Daily and on-demand HIV pre-exposure prophylaxis with emtricitabine and tenofovir disoproxil (ANRS PREVENIR): a prospective observational cohort study

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Summary

Background There are few data available regarding the use of on-demand pre-exposure prophylaxis (PrEP) for HIV prevention. We aimed to assess PrEP effectiveness, adherence, and safety in adults using daily or on-demand PrEP.

Methods We conducted a prospective observational cohort study (ANRS PREVENIR) at 26 sites in the Paris region, France. We enrolled HIV-negative adults (aged ≥18 years) at high risk of HIV infection who were starting or continuing PrEP. PrEP was prescribed as a fixed-dose combination of tenofovir disoproxil and emtricitabine (245 mg and 200 mg, respectively, per pill). PrEP could be prescribed as a daily regimen with one pill per day or, in men who have sex with men (MSM) or in transgender women who have sex with men, as an on-demand regimen following the IPERGAY dosing recommendation. At enrolment and every 3 months thereafter, participants were tested for HIV and provided information regarding the PrEP dosing regimen used. Adherence to PrEP was assessed by self-report and by tenofovir diphosphate concentrations in dried blood spots. The primary outcome of HIV-1 incidence was assessed using Poisson regression among participants who started PrEP. This study is registered with ClinicalTrials.gov, NCT03113123, and EudraCT, 2016A0157744.

Findings Between May 3, 2017, and May 2, 2019, 3082 people were assessed for eligibility and 3065 participants were enrolled. 3056 (99·7%) of 3065 participants reported using PrEP and were included in the analyses. The median age was 36 years (IQR 29–43), 1344 (44·0%) of 3056 participants were PrEP-naive, and 3016 (98·7%) were MSM. At enrolment, 1540 (50·5%) of 3049 participants opted for daily PrEP dosing and 1509 (49·5%) opted for on-demand PrEP dosing; these proportions remained stable during follow-up. Median follow-up was 22·1 months (IQR 15·9–29·7) and incidence of study discontinuation was 17·6 participants (95% CI 16·5–18·7) per 100 person-years. At the data cutoff on Sept 30, 2020, there had been six HIV-1 seroconversions (three participants using daily PrEP and three using on-demand PrEP; all were MSM) over 5623 person-years. Overall HIV-1 incidence was 1·1 cases (95% CI 0·4–2·3) per 1000 person-years, and did not differ between participants using daily PrEP and those using on-demand PrEP (incidence rate ratio 1·00, 95% CI 0·13–7·49; p=0·99). Four participants (two using daily PrEP and two using on-demand PrEP) discontinued PrEP due to treatment-related adverse events (nausea [n=2], vomiting and diarrhoea [n=1], and lumbar pain [n=1]).

Interpretation In this study, which enrolled mainly MSM, HIV-1 incidence on PrEP was low and did not differ between participants using daily PrEP and those using on-demand PrEP. On-demand PrEP therefore represents a valid alternative to daily PrEP for MSM, providing greater choice in HIV prevention.

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Introduction

More than a decade after the efficacy of daily oral HIV pre-exposure prophylaxis (PrEP) was shown, the number of people who have initiated PrEP worldwide unfortunately remains too low.[1–3] The UNAIDS goal for 2030 of a 95% reduction in new HIV infections can only be achieved if combination HIV prevention strategies, including test and treat and PrEP, are upscaled and reach all populations at risk.[3–6]

In France, following the introduction of PrEP in January, 2016, a small (7%) decline in new HIV diagnoses was reported for the first time in 2018, compared with the years 2010–17, with a 16% reduction among men who have sex with men (MSM) born in France.[6] MSM still accounted for 43% of all HIV diagnoses in France in 2019–20, and 40% of all HIV diagnoses were reported in Ile de France (ie, the Paris region), which is a hotspot for HIV transmission.[6,7]

Research in context

Evidence before this study

More than a decade ago, pre-exposure prophylaxis (PrEP) with a daily pill comprising a fixed-dose combination of tenofovir disoproxil and emtricitabine was shown to be efficacious in preventing HIV-1 acquisition among men who have sex with men (MSM) and heterosexual people at high risk of infection. In 2015, following the results of two European PrEP trials that showed a high effectiveness of PrEP to prevent HIV acquisition among MSM at high risk of infection, PrEP was recommended by WHO as an additional prevention tool for people at high risk of HIV infection, including MSM, heterosexual men and women, intravenous drug users, and HIV-negative partners in serodiscordant couples.

Since then, roll-out of PrEP has been slow and only 1 million people worldwide had initiated PrEP by 2020, which is short of the 3 million target set by UNAIDS, with large disparities across countries. Offering alternatives to a daily pill regimen could promote PrEP implementation and, pending the availability of long-acting PrEP regimens, on-demand or event-driven PrEP (also known as the 2-1-1 schedule; taken around the time of sexual activity), might represent another choice of PrEP for people not willing to be committed to a daily regimen. A single efficacy trial, the ANRS IPERGAY trial, for which results were published in 2015, showed an 86% (95% CI 40–98) relative reduction of HIV incidence with on-demand PrEP compared with placebo among MSM at high risk of HIV infection in France and Canada. However, this trial enrolled a low number of participants, with a short follow-up of only 9 months, and more data are needed to confirm the efficacy of on-demand PrEP and for the incorporation of on-demand PrEP in international guidelines.

We searched PubMed on Dec 21, 2021, with no date or language restrictions, using the terms ("pre-exposure prophylaxis" OR "PrEP" OR "preexposure prophylaxis") AND "HIV" AND ("on demand" OR "on-demand" OR "intermittent" OR "event driven" OR "event-driven" OR "event-based" OR "event based" OR "sex driven"). This search yielded 319 publications. We identified several demonstration studies that assessed on-demand PrEP among MSM in various countries, but these studies enrolled few participants and had short follow-up.

Added value of this study

This study, which enrolled more than 3000 participants (most of whom were MSM) in the Paris region, a hotspot for HIV transmission in France, provided valuable information about the interest in and effectiveness and safety of on-demand PrEP. When given the choice between daily and on-demand PrEP, nearly 50% of participants opted for on-demand PrEP and this proportion remained stable over time, despite frequent switches between daily and on-demand PrEP dosing regimens. As expected, MSM opting for on-demand PrEP were older and had fewer sexual partners than those opting for daily PrEP. This study also showed a remarkably low HIV-1 incidence of 1·1 cases (95% CI 0·2–3·2) per 1000 person-years among MSM using on-demand PrEP. To our knowledge, this study accumulated by far the largest number of person-years of follow-up with on-demand PrEP (more than 2700 person-years). The tolerable safety profile of on-demand PrEP was also confirmed, as very few participants discontinued PrEP because of treatment-related adverse events, which were mostly gastrointestinal adverse events with slightly higher incidence in participants using on-demand PrEP than in those using daily PrEP. These results confirm and extend the previously reported findings on the effectiveness of on-demand PrEP.

Implications of all the available evidence

Oral PrEP with tenofovir disoproxil and emtricitabine in an on-demand dosing regimen is an effective and safe alternative to daily PrEP among MSM and provides greater choice in HIV prevention. Research is needed to assess this on-demand regimen in other groups at high risk of HIV infection (among heterosexual men and women) and with different drug combinations within the PrEP pill. Results from this study have led WHO to fully endorse on-demand PrEP for MSM.

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See **Online** for appendix 2

PrEP roll-out has been slow in France and by July, 2017, only 5352 people had initiated PrEP, 48·9% of whom lived in the Paris region.[8,9] Long-term adherence to a daily dosing regimen remains a challenge, and alternatives to daily oral PrEP are being developed, including vaginal rings, injectable antiretrovirals, and implants.[10,11] On-demand oral PrEP, with tenofovir disoproxil fumarate and emtricitabine, has been shown to be highly efficacious in preventing HIV incidence among MSM.[12,13] However, there have been few studies evaluating on-demand PrEP, and these studies have had low numbers of participants and short follow-up.[14–20] Although on-demand PrEP has been gradually incorporated into guidelines, its use remains scarce and more data are needed.[21,22]

We aimed to assess PrEP effectiveness, adherence, and safety in adults using daily or on-demand PrEP.

Methods

Study design and participants

We conducted a prospective observational cohort study (ANRS PREVENIR) at 26 sites in the Paris region, France (appendix 2 p 2). We enrolled HIV-negative adults (aged ≥18 years) who were at high risk of HIV infection and were initiating PrEP (PrEP-naive at enrolment) or continuing PrEP (PrEP-experienced) according to French guidelines.[23] Key exclusion criteria were HBsAg-positivity for participants opting for on-demand PrEP, and a creatinine clearance of less than 50 mL/min, as assessed by the Cockroft-Gault formula.

The protocol was approved by the French Drug Agency (Agence nationale de sécurité du médicament et des produits de santé) and by the CPP Paris Ile de France IV ethics committee. All participants provided written informed consent to take part.

Procedures

PrEP was not provided within the study as it had been approved and was fully subsidised in France since January, 2016, and prescriptions could be delivered by hospital or private pharmacies. PrEP was prescribed as a fixed-dose combination of tenofovir disoproxil and emtricitabine (245 mg and 200 mg per pill, respectively). PrEP could be prescribed as a daily regimen with one pill per day or, in MSM and transgender women who have sex with men, as an on-demand regimen following the IPERGAY dosing recommendation.[12,13] The choice of PrEP dosing regimen was made by the participants, and switching between regimens was permitted.

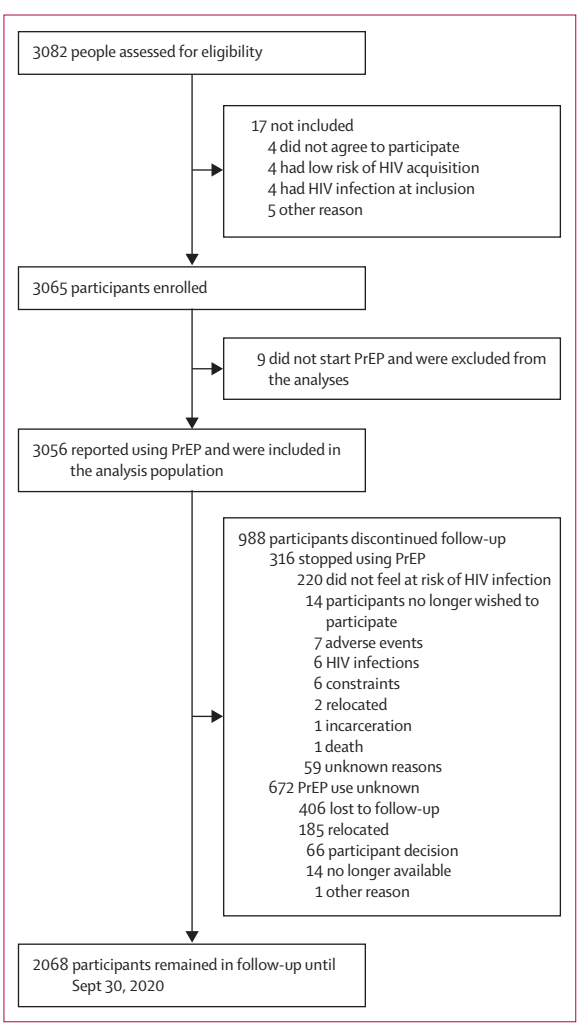

Figure 1: **Study profile**
PrEP=pre-exposure prophylaxis.

Study visits were scheduled at enrolment, 1 month later for participants who were PrEP-naive at enrolment, and then every 3 months thereafter. Each visit included a prescription to cover daily use of PrEP between visits, adherence counselling by a peer counsellor or a nurse available on site or by phone, serum testing for HIV infection using a fourth-generation assay, and tests for plasma creatinine. Before each visit, participants were asked to complete at home a computer-assisted structured interview to collect information about socio-demographic characteristics, alcohol and recreational drug use, and sexual behaviour. Alanine amino-transferase (ALT) concentrations were checked every 6 months.

At every visit, participants were offered a comprehensive package of prevention services, including face-to-face risk-reduction counselling with a peer community member or a specialised nurse, free condoms and lubricant gel, and testing and treatment of sexually transmitted infections (STIs) as recommended.[12]

The frequency of STI screening for syphilis, chlamydia, gonorrhoea, and viral hepatitis was at the physicians' discretion, following guidelines that recommended testing for STIs every 3 months in MSM with high-risk behaviours.[23] These tests were done at least once a year in all participants.

Outcomes

The primary outcome was incidence of HIV-1 infection, defined as the first evidence of HIV antibodies or p24 antigen in serum using a fourth-generation assay or HIV-1 RNA in plasma using a PCR assay. Genotypic testing for drug resistance was performed on the sample obtained near the time of diagnosis.[12]

For the assessment of adherence, participants were asked by the study investigator at each visit about the PrEP regimen used in the previous 3 months, and the number of pills taken in the week before the visit. Coverage by PrEP or condoms for the most recent sexual intercourse was also assessed at each visit, according to the definition used in the ANRS IPERGAY trial.[12,13] We also measured tenofovir diphosphate and emtricitabine triphosphate concentrations in dried blood spots in all participants at the 12-month visit, as previously described.[24]

We assessed the number of sexual partners during the 3 months before each visit, the total number of condomless sexual acts in the 4 weeks before each visit, and the proportion of participants who had condomless receptive anal sex at their most recent sexual intercourse. Additionally, we assessed the incidence rate of bacterial STIs and viral hepatitis.

Safety analyses included all participants enrolled in the study. Adverse events were recorded at each visit, regardless of any relation to study drug. Toxicity was graded according to the ANRS scale of the severity of adverse events in adults.[25]

Statistical analysis

Primary and secondary analyses were done in participants enrolled in the study who started PrEP. Descriptive statistics, including tables and bar charts, were used to summarise data. Baseline characteristics were compared by Mann-Whitney-Wilcoxon test for continuous variables and χ^2 or Fisher's exact tests for categorical variables.

HIV incidence rates per 1000 person-years were calculated using Poisson regression and compared between participants using daily PrEP dosing and on-demand PrEP dosing. The follow-up time per dosing regimen was calculated according to the dosing regimen reported by participants between visits. Additional information about the statistical analysis is provided in appendix 2 (p 1). The estimated number of HIV infections that were averted were calculated assuming an HIV incidence without PrEP in this cohort, similar to that reported in the placebo group of the ANRS IPERGAY study among MSM (6·6 cases per 100 person-years).[12] The same approach was used to estimate the cumulative incidence of STIs and viral hepatitis per dosing regimen during follow-up. Unfortunately, due to the COVID-19 pandemic, data on new HIV diagnoses in France were not available for the year 2019, and we therefore focused our analysis on the incidence of HIV and PrEP adherence, safety, and retention, using data collected up to Sept 30, 2020.

Kaplan-Meier survival curves were used to assess the probability of a first change in PrEP initial dosing regimen over time. Sexual behaviour over time was analysed graphically using trend analysis. Changes from baseline in sexual behaviour were evaluated using a negative binomial regression model with generalised estimating equations, while accounting for within-participant variability with an unstructured correlation matrix.

Safety and tolerability were assessed by the occurrence of a first episode of adverse events, serious adverse events, treatment discontinuations due to drug-related adverse events, deaths, grade 3 or 4 ALT increases, and estimated glomerular filtration rate (eGFR) of less than 70 mL/min or less than 50 mL/min using the Modification of Diet in Renal Disease formula, and were compared between participants using daily PrEP or on-demand PrEP using a Poisson regression model.

Analyses were conducted using Stata/SE (version 13.0) and SAS (version 9.4). All p values and 95% CIs were two-sided, with a significance level set at 0·05.

This study is registered with ClinicalTrials.gov, NCT03113123, and EudraCT, 2016A0157744.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 3, 2017, and May 2, 2019, 3082 people were assessed for eligibility and 3065 participants were enrolled. All participants received a PrEP prescription and had at least one follow-up HIV test available. 3056 (99·7%) of 3065 participants reported using PrEP and were included in the analyses (figure 1). At the data cutoff on Sept 30, 2020, median follow-up was 22·1 months (IQR 15·9–29·7), with a total of 5623 person-years. 988 (32·3%) of 3056 participants prematurely discontinued the study during follow-up, with a rate of study discontinuation of 17·6 participants (95% CI 16·5–18·7) per 100 person-years.

	Total (n=3056)	Daily PrEP at enrolment (n=1540)	On-demand PrEP at enrolment (n=1509)	p value
Age, years	36 (29–43)	35 (28–43)	36 (30–44)	<0·0001
Gender and sexual orientation	..	..	..	0·0012
Female, heterosexual	13 (0·4%)	11 (0·7%)	2 (0·1%)	..
Male, homosexual	3016 (98·7%)	1510 (98·1%)	1499 (99·3%)	..
Male, heterosexual	13 (0·4%)	6 (0·4%)	7 (0·5%)	..
Transgender woman, bisexual	12 (0·4%)	11 (0·7%)	1 (0·1%)	..
Transgender man, bisexual	2 (0·1%)	2 (0·1%)	0	..
Ethnicity	..	..	..	0·0046
Data available	3053	1538	1508	..
White	2615 (85·7%)	1284 (83·5%)	1326 (87·9%)	..
Black	85 (2·8%)	50 (3·3%)	35 (2·3%)	..
Asian	78 (2·6%)	42 (2·7%)	36 (2·4%)	..
Other	275 (9·0%)	162 (10·5%)	111 (7·4%)	..
Education level	..	..	..	0·0044
Data available	2576	1296	1277	..
High-school diploma	363 (14·1%)	208 (16·0%)	155 (12·1%)	..
2-year university degree or higher	2213 (85·9%)	1088 (84·0%)	1122 (87·9%)	..
Employed	2203 (85·7%)	1101 (85·2%)	1101 (86·4%)	0·38
Place of residence	..	..	..	0·11
Data available	2552	1282	1267	..
Paris	1722 (67·5%)	871 (67·9%)	850 (67·1%)	..
Île de France	782 (30·6%)	394 (30·7%)	386 (30·5%)	..
Outside of the Paris region	48 (1·9%)	17 (1·3%)	31 (2·5%)	..
Place of birth	..	..	..	0·076
Data available	3045	1533	1505	..
France	2492 (81·8%)	1232 (80·4%)	1255 (83·4%)	..
DOM-TOM	22 (0·7%)	15 (1·0%)	7 (0·5%)	..
Europe	145 (4·8%)	76 (5·0%)	69 (4·6%)	..
Asia	98 (3·2%)	48 (3·1%)	49 (3·3%)	..
Latin America, Caribbean	129 (4·2%)	82 (5·4%)	47 (3·1%)	..
North Africa	74 (2·4%)	38 (2·5%)	35 (2·3%)	..
Sub-Saharan Africa	61 (2·0%)	30 (2·0%)	31 (2·1%)	..
North America	24 (0·8%)	12 (0·8%)	12 (0·8%)	..
Site of enrolment	..	..	..	0·41
Paris	2798 (91·6%)	1417 (92·0%)	1376 (91·2%)	..
Outside Paris	258 (8·4%)	123 (8·0%)	133 (8·8%)	..
Use of recreational drugs for sex*	423 (13·8%)	222 (14·4%)	200 (13·3%)	0·35
Regular sexual partner	1365 (44·8%)	674 (43·8%)	690 (46·0%)	0·28
Main sexual partner HIV-positive	237 (17·4%)	121 (18·0%)	116 (16·9%)	0·85
Circumcised	698 (23·0%)	369 (24·2%)	324 (21·7%)	0·034

(Table 1 continues on next page)

	Total (n=3056)	Daily PrEP at enrolment (n=1540)	On-demand PrEP at enrolment (n=1509)	p value
(Continued from previous page)				
Sexual risk factors at baseline				
Number of sexual partners in previous 3 months	10 (5–20)	12 (6–25)	10 (5–15)	<0·0001
Number of condomless sex acts in previous 4 weeks	2 (0–5)	2 (0–6)	2 (0–4)	<0·0001
Bacterial STIs in the previous 12 months†	1542 (50·5%)	812 (52·8%)	726 (48·1%)	0·010
PrEP-experienced at enrolment	1712 (56·0%)	843 (54·7%)	867 (57·5%)	0·13

Data are median (IQR) or n (%). The daily PrEP at enrolment and on-demand PrEP at enrolment groups correspond to dosing regimens chosen by the participant at enrolment. For seven participants, PrEP regimen choice at enrolment was not known. Continuous variables were described by medians and IQRs and categorical variables by numbers and percentages. Mann-Whitney-Wilcoxon test was used to compare continuous variables between groups and χ^2 or Fisher's exact test was used to compare categorical variables between groups. DOM-TOM=French overseas departments and territories. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. *Recreational drugs used for sex included ecstasy, crack, cocaine, GHB (gamma hydroxybutyrate), MDMA (3,4-methylenedioxymethamphetamine), and mephedrone. †Bacterial STIs included syphilis, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, and *Chlamydia trachomatis*.

Table 1: **Baseline characteristics**

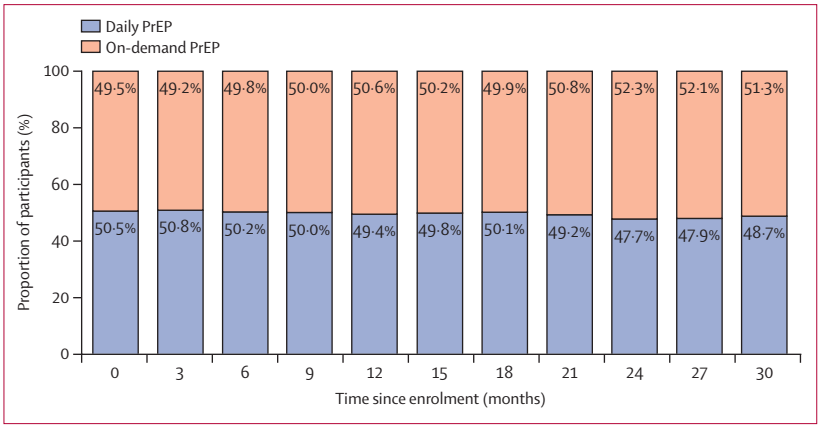

Figure 2: **Proportions of participants using each PrEP dosing regimen over time**
PrEP=pre-exposure prophylaxis.

The median age was 36 years (IQR 29–43), 1344 (44·0%) of 3056 participants were PrEP-naive, 1712 (56·0%) were PrEP-experienced, and 3016 (98·7%) were MSM (table 1). Median duration of PrEP in PrEP-experienced participants was 9·6 months (IQR 3·4–18·0). At enrolment, 1540 (50·5%) of 3049 participants opted for daily PrEP dosing and 1509 (49·5%) opted for on-demand PrEP. Multivariable analysis showed that participants who opted for on-demand PrEP at enrolment were older, had higher education level, and reported fewer sexual partners in the previous 3 months than those who opted for daily PrEP at enrolment (appendix 2 p 3).

During the study period, the proportion of participants opting for daily PrEP or on-demand PrEP remained stable overall (figure 2), and total follow-up was 2713 person-years with daily PrEP and 2723 person-years with on-demand PrEP. Overall, 671 (43·6%) of 1540 participants switched from daily PrEP to on-demand PrEP and 586 (38·8%) of 1509 participants switched from on-demand PrEP to daily PrEP. 475 (15·6%) of 3049 participants switched dosing regimens once, 455 (14·9%) switched twice, and 327 (10·7%) switched more than twice during the study period. Probability of first PrEP regimen switch over time and per initial dosing regimen is shown in appendix 2 (p 7). During the study period, most participants used generic tenofovir disoproxil and emtricitabine pills and this proportion increased from 74·8% at enrolment to 93·8% at 3 years.

Breakthrough HIV-1 infections were observed in six participants (three using daily PrEP and three using on-demand PrEP) during follow-up and the overall HIV-1 incidence was 1·1 cases (95% CI 0·4–2·3) per 1000 person-years (table 2). Assuming that there would have been an HIV-1 incidence without PrEP in this cohort similar to that reported in the placebo group of the ANRS IPERGAY study, we estimated that 361 HIV-1 infections (95% CI 195–609) were averted during the study. HIV-1 incidence was similar in participants using daily PrEP and those using on-demand PrEP (incidence rate ratio 1·00, 95% CI 0·13–7·49; p=0·99; table 2). All six participants who acquired HIV-1 during the study were MSM and all had discontinued PrEP weeks to months before HIV diagnosis (appendix 2 p 4). Resistance mutation to emtricitabine (Met184Val) was detected in a single participant.

Dried blood spots were obtained from 1779 (70·8%) of 2512 participants at the 12-month visit. Only 1613 (90·7%) of 1779 dried blood spot samples were valid and could be analysed (appendix 2 p 5). In participants using daily PrEP, median tenofovir diphosphate concentration was 1250 fmol (IQR 945–1599) per punch, which was consistent with the use of at least six PrEP pills per week in the previous 6–8 weeks. Whereas, in participants using on-demand PrEP, median tenofovir diphosphate concentration was 621 fmol (IQR 270–984) per punch, consistent with the use of three PrEP pills per week in the previous 6–8 weeks.[26] These data were consistent with the median number of pills used in the week before the visit according to participants' self-report, which was 6·0 pills (IQR 4·7–6·8) in participants using daily PrEP and 2·7 pills (1·2–4·3) in participants using on-demand PrEP (p<0·0001). The proportion of participants who had undetectable emtricitabine triphosphate in dried blood spot, consistent with no drug intake in the previous 7 days, was 5·9% of participants using daily PrEP and 35·7% of participants using on-demand PrEP (p<0·0001).

Overall, 8339 (91·5%) of 9112 sexual acts were covered by PrEP use in participants using daily PrEP and 6875 (78·4%) of 8770 sexual acts were covered by PrEP use in participants using on-demand PrEP (p<0·0001; appendix 2 p 6). 381 (4·2%) sexual acts among participants using daily PrEP and 1548 (17·6%) sexual acts among participants using on-demand PrEP were not

covered by PrEP use (p<0·0001). When PrEP was used to cover sexual acts, PrEP use was correct in 14 833 (97·5%) of 17 883 acts among participants using daily PrEP or on-demand PrEP. 270 (3·0%) of 9112 sexual acts among participants using daily PrEP and 1148 (13·1%) of 8770 sexual acts among participants using on-demand PrEP were not covered by PrEP use or condoms (p<0·0001).

Overall, there was a significant reduction in the number of sexual partners during the study period (appendix 2 pp 8, 9). There was a significant increase over time in the number of condomless sexual acts in participants who were PrEP-naive at enrolment and in those using daily PrEP during the study. Also, there was a significant increase in condomless receptive sex among participants who were PrEP-naive at enrolment, which was not observed in participants who were PrEP-experienced at enrolment (appendix 2 pp 8, 9).

During the study period, 43 participants acquired viral hepatitis, 39 of whom acquired hepatitis C virus infection with an incidence of 6·9 cases (95% CI 4·9–9·5) per 1000 person-years. Two cases of acute hepatitis B virus infection were also reported in participants who had received an incomplete hepatitis B virus vaccine regimen and were using on-demand PrEP. One participant acquired hepatitis A virus infection and one acquired hepatitis E virus infection. Regarding bacterial STIs, the cumulative incidence was 75·8 cases per 100-person-years for all STIs, 42·7 cases per 100-person-years for rectal STIs, 29·4 cases per 100-person-years for chlamydia, 39·3 cases per 100-person-years for gonorrhoea, 16·9 cases per 100-person-years for *Mycoplasma genitalium*, and 9·3 cases per 100-person-years for syphilis.

The incidence of serious adverse events was low and similar with both PrEP dosing regimens (incidence rate ratio 1·17, 95% CI 0·89–1·53; table 3). Most serious adverse events were related to infections (hepatitis C virus and COVID-19). The incidence of drug-related adverse events was low overall, but was significantly lower among participants using daily PrEP than in those using on-demand PrEP (5·93 events per 100 person-years *vs* 7·42 events per 100 person-years; incidence rate ratio 0·80, 95% CI 0·65–0·99). This difference was mainly driven by a higher rate of gastrointestinal adverse events in participants using on-demand PrEP than in those using daily PrEP, as most drug-related adverse events were gastrointestinal events. Four participants (two using daily PrEP and two using on-demand PrEP) permanently discontinued PrEP because of drug-related gastrointestinal adverse events (including nausea and vomiting and diarrhoea) in three participants and lumbar pain in one. 15 participants reported post-traumatic bone fractures that were not considered to be treatment-related and did not meet the definitions of fragility fractures.

The incidence of grade 3 or 4 ALT increases was low and similar with both PrEP dosing regimens (table 3). These grade 3 or 4 adverse events were related to acute hepatitis and not related to study drug. There was no difference in the incidence of grade 1 creatinine plasma concentration increase, or in the proportion of participants with eGFR of less than 70 mL/min or less than 50 mL/min between PrEP dosing regimens. Five participants with eGFR of less than 50 mL/min transiently discontinued PrEP. No cases of Fanconi syndrome were reported.

	Person-years	Number of HIV-1 seroconversions	Incidence per 1000 person-years (95% CI)	p value
Overall	5623	6	1·1 (0·4–2·3)	..
PrEP regimen*	..	..	..	0·99
Daily	2713	3	1·1 (0·2–3·2)	..
On-demand	2723	3	1·1 (0·2–3·2)	..
Period of follow-up	..	..	..	0·69
1st year	2821	1	0·3 (0·0–2·0)	..
2nd year	2024	3	1·5 (0·3–4·3)	..
3rd and 4th years	778	2	2·6 (0·3–9·3)	..
Calendar period of follow-up	..	..	..	0·66
May, 2017–April, 2018	668	0	0·0 (0·0–5·5)	..
May, 2018–April, 2019	1975	2	1·0 (0·1–3·7)	..
May, 2019–September, 2020	2980	4	1·3 (0·4–3·4)	..

Data are n unless otherwise stated. HIV-1 incidences rates were calculated as the total number of infections over person-years of observation, and were compared between groups using a Poisson distribution. According to the type of dosing regimen used by participants between visits, the follow-up time per dosing regimen was calculated during the study period to assess HIV-1 incidence per dosing regimen. PrEP=pre-exposure prophylaxis. *Information on the PrEP dosing regimen was missing for seven participants.

