipt of complementary universal health insurance via *couverture maladie universelle complémentaire* (CMUC; a system that provides

free access to health care for people with an annual income below 50% of the French poverty threshold), and death (if applicable). The patient's status for 100% reimbursement of care related to a severe and costly long-term disease is recorded and the diagnosis for a long-term disease is coded according to the ICD-10.

The SNDS has been used extensively to do pharmaco-epidemiological studies, especially on the use, safety, and effectiveness of health products.^{18–21}

This study was approved by the French Data Protection Supervisory Authority (*Commission Nationale de l'Informatique et des Libertés*). No informed consent is required for studies based on the SNDS databases, as these data are anonymous.

Study population

All men aged 18–65 years, living in mainland France, and identified as being at high risk of sexually acquired HIV infection between Jan 1, 2016 and June 30, 2020 (the inclusion period) were included. Individuals were considered to be at high risk of sexually acquired HIV infection if they did not have prevalent HIV infection at baseline based on criteria detailed in the appendix (p 2) and if, between Jan 1, 2016, and Dec 31, 2020 (the study period), they either used PrEP or had a history of at least four HIV screening tests combined with at least one STI event within a 2-year time span followed by at least one subsequent HIV screening test. PrEP use was defined as tenofovir disoproxil fumarate plus emtricitabine alone

See Online for appendix

(ie, without any other antiretroviral drug being codispensed on the same day) being dispensed two or more times, with the first time being during the inclusion period. STI events (eg, syphilis, gonorrhoea, and chlamydia infection) were defined by the combination of a specific biology test²² followed within a 30-day period by a specific antibiotic treatment (appendix p 2).²³

The inclusion date was defined as either the date when PrEP was first dispensed, or the date of the most recent HIV screening test within the 2-year time span that was considered for defining high risk of HIV infection. Participants were followed up from inclusion until HIV infection, death, or Dec 31, 2020, whichever occurred first.

Identification of cases and matched controls

Cases were men with a newly diagnosed HIV infection identified at least 3 months after study inclusion (to exclude non-incident cases). HIV infection was identified by the combination of the following criteria during the study period: a CD4 cell count, an HIV-specific biology test (appendix p 2), and the initiation of an antiretroviral treatment, or a hospital discharge, or a long-term disease diagnosis of HIV infection. The HIV infection date (index date) was defined as the date on which the first of these criteria occurred.

Controls were patients not infected with HIV and who were randomly selected (using risk-set sampling) from among individuals still at risk of HIV infection at the index date of each case.²⁴ Cases were individually matched with up to five controls on age (split into 5-year categories), region of residence (Paris region; non-Paris regions with a high HIV prevalence [ie, Auvergne-Rhône-Alpes, Grand Est, Occitanie, Nouvelle-Aquitaine, and Provence-Alpes-Côte d'Azur]; and other regions), population size of the residential area (≤ 9999 , 10 000–49 999, 50 000–199 999, $\geq 200 000$, and unknown), CMUC status, calendar year at inclusion, and on follow-up duration at index date.

Mode of PrEP use

Among PrEP users, the overall amount of PrEP consumption was estimated by the ratio of the number of days covered by PrEP dispensing during follow-up (assuming a daily consumption—eg, a box of 30 oral tablets would cover a period of 30 days) to the total number of days in the period. PrEP consumption was categorised as: low (<50% of the days covered), intermediate (50–74%), and high ($\geq 75\%$). Interruption of PrEP supply was defined as the absence of any PrEP dispensing for at least 90 days, and was categorised as a temporary cessation if it was followed by subsequent PrEP resumption, or as PrEP discontinuation if resumption did not occur. Considering the effect of the COVID-19 pandemic on HIV risk exposure and PrEP use in France,^{15,25} indicators of PrEP consumption and interruption of supply were estimated on the basis of data restricted to the period preceding the epidemic (ie, before March 1, 2020).

Statistical analysis

Multivariable conditional logistic regression was used to estimate adjusted odds ratios (ORs) of PrEP use associated with HIV infection and their 95% CIs. Models were adjusted for available proxies of the risk of HIV infection—ie, occurrence of at least one STI (including syphilis, gonorrhoea, and chlamydia infection) and use of post-exposure prophylaxis during follow-up (appendix p 2). PrEP effectiveness, computed as 1-adjusted OR, was estimated overall and by the amount of PrEP consumption. PrEP effectiveness excluding periods after discontinuation was estimated by censoring follow-up 90 days after the PrEP users' most recent PrEP dispensing. Subgroup analyses were done by age group, CMUC status, region of residence, and population size of residential area. Interactions between PrEP use and the stratification variables were tested using the

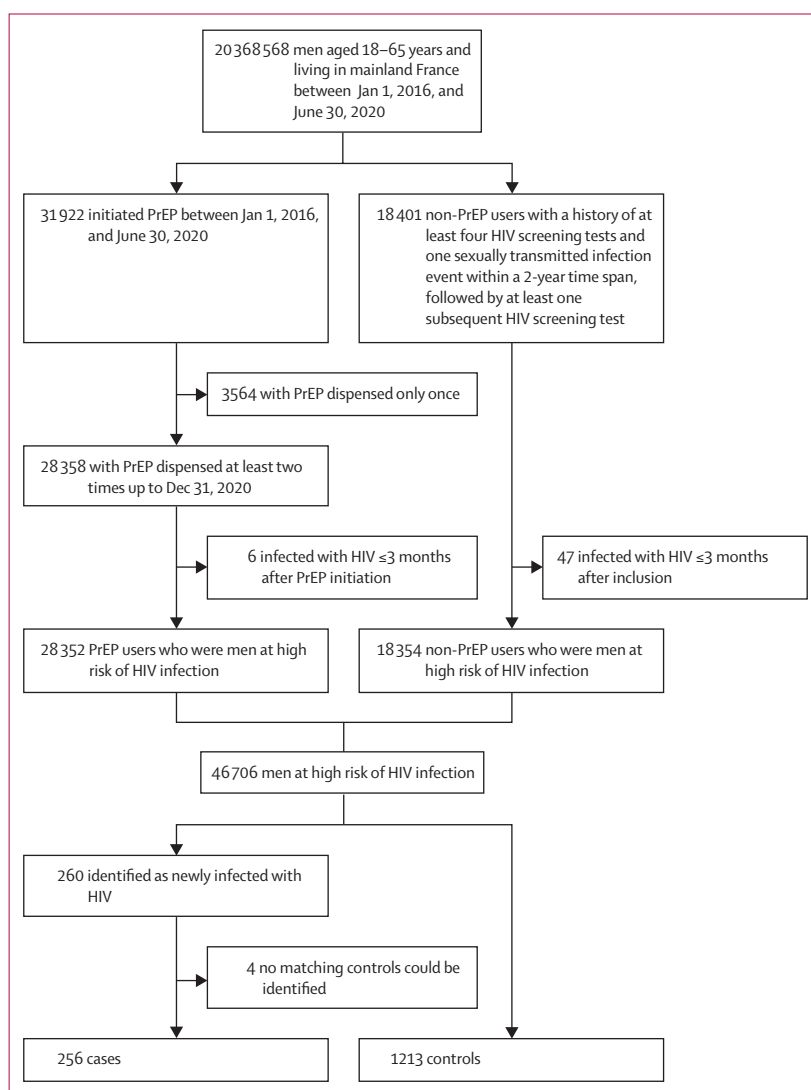


Figure: Study profile
PrEP=pre-exposure prophylaxis.

	Cases (n=256)	Controls (n=1213)	Total (n=1469)
Year of inclusion			
2016	119 (46%)	563 (46%)	682 (46%)
2017	64 (25%)	306 (25%)	370 (25%)
2018	54 (21%)	256 (21%)	310 (21%)
2019	18 (7%)	83 (7%)	101 (7%)
2020	1 (<1%)	5 (<1%)	6 (<1%)
Age (years)			
Median age at baseline	32 (26–38)	32 (26–39)	32 (26–39)
18–29	102 (40%)	480 (40%)	582 (40%)
30–39	93 (36%)	453 (37%)	546 (37%)
40–49	46 (18%)	212 (17%)	258 (18%)
50–65	15 (6%)	68 (6%)	83 (6%)
Region of residence			
Paris region	98 (38%)	487 (40%)	585 (40%)
Non-Paris region with a high HIV prevalence*	92 (36%)	437 (36%)	529 (36%)
Other regions	66 (26%)	289 (24%)	355 (24%)
Population size of the residential area			
≤9999	29 (11%)	135 (11%)	164 (11%)
10 000–49 999	11 (4%)	41 (3%)	52 (4%)
50 000–199 999	23 (9%)	91 (8%)	114 (8%)
≥200 000	190 (74%)	941 (78%)	1131 (77%)
Missing data	3 (1%)	5 (<1%)	8 (1%)
CMUC complementary universal health insurance	20 (8%)	79 (7%)	99 (7%)
Median follow-up duration, years	1.2 (0.7–2.0)	1.2 (0.7–2.0)	1.2 (0.7–2.0)
Sexually transmitted infections during follow-up			
At least one event	136 (53%)	473 (39%)	609 (41%)
Incidence rate per 100 person-years	59.1 (54.1–64.1)	42.7 (40.4–45.0)	45.5 (43.4–47.6)
Post-exposure prophylaxis use during follow-up			
At least once	11 (4%)	37 (3%)	48 (3%)
Incidence rate per 100 person-years	3.2 (1.4–5.0)	2.2 (1.6–2.9)	2.4 (1.8–3.1)

Data are n (%) or median (IQR) unless otherwise stated. CMUC=couverture maladie universelle complémentaire (complementary universal health insurance). *Auvergne-Rhône-Alpes, Grand Est, Occitanie, Nouvelle-Aquitaine, and Provence-Alpes-Côte d'Azur.

Table 1: Characteristics of included cases and controls

likelihood ratio test, comparing the main model with a model that included the appropriate interaction term.

Various sensitivity analyses were done to assess the robustness of the results. First, three alternative definition criteria were used for the identification of non-PrEP users at high risk of HIV infection. The first criterion was at least four HIV screening tests and one STI event within a 2-year time span, regardless of subsequent HIV screening. The second was at least three HIV screening tests and one STI event within a 1-year time span, followed by at least one subsequent HIV screening test. The third criterion was PrEP being dispensed just once without any subsequent renewal during the study period. Second, analysis was restricted to the pre-COVID-19 epidemic period by censoring follow-up as of Feb 29, 2020. Third, the risk of HIV infection associated with PrEP use was alternatively estimated using a Cox proportional hazards

	Cases (n=256)	Controls (n=1213)	p value
PrEP consumption			
Yes	73/256 (29%)	591/1213 (49%)	<0.0001
No	183/256 (71%)	622/1213 (51%)	..
Proportion of follow-up in which PrEP was consumed			
Low: <50%	57/73 (78%)	239/591 (40%)	<0.0001
Intermediate: 50% to 74%	11/73 (15%)	117/591 (20%)	..
High: ≥75%	5/73 (7%)	235/591 (40%)	..
Mean	35% (24)	61% (35)	<0.0001
Participants with at least one interruption of PrEP supply			
All	64/73 (88%)	365/591 (62%)	<0.0001
Temporary cessation	34/73 (47%)	204/591 (35%)	0.058
Mean duration of temporary cessation, days	184 (119)	178 (129)	0.73
PrEP discontinuation	54/73 (74%)	238/591 (40%)	<0.0001
Mean duration of discontinuation, days	385 (275)	286 (203)	0.015

Data are n/N (%) or mean (SD). p values were computed by χ^2 tests for categorical variables and by Student's t tests for mean comparisons. PrEP=pre-exposure prophylaxis.

Table 2: PrEP use modalities in cases and controls during follow-up

model, adjusted for age, region of residence, population size of residential area, CMUC status, and calendar year at time of inclusion.

Data were analysed with SAS Enterprise Guide software version 9.4 and R version 3.5.2. The threshold for statistical significance was set at two-sided $p < 0.05$. Our study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist (appendix pp 10–11).

Role of the funding source

There was no funding source for this study.

Results

Among a total of almost 20.4 million men aged 18–65 years and living in mainland France between Jan 1, 2016, and June 30, 2020, 46 706 men were identified as being at high risk of sexually acquired HIV infection (figure). Of these, 28 352 (61%) men were PrEP users and 18 354 (39%) were not. The median year of inclusion was 2018 (IQR 2017–2019) for PrEP users and 2017 (2016–2019) for non-PrEP users. Compared with non-PrEP users, PrEP users were slightly older (median age 35 years [IQR 28–44] vs 32 years [27–41]), were more often residents of the Paris region (48% vs 34%) or from cities with 200 000 or more inhabitants (77% vs 67%), and were less often CMUC beneficiaries (7% vs 12%). In addition, PrEP users had higher incidence rates of STI (41.2 vs 29.7 events per 100 person-years) and post-exposure prophylaxis use (2.1 vs 1.7 events per 100 person-years) than non-PrEP users (appendix p 3).

	Cases	Controls	Odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	PrEP effectiveness (95% CI)
PrEP non-consumers	183 (71%)	622 (51%)	Ref	Ref	Ref
PrEP consumers					
All	73 (29%)	591 (49%)	0.37 (0.27 to 0.51)	0.40 (0.29 to 0.54)	60% (46 to 71)
By proportion of follow-up in which PrEP was consumed					
Low: <50%	57 (22%)	239 (20%)	0.73 (0.51 to 1.05)	0.82 (0.57 to 1.18)	18% (-18 to 43)
Intermediate: 50% to 74%	11 (4%)	117 (10%)	0.29 (0.15 to 0.56)	0.31 (0.16 to 0.59)	69% (41 to 84)
High: ≥75%	5 (2%)	235 (19%)	0.06 (0.03 to 0.16)	0.07 (0.03 to 0.16)	93% (84 to 97)
Excluding periods after PrEP discontinuation	21 (10%)	417 (43%)	0.13 (0.08 to 0.21)	0.14 (0.08 to 0.22)	86% (78 to 92)

Data are n (%), odds ratio (95% CI), or effectiveness (95% CI). PrEP=pre-exposure prophylaxis. *Odds ratios obtained from conditional logistic regression adjusted for sexually transmitted infection occurrence and post-exposure prophylaxis use during follow-up.

Table 3: Estimation of PrEP effectiveness overall and by mode of PrEP use

As of Dec 31, 2020, 260 men had been identified as newly infected with HIV (incidence: 0.22 per 100 person-years). Of these, 256 were matched with 1213 controls: 232 (89%) with a 5:1 ratio, 24 (9%) with a ratio between 4:1 and 1:1, and for four (2%), no matching controls could be identified in the study population. Cases and their matched controls had a median age of 32 years (IQR 26–39), 76% were residents of regions with high HIV prevalence (40% Paris region and 36% other regions) and 77% of cities of at least 200 000 inhabitants, and 7% were CMUC beneficiaries. Median follow-up was 1.2 years (IQR 0.7–2.0) for cases and controls. During follow-up, compared with controls, cases had higher incidence rates of STIs (59.1 vs 42.7 per 100 person-years) and post-exposure prophylaxis use (3.2 vs 2.2 per 100 person-years; table 1).

PrEP users accounted for 29% of cases (n=73) versus 49% of controls (n=591). Among PrEP users, cases were more likely than controls to have low PrEP consumption (78% of cases vs 40% of controls, $p < 0.0001$) and to have discontinued PrEP (74% vs 40%, $p < 0.0001$; table 2). On the basis of multivariable conditional logistic regression modelling that included all 256 cases and 1213 controls, overall PrEP effectiveness was 60% (95% CI 46 to 71). PrEP effectiveness increased with the extent of PrEP consumption, ranging from 18% (95% CI -18 to 43) for low consumption (with the negative value of the 95% CI lower limit suggesting no PrEP effectiveness), to 69% (41 to 84) for intermediate consumption, and to 93% (84 to 97) for high consumption. PrEP effectiveness reached 86% (95% CI 78 to 92) if excluding periods after PrEP discontinuation (table 3).

PrEP effectiveness was significantly lower in men younger than 30 years (26% [95% CI -21 to 54]) compared with those aged 30–40 years (66% [42 to 80]) or 40 years or older (83% [65 to 92]; $p_{\text{interaction}} = 0.0016$). Similarly, PrEP effectiveness was significantly lower in men affiliated to CMUC (-64% [95% CI -392 to 45]), of whom there were only 20 cases and 79 controls, than in men not affiliated to CMUC (65% [51 to 75]; $p_{\text{interaction}} = 0.0096$; table 4). Among the 28 352 PrEP users in the whole study

population, individuals showed lower PrEP consumption and higher rates of PrEP discontinuation if they were younger than 30 years than for men who were older, and if they were CMUC beneficiaries than if they were not CMUC affiliated (appendix p 4). PrEP effectiveness did not differ according to region or size of residential area (table 4).

The PrEP effectiveness estimation remained consistent across various sensitivity analyses (appendix p 5).

Discussion

In this population-based matched case-control study nested among men at high risk of sexually acquired HIV infection in France, PrEP use was associated with an overall 60% reduction in the risk of HIV infection, reaching 93% with a high PrEP consumption, and 86% if periods after PrEP discontinuation were excluded. PrEP effectiveness was significantly reduced in men who were younger than 30 years and in those who were socioeconomically deprived, both of which groups showed a low amount of PrEP consumption and high rates of PrEP discontinuation.

The extent of PrEP effectiveness reported in the present study appears substantially reduced compared with the approximately 90% risk reduction obtained in clinical trials,^{1,4} and it is also lower than the 75–80% effectiveness estimated in observational studies done in STI clinics in the USA.^{13,14} Our findings suggest that suboptimal PrEP consumption and treatment discontinuations are common when considering a diverse population of men at high risk of HIV infection within the general population, which probably explains such a reduced degree of PrEP effectiveness when compared with more selected populations of RCT participants or STI clinic attendees. Consistent with our results, previous observational studies have identified low adherence to PrEP and treatment discontinuation as strong predictors of PrEP failure,^{6,7,11,13,14,26} especially among young,^{11,27,28} underserved,²⁷ and minority ethnic populations, who are increasingly likely to face socioeconomic and

	Cases	Controls	Adjusted OR*	PrEP effectiveness
Age (p_{interaction}=0.0016†)				
<30 years				
Not a PrEP user	66 (65%)	277 (58%)	Ref	Ref
PrEP user	36 (35%)	203 (42%)	0.74 (0.46 to 1.21)	26% (-21 to 54)
30–39 years				
Not a PrEP user	70 (75%)	232 (51%)	Ref	Ref
PrEP user	23 (25%)	221 (49%)	0.34 (0.20 to 0.58)	66% (42 to 80)
≥40 years				
Not a PrEP user	47 (77%)	113 (40%)	Ref	Ref
PrEP user	14 (23%)	167 (60%)	0.17 (0.08 to 0.36)	83% (65 to 92)
By CMUC status (p_{interaction}=0.0096)				
Not affiliated				
Not a PrEP user	172 (73%)	572 (50%)	Ref	Ref
PrEP user	64 (27%)	562 (50%)	0.35 (0.25 to 0.49)	65% (51 to 75)
Affiliated				
Not a PrEP user	11 (55%)	50 (63%)	Ref	Ref
PrEP user	9 (45%)	29 (37%)	1.64 (0.55 to 4.92)	-64% (-392 to 45)
By region of residence (p_{interaction}=0.081)				
Paris region				
Not a PrEP user	67 (68%)	210 (43%)	Ref	Ref
PrEP user	31 (32%)	277 (57%)	0.33 (0.21 to 0.54)	67% (46 to 79%)
Non-Paris regions with high HIV prevalence				
Not a PrEP user	74 (80%)	260 (59%)	Ref	Ref
PrEP user	18 (20%)	177 (41%)	0.30 (0.16 to 0.57)	70% (43 to 84%)
Other regions				
Not a PrEP user	42 (64%)	152 (53%)	Ref	Ref
PrEP user	24 (36%)	137 (47%)	0.76 (0.42 to 1.39)	24% (-39 to 58%)
By population size of residential area (p_{interaction}=0.28)				
≤9999				
Not a PrEP user	20 (69%)	81 (60%)	Ref	Ref
PrEP user	9 (31%)	54 (40%)	0.72 (0.27 to 1.90)	28% (-90 to 73%)
10 000–199 999				
Not a PrEP user	24 (71%)	72 (55%)	Ref	Ref
PrEP user	10 (29%)	60 (45%)	0.57 (0.23 to 1.43)	43% (-43 to 77)
≥200 000				
Not a PrEP user	136 (72%)	468 (50%)	Ref	Ref
PrEP user	54 (28%)	473 (50%)	0.35 (0.25 to 0.51)	65% (49 to 76)

Data are n (%), adjusted odds ratio (95% CI), or effectiveness (95% CI). CMUC=couverture maladie universelle complémentaire complementary universal health insurance. PrEP=pre-exposure prophylaxis. *Odds ratios were obtained from conditional logistic regression adjusted for sexually transmitted infection occurrence and post-exposure prophylaxis use during follow-up. †p value of the interaction term (PrEP use) × (stratification variable).

Table 4: Estimation of PrEP effectiveness by age, CMUC affiliation, region of residence, and population size of residential area

psychological distress that makes adherence to PrEP challenging.^{7,14,29}

This study, based on a large national population-based cohort of more than 46700 men at high risk of sexually acquired HIV infection, constitutes a major source of information about the degree and determinants of PrEP effectiveness in the real world. On the basis of comprehensive information on reimbursed drugs, health-care use, and medical diagnoses of all beneficiaries of mandatory national health insurance in France, we

were able to assess PrEP effectiveness by considering the vast majority of adult men who initiated PrEP in France since it was first prescribed in January, 2016. Although complimentary PrEP dispensing can be provided in sexual health centres, this remains limited to rare instances (eg, for non-insured people), suggesting that the identification of PrEP use based on the SNDS claims databases is almost complete. In addition, available information allowed us to characterise individual PrEP consumption amounts and treatment discontinuations, which could therefore be used to provide accurate estimations of PrEP effectiveness. These findings are likely to be extrapolated to other countries with PrEP promotion programmes for large and diverse populations.

Several limitations, mainly related to the medico-administrative nature of the SNDS databases, should be considered when interpreting these results. First, in the absence of information on sexual behaviours, the identification of a valid group of non-PrEP users at high risk of sexually acquired HIV infection was challenging. The criteria used for the identification of this group, specifically a high frequency of HIV testing combined with history of STIs, ensured the selection of individuals at sexual health risk, reflected in our study by a high proportion (54%) with a new STI identified during their 3-year follow-up (and 46% over 2.1 years among PrEP users). Still, these criteria probably failed to identify a part of the population of men at high risk of sexually acquired HIV infection in France, especially those with low use of the health-care system. However, two points provide strong arguments to support the robustness of our estimation of PrEP effectiveness based on this group of non-PrEP users. The first point is that for individuals with high PrEP consumption and if we exclude periods after PrEP discontinuation (ie, under conditions approaching those of clinical trials), our estimates of PrEP effectiveness (ie, 93% with high PrEP consumption and 86% after excluding periods after discontinuation) were similar to those reported in RCTs. The second point is that our estimations were robust in sensitivity analyses across various definitions of the group of non-PrEP users. Although PrEP effectiveness tended to be increased if non-PrEP users were defined as patients with one single PrEP dispensing, this estimation must be interpreted cautiously, as it was based on a small number of individuals.

In addition, because information on blood test results is not available in the SNDS databases, identification of new HIV infections was obtained using an algorithm that combined specific indicators of health-care use, which implies that only individuals traceable through a recourse to the health-care system were considered. However, applying our algorithm to the whole French population showed that it captured approximately 85–90% of the annual number of new cases of HIV infections reported by the national surveillance system during the study period, suggesting that the large

majority of people who had been newly diagnosed with HIV were considered in our study. In addition, HIV incidence among PrEP users in our study reached 0.11 per 100 person-years—ie, the same rate as that which was reported among MSM PrEP users at high risk included in the ANRS-Prevenir study.¹⁶ Information on the amount of sexual exposure to HIV risk (eg, number of sexual partners and types of sexual practices) was also missing. However, models were systematically adjusted for available proxies of HIV-risk exposure, namely STIs and use of post-exposure prophylaxis, to reduce residual confounding. Finally, as information on dispensing is not sufficient to make the distinction between daily and on-demand PrEP use, PrEP effectiveness could not be assessed across these two modalities of treatment. However, in the ANRS-Prevenir study,¹⁶ similar low amounts of HIV incidence were reported in the groups with daily versus on-demand PrEP use, suggesting a high degree of PrEP effectiveness for both (although this does not mean that the two regimens are equally effective).

In conclusion, PrEP effectiveness appears lower in real-world conditions than is reported in clinical trials, as a result of frequent suboptimal PrEP consumption and treatment discontinuations. These findings, by providing new insights on the degree and determinants of PrEP effectiveness in the real world, are of major public health importance, particularly in the current context of worldwide PrEP scale up. Strengthening efforts to improve the monitoring of PrEP compliance will be essential to ensure PrEP effectiveness, especially among young and socioeconomically deprived recipients.

Contributors

HJ, SBdG, and RD-S conceived the study, interpreted the findings, and did the literature review. DD did the data extraction and collection. HJ did the statistical analysis. DD and HJ had access to all of the data and verified the data. HJ drafted the first version of the manuscript. SBdG and RD-S reviewed the manuscript. RD-S supervised the study. All authors had full access to all the data in the study, read and approved the final manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

HJ was an employee of AstraZeneca, France from January, 2019 to July, 2020. All other authors declare no competing interests.

Data sharing

According to data protection and French regulations, the authors cannot publicly release the data from the French National Health Data System (SNDS). However, any person or organisation (public or private; for-profit or non-profit), can access anonymised SNDS data to do a study, research, or an evaluation of public interest, upon authorisation from the French Data Protection Office (see <https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees> and <https://documentation.snds.health-data-hub.fr/introduction/03-acces-snds.html>).

Acknowledgments

We thank France Lert, Florence Lot, Nathalie Lydié, and Annie Velter for the fruitful exchanges and Marc-Florent Tassi for information and experience sharing.

References

- Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**: 2587–99.
- McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016; **387**: 53–60.
- Molina J-M, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; **373**: 2237–46.
- Molina J-M, Charreau I, Spire B, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. *Lancet HIV* 2017; **4**: e402–10.
- AIDS Vaccine Advocacy Coalition. The global PrEP tracker. 2021. <https://data.prepwatch.org/> (accessed June 14, 2021).
- Van Epps P, Wilson BM, Garner W, Beste LA, Maier MM, Ohl ME. Brief report: incidence of HIV in a nationwide cohort receiving pre-exposure prophylaxis for HIV prevention. *J Acquir Immune Defic Syndr* 2019; **82**: 427–30.
- Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med* 2016; **176**: 75–84.
- Smith DK, Sullivan PS, Cadwell B, et al. Evidence of an association of increases in pre-exposure prophylaxis coverage with decreases in human immunodeficiency virus diagnosis rates in the United States, 2012–2016. *Clin Infect Dis* 2020; **71**: 3144–51.
- Brown AE, Mohammed H, Ogaz D, et al. Fall in new HIV diagnoses among men who have sex with men (MSM) at selected London sexual health clinics since early 2015: testing or treatment or pre-exposure prophylaxis (PrEP)? *Euro Surveill* 2017; **22**: 30553.
- Estcourt C, Yeung A, Nandwani R, et al. Population-level effectiveness of a national HIV pre-exposure prophylaxis programme in men who have sex with men. *AIDS* 2021; **35**: 665–73.
- Gulich AE, Jin F, Bavinton BR, et al. Long-term protection from HIV infection with oral HIV pre-exposure prophylaxis in gay and bisexual men: findings from the expanded and extended EPIC-NSW prospective implementation study. *Lancet HIV* 2021; **8**: e486–94.
- Tassi M-F, Laurent E, Gras G, et al. PrEP monitoring and HIV incidence after PrEP initiation in France: 2016–18 nationwide cohort study. *J Antimicrob Chemother* 2021; **76**: 3002–08.
- Johnson KA, Hessel NA, Kohn R, et al. HIV seroconversion in the era of pharmacologic prevention: a case-control study at a San Francisco STD clinic. *J Acquir Immune Defic Syndr* 2019; **82**: 159–65.
- Pagkas-Bather J, Khosropour CM, Golden MR, Thibault C, Dombrowski JC. Population-level effectiveness of HIV pre-exposure prophylaxis among MSM and transgender persons with bacterial sexually transmitted infections. *J Acquir Immune Defic Syndr* 2021; **87**: 769–75.
- EPI-PHARE. Use of HIV pre-exposure prophylaxis (PrEP) in France as of 30 June 2020. Dec 1, 2020 (in French). <https://www.epi-phare.fr/rapports-detudes-et-publications/prep-vih-2020/> (accessed June 14, 2021).
- Molina J-M, Ghosn J, Delaugerre C, et al. Incidence of HIV-infection with daily or on-demand oral PrEP with TDF/FTC in France. 28th Conference on Retroviruses and Opportunistic Infections. March 6–10, 2021 (abstr 148).
- Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: from the Système National d'Information Interrégimes de l'Assurance Maladie (SNIIRAM) to the Système National des Données de Santé (SNDS) in France. *Rev Epidemiol Sante Publique* 2017; **65** (suppl 4): S149–67.
- Meyer A, Rudant J, Drouin J, Weill A, Carbonnel F, Coste J. Effectiveness and safety of reference infliximab and biosimilar in Crohn disease: a French equivalence study. *Ann Intern Med* 2019; **170**: 99–107.
- Weill A, Nguyen P, Labidi M, et al. Use of high dose cyproterone acetate and risk of intracranial meningioma in women: cohort study. *BMJ* 2021; **372**: n37.
- Semenzato L, Botton J, Drouin J, et al. Chronic diseases, health conditions, and risk of COVID-19-related hospitalisation and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. *Lancet Reg Health Eur* 2021; **8**: 100158.
- Billioti de Gage S, Bertrand M, Grimaldi S, Zureik M. Intravitreal anti-VEGF use in France: a cross-sectional and longitudinal nationwide observational study. *Acta Ophthalmol* 2022; **100**: e502–11.

- 22 Viriot D, Ndeikoundam Ngangro N, Lucas E, et al. Bacterial STI screening in the private sector in France, 2006–2018. *Bull Épidémiol Hebd* 2019; **31–32**: 634–41 (in French).
- 23 Ndeikoundam Ngangro N, Viriot D, Lucas E, et al. Relevance of healthcare reimbursement data to monitor syphilis epidemic: an alternative surveillance through the national health insurance database in France, 2011–2013. *BMJ Open* 2018; **8**: e020336.
- 24 Rothman KJ, Greenland S, Lash TL. Case–control studies. In: Melnick EL, Everitt BS, eds. *Encyclopedia of quantitative risk analysis and assessment*. Sept 15, 2008. <https://onlinelibrary.wiley.com/doi/10.1002/9780470061596.risk0599> (accessed July 21, 2021).
- 25 Velter A, Champenois K, Rojas Castro D, Lydié N. Perceived impact of the COVID-19 pandemic on men who have sex with men in France. Eras COVID-19 survey, 30 June–15 July 2020. *Bull Épidémiol Hebd* 2020; **33–34**: 666–72 (in French).
- 26 Spinelli MA, Laborde N, Kinley P, et al. Missed opportunities to prevent HIV infections among pre-exposure prophylaxis users: a population-based mixed methods study, San Francisco, United States. *J Int AIDS Soc* 2020; **23**: e25472.
- 27 Whitfield THF, John SA, Rendina HJ, Grov C, Parsons JT. Why I quit pre-exposure prophylaxis (PrEP)? A mixed-method study exploring reasons for PrEP discontinuation and potential re-initiation among gay and bisexual men. *AIDS Behav* 2018; **22**: 3566–75.
- 28 Morgan E, Ryan DT, Newcomb ME, Mustanski B. High rate of discontinuation may diminish PrEP coverage among young men who have sex with men. *AIDS Behav* 2018; **22**: 3645–48.
- 29 Serota DP, Rosenberg ES, Sullivan PS, et al. Pre-exposure prophylaxis uptake and discontinuation among young Black men who have sex with men in Atlanta, Georgia: a prospective cohort study. *Clin Infect Dis* 2020; **71**: 574–82.