Infect Dis Trop Med 2016; 2 (4): e339

PrEP in Europe: two different studies, one incontrovertible result

L. Taramasso, F. Del Puente, N. Riccardi, A. Di Biagio

Infectious Diseases, IRCCS AOU San Martino-IST, Genoa, Italy

ABSTRACT:

Several studies have demonstrated the efficacy of the oral pre-exposure prophylaxis with daily tenofovir plus emtricitabine on preventing HIV negative partners to become infected, and many trials are investigating its role in a real-life setting and different populations. PrEP is already available in the United States, approved by European Medicine Agency, but not available in Italy. In this short review we analyze two different studies carried out in Europe.

Keywords: PrEP, Tenofovir, Emtricitabine, men who have sex with men (MSM).

INTRODUCTION

Globally, at the end of 2014, there were 36.9 million individuals living with HIV. New infections were reported in 2 million people worldwide in the same year[1], while in Europe, excluding Russia, 142,000 new diagnoses of HIV were registered, the highest since reporting started in the 1980s[2]. Despite multiple efforts to reduce new HIV infections, the number of new diagnoses per year remains stable. In the men who have sex with men (MSM) subgroup, the number of HIV diagnosis increased by 11% from 2006 to 2012[3]. Therefore, MSM is now considered the most vulnerable population. Pre-Exposure Prophylaxis (PrEP) has shown high efficacy in preventing HIV infection in several large clinical trials on MSM. Oral PrEP could be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of a combined prevention approach. Oral PrEP is based on a combination of tenofovir (TDF) plus emtricitabine (FTC) as a single tablet regimen (STR) (Truvada®). PrEP is already available in the United States and now is approved by European Medicine Agency (EMA). In this review, we analyzed two different approaches: PrEP with TDF/FTC once daily or PrEP with TDF/FTC on-demand.

PROUD STUDY

The PROUD study has been published in the Lancet scientific journal in september 2015[4]. Proud was an open-label randomized trial performed in England involving 544 persons between November 29, 2012 and April 30, 2014. All participants were HIV-negative MSM who had unprotected anal intercourse during the previous 90 days. All these persons were assigned with 1:1 ratio to receive PrEP either immediately or after a deferral of twelve months. PrEP was given as a single tablet regimen (STR) of TDF (200 mg) and FTC (245 mg). All persons who started PrEP were screened for potential renal adverse effects and informed about the time necessary to achieve steady-state drug concentration and, consequently, maximum protection. Clinical assessment, evaluation of potential side-effects of study drug, compliance to care, screening for bacterial sexually transmitted disease (STD) and HIV test were performed regularly every three months. Yearly evaluation of renal function was performed using serum creatinine and urine dipstick to to determine the presence of trace of protein. Plasma concentrations of TDF were monitored in a relatively small subgroup of patients (52 persons). PrEP was prescribed for 261 participants in the immediate group. Twenty-one persons reported interrupted or missed dose because of an adverse event. Twenty of 21 re-started study drug. Nausea, headache and arthralgia were the most reported drug-related symptoms.

Three of 21 persons interrupted study drug because of high creatinine concentration (2 had renal comorbidities). A total of 29 serious adverse events (including one death) were reported, none was attributed to study drug. Post-exposure prophylaxis was prescribed for 12 participants for a total of 14 courses.

Corresponding Author: Antonio Di Biagio, MD; e-mail: adibiagioa@gmail.com

In the deferred group, at least one course of post-exposure prophylaxis for 85 participants was prescribed, for a total of 174 courses. In the deferred group 20 patients had new incident HIV diagnosis, on the other hand, 3 patients have been infected by HIV in the immediate group, two of three cases due to absent compliance to the procedure of the study while the remaining infection was thought to occur before the start of PROUD study. Confronting the data from the two groups a proportion reduction of 86% of HIV infection and a rate difference of 7-8 per 100 person-years in incidence was obtained if PrEP had been regularly used in the population study. No significant difference between groups was observed in sexual behavior. A difference was noted in the number of STD diagnosis in the immediate group (57%) versus the deferred group (50%). This result was considered biased by the greater number of screens in the immediate group. The study concluded that, even considering the potential disadvantage of PrEP in the generation of drug resistant viruses and adverse effects, the rate of reduction of HIV diagnosis achieved in the immediate group suggested a prospective benefit of using PrEP in managing HIV epidemic, in populations considered at high risk of HIV infection.