Table 2: **HIV-1 incidence over time and by PrEP regimen**

Discussion

This large, prospective, observational study—in which most participants were MSM—conducted in the Paris region of France over a 3-year period, provides important information about the use of daily PrEP and on-demand PrEP in a real-world setting. First, our findings confirm the high effectiveness of oral PrEP, with an overall incidence of HIV-1 of only 1·1 cases per 1000 person-years in this study, which is one of the lowest HIV incidences reported in the literature, similar to that of a study among MSM in Australia published in 2021.[27] Second, this study confirms and extends, with more than 2700 person-years of follow-up, the finding of high effectiveness of on-demand PrEP among MSM, as there was a very low HIV incidence in participants who opted for this regimen, similar to that reported in participants using daily PrEP in this study. This low incidence of HIV-1 among participants using on-demand PrEP is also similar to that reported in the open-label extension of the ANRS IPERGAY study (1·9 cases per 1000 person-years of follow-up) and other demonstration studies using on-demand PrEP.[13,15,19] A study among MSM in west Africa reported a high incidence of HIV with on-demand PrEP (27 cases per 1000 person-years in participants using on-demand PrEP *vs* six cases per 1000 person-years in participants using daily PrEP; p=0·20), but in this

	Total (5623 person-years)		Daily PrEP (2713 person-years)		On-demand PrEP (2723 person-years)		Incidence rate ratio (95% CI)
	Patients, n	Incidence per 100 person-years (95% CI)	Patients, n	Incidence per 100 person-years (95% CI)	Patients, n	Incidence per 100 person-years (95% CI)	
Any serious adverse event*	225	4·00 (3·49–4·56)	121	4·46 (3·70–5·33)	104	3·82 (3·12–4·63)	1·17 (0·89–1·53)
Infections	129	..	65	..	64	..	..
Neuropsychiatric	26	..	15	..	11	..	..
Death†	1	..	1	..	0	..	..
Drug-related adverse events	363	6·45 (5·81–7·15)	161	5·93 (5·05–6·93)	202	7·42 (6·43–8·51)	0·80 (0·65–0·99)
Gastrointestinal disorders	272	4·84 (4·28–5·44)	116	4·28 (3·53–5·13)	156	5·73 (4·86–6·70)	0·75 (0·58–0·95)
Asthenia	35	..	16	..	19	..	..
Cutaneous events	14	..	8	..	6	..	..
Headache	23	..	11	..	12	..	..
Bone fracture	15	0·27 (0·15–0·44)	10	0·37 (0·18–0·68)	5	0·18 (0·06–0·43)	2·01 (0·63–7·48)
Elevated ALT concentrations							
All grades	1045	18·58 (17·47–19·74)	574	21·15 (19·39–22·88)	471	17·29 (15·77–18·93)	1·22 (1·08–1·38)
Grade 3–4	49	0·87 (0·64–1·15)	26	0·96 (0·62–1·40)	23	0·84 (0·54–1·27)	1·13 (0·62–2·08)
Grade 1 plasma creatinine increase	380	6·76 (6·09–7·47)	198	7·30 (6·31–8·39)	182	6·68 (5·75–7·73)	1·09 (0·89–1·34)
Creatinine clearance, eGFR							
<50 mL/min‡	14	0·25 (0·14–0·42)	6	0·22 (0·08–0·48)	8	0·29 (0·13–0·58)	0·75 (0·21–2·47)
<70 mL/min	535	9·51 (8·72–10·35)	250	9·21 (8·11–10·43)	285	10·47 (9·29–11·75)	0·88 (0·74–1·05)

Incidence rate was defined as the number of participants who had the event of interest divided by the number of person-years. ALT=alanine aminotransferase. eGFR=estimated glomerular filtration rate. PrEP=pre-exposure prophylaxis. *There were six drug-related serious adverse events (four ALT elevations, one pancreatitis, one creatinine increase) reported by the investigators, but all participants resumed PrEP after the adverse events were resolved. †One death (among participants using daily PrEP) was due to suicide. ‡Five participants temporarily discontinued PrEP due to an eGFR of less than 50 mL/min.

Table 3: **Adverse events**

study adherence to the on-demand PrEP dosing regimen at the time of sex acts was low (45% for on-demand PrEP *vs* 75% for daily PrEP).[14] By contrast, in our study, reported PrEP coverage for sex acts was 78·4% with on-demand PrEP and 91·5% with daily PrEP. However, our definition of PrEP coverage of sex events was less stringent and we could not assess whether the PrEP pills were taken at least 2 h before sex. Still, among participants who opted for on-demand PrEP in our study, about 13% reported no PrEP or condom use at their most recent sexual act, putting them at risk of HIV acquisition. More in-depth analysis should be done to identify the type of sexual acts and the type of partners in these cases, to determine whether participants have correctly assessed their risk of HIV infection. The amount of unprotected sexual acts among people using on-demand PrEP was, however, similar to that reported in the open-label extension phase of the ANRS IPERGAY trial, in which 85% of these sexual acts were reported with the main sexual partners.[28] Indeed, as so few HIV-1 infections were observed in our study, this might suggest that most of these events were not high risk.

This study also provides interesting information about the proportion of MSM interested in using on-demand PrEP when given the choice. About 50% of participants opted for on-demand PrEP, confirming findings from previous studies and surveys that suggested a high interest for this dosing regimen among MSM.[17] Also, as reported in previous studies, during the course of our study, a substantial number of participants switched from daily PrEP to on-demand PrEP and vice versa, to adapt PrEP use to their needs.[14,19] Other studies, however, have found that a lower proportion of MSM were interested in the use of on-demand PrEP than we found among participants in our study.[15,16] Our study also shows that participants opting for on-demand PrEP were usually older, more highly educated, and had a lower number of sexual partners than those opting for daily PrEP.[14,18,19]

The high rate of condomless sex reported in this study might explain the high rate of STIs, and this will need to be addressed in future studies. PrEP programmes are an opportunity for more frequent testing and earlier treatment of STIs. Also, the high rate of STIs reported in PrEP studies did not undermine its efficacy.

This study also provides reassuring information about the safety of on-demand PrEP dosing, and confirms its tolerable safety profile. Indeed, self-limiting gastrointestinal adverse events were the most frequent drug-related adverse events, with an incidence of 4·84 events (95% CI 4·28–5·44) per 100 person-years, consisting mainly of nausea, vomiting, abdominal pain, and diarrhoea. Still, the incidence of gastrointestinal adverse events was significantly higher in participants

using on-demand PrEP than in those using daily PrEP, possibly due to the starting and stopping of PrEP with the on-demand regimen. Of note, no cases of Fanconi syndrome were reported in this study, and the incidence of participants who had an eGFR of less than 50 mL/min was low and similar in those using daily and those using on-demand PrEP, confirming the good renal tolerability of oral PrEP over a median of 2 years of follow-up in this population.[29] Serious adverse events were rare, with an incidence of 4·00 events (95% CI 3·49–4·56) per 100 person-years, and consisted mainly of infections (viral hepatitis and COVID-19) and psychiatric disorders, and only six were considered to be treatment-related. These serious adverse events underline the need for a comprehensive sexual health approach in people using PrEP who frequently use recreational drugs for sex (also referred to as chemsex), some of whom might also have underlying neuropsychiatric conditions.

This study has some limitations. First, we were not able to assess the effect of this PrEP cohort on the HIV epidemic among MSM in the Paris region, which was our initial objective, due to the scarcity of reliable data about the number of new HIV diagnoses in France because of the under-reporting during the COVID-19 pandemic in 2020.[8] Second, this study was not a randomised comparison of daily PrEP versus on-demand PrEP, and we therefore cannot directly compare the efficacy of the two dosing regimens. Furthermore, the participants opting for daily PrEP and those opting for on-demand PrEP at enrolment were not similar with regards to their risk of HIV acquisition. Additionally, without a control group to assess HIV incidence without PrEP, we could not properly assess the effectiveness of on-demand PrEP in our cohort. Also, because of the high rate of participants who discontinued follow-up, we might have overestimated the effectiveness of on-demand PrEP and daily PrEP in our cohort. Similarly, we might have overestimated the good tolerability profile of PrEP, because some participants might have discontinued PrEP or follow-up for drug-related adverse events without providing this information. Finally, we did not enrol in this cohort non-MSM individuals at risk of HIV acquisition. As MSM only represent 43% of all new HIV diagnoses in France, it is crucial to deliver PrEP to other key populations to have a substantial impact on the HIV epidemic. Future PrEP studies in France should address this issue.

In conclusion, our study has confirmed, in a large number of participants followed-up for a median of 22 months, where a high proportion of MSM opted for the use of on-demand PrEP, that on-demand PrEP is associated with a low HIV incidence and has a tolerable safety profile. These data have led WHO to formally endorse the on-demand (or 2-1-1) PrEP regimen as an alternative to daily PrEP for MSM, providing greater choice in HIV prevention for this population.[30] Additional studies are needed to assess whether on-demand PrEP could be used in other populations at high risk of HIV infection, or with other antiretroviral drug combinations within the PrEP pill.

Contributors

J-MM, JG, and DC designed and led the study. DC and LA designed the analysis. DC, LA, JG, and J-MM analysed the data. DC coordinated the study and oversaw data management. LA directly accessed and verified the underlying data reported in the manuscript. BS and DR-C designed the counselling interventions. LG did the pharmacological assays. J-MM, GL, JG, GP, CK, HM, MO, BL, LSl, JL, JP, and LSu conducted the study at their sites. CD reviewed the virology data. J-MM wrote the first draft of the report. DC, LA, LB, MA-G, JG, and J-MM had full access to all the data in this study and had final responsibility for the decision to submit for publication. All other authors critically reviewed and approved the manuscript.

Declaration of interests

J-MM reports receiving support as an advisor for Gilead Sciences, Merck, Janssen, and ViiV; and research grants from Gilead Sciences. JG reports receiving support as an advisor for Gilead Sciences, Merck, Janssen, Roche, AstraZeneca, Theratechnologies, and ViiV; and research grants from Gilead Sciences and ViiV. CK reports research grants from Merck; and personal fees from Gilead Sciences, Merck, and ViiV. GP reports consulting fees from Gilead, Merck, and ViiV; and research grants from AbbVie and Gilead Sciences. CD reports support as an advisor for Gilead Sciences, Merck, and ViiV; and research grants from Merck, ViiV, and Gilead Sciences. DC reports a research grant from Janssen; and personal fees from Gilead for lectures. MB-M reports a research grant from Gilead Sciences. All other authors declare no competing interests.

Data sharing

Data requests may be submitted to the scientific committee of the ANRS PREVENIR study (by email to jean-michel.molina@aphp.fr) and must be approved by the French data protection authority, la Commission Nationale de l'Informatique et des Libertes (CNIL). French law requires that everyone who wishes to access cohort data or clinical study data on humans must ask the French data protection authority (the CNIL) for permission, by completing a form that can be provided by Lambert Assoumou (lambert.assoumou@iplesp.upmc.fr). For further information, please see https://www.cnil.fr/. The ANRS PREVENIR scientific committee will evaluate each proposal for compatibility with general objectives, ethical approval, and informed consent forms of the ANRS PREVENIR project, and for potential overlap with ongoing work.

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