IPERGAY

The Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) was designed to assess the efficacy and safety of sexual activity–dependent PrEP with TDF-FTC among HIV-1 negative high-risk MSM in seven different study sites, six in France and one in Canada[5]. The primary end point of the study was the diagnosis of HIV-1 infection. Adherence to PrEP was a secondary end point evaluated by pill count at every visit and plasma drug level monitoring of TDF and FTC; all participants that received TDF/FTC were monitored for possible side effects. Inclusion criteria were: HIV-negative status, age of 18 or older, male or transgender female sex and high risk for HIV infection, defined as a history of unprotected anal sexual intercourse with at least two partners during the previous 6 months. Exclusion criteria included positive hepatitis B surface antigen, hepatitis C virus chronic infection, creatinine clearance less than 60 ml per minute at Cockroft–Gault equation, alanine aminotransferase level higher than 2.5 times the upper limit of the normal range, and glycosuria or proteinuria more than 1+ on urine dipstick testing. During enrollment visit, eligible HIV-negative participants were assigned in a 1:1 ratio to receive either TDF-FTC or placebo. Participants were instructed to take two pills of TDF-FTC or placebo with food 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later. In the case of multiple consecutive sexual intercourses, participants were instructed to take one pill per day until the last episode and then to take the two post-exposure pills at a distance of 24 and 48 hours of the last one. When resuming pre-exposure prophylaxis, participants were instructed to take a loading dose of two pills unless the last drug intake was less than 1 week earlier, in which case they were instructed to take only one pill. The population was evaluated at 4 and 8 weeks after enrollment and every 8 weeks thereafter. At every visit drug dispensation was ensured to cover the daily use of TDF-FTC or placebo; moreover, pills count and adherence counseling, serum testing for HIV-1 and HIV-2, and biochemical analyses were performed. A computer-assisted structured interview was performed before each visit, in order to collect information about sociodemographic characteristics, use of alcohol and recreational drugs, sexual behavior, and adherence to PrEP. In every newly infected patient, genotypic testing for drug resistance was performed to detect major resistance mutations to TDF-FTC. Four hundred and fourteen (414) patients underwent randomization and 206 were assigned to receive TDF-FTC (49.7%), while 208 (51.3%) received placebo. Main baseline characteristics of study participants were similar in the two groups (Table 1). Of the 400 participants, 56 (14%) (31 in the TDF-FTC group and 25 in the placebo group) received post-exposure prophylaxis during the study period. A total of 431.3 person-years of follow-up were covered for the assessment of the incidence of HIV-1 infection after enrollment, with a median follow-up of 9.3 months, while premature study discontinuation occurred in 49 participants (12%). Sixteen HIV-1 infections developed after enrollment: 2 in the TDF-FTC group (incidence of 0.91 per 100 person/years) and 14 in the placebo group (incidence of 6.60 per 100 person/years), indicating a relative reduction in the incidence of HIV-1 acquisition in the TDF-FTC group of 86% (95% confidence interval [CI], 40 to 98; p=0.002). In the intention-to-treat analysis, the relative reduction in the incidence of HIV-1 acquisition was 82% (95% CI, 36 to 97; p=0.002). The 2 participants in the TDF-FTC group were non-adherent to study protocol and PrEP administration. Study drugs were not detected in plasma samples obtained from these 2 participants at the time of HIV-1 diagnosis. None of the 16 participants who acquired HIV-1 infection after enrollment had resistance

Table 1. Comparison PROUD and IPERGAY.

Clinical trial	Participants	Patients	Drug	mITTa efficacy of % reduction in acquisition of HIV infectionb	
				%	(95% CI)
PROUD4	MSM	544	FTC/TDF	86	(64-96)
IPERGAY[5§]	MSM	400	on demand FTC/TDF[¥]	86	(40-98)

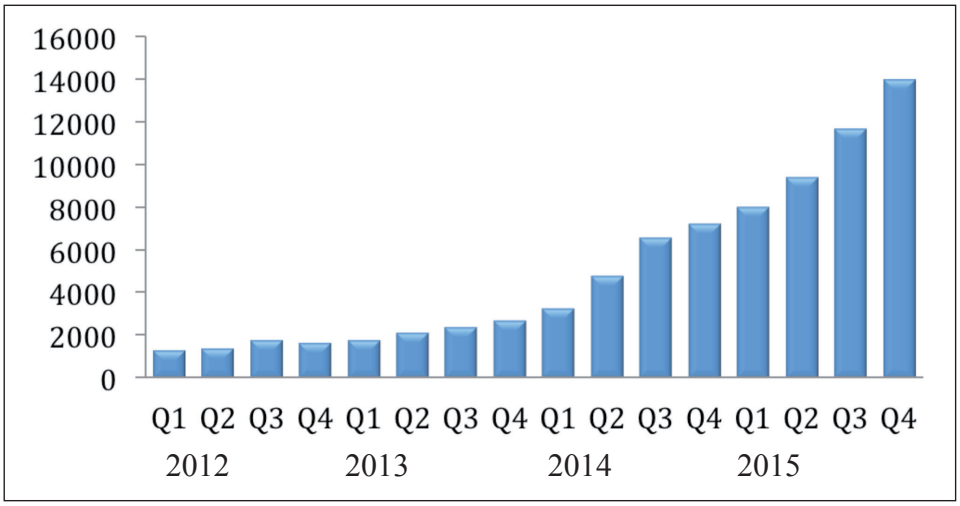

Figure 1. TDF/FTC for HIV pre-exposure prophylaxis PrEP utilization in the United States: 2012-2015. (Modified. Mera R, AIDS 2016, Durban, South Africa. Oral TUAX0105LB).

mutations to study medications. A median number of 15 pills per month were taken in the TDF-FTC group and in the placebo group (p = 0.57). TDF and FTC plasma levels were measured for the first 113 participants enrolled. In the TDF-FTC group, the rates of detection were 86% for TDF and 82% for FTC, respectively. Overall, 28% of participants did not take TDF-FTC or placebo, 29% took the assigned drug at a suboptimal dose, and 43% took the assigned drug correctly. No deaths or significant differences between the groups in terms of side effect were reported during the study. One patient discontinued TDF-FTC due to possible drug-drug interaction with dabigatran. Elevations in serum creatinine levels were seen in 35 participants (18%) in the TDF-FTC group and 20 participants (10%) in the placebo group (p = 0.03). Sexual practices and the number of participants with a new STD did not change overall during the study period compared to baseline.

DISCUSSION

The above-reported studies have definitively demonstrated the effectiveness of PrEP strategy in high-risk populations. Both studies enrolled MSM population only, considering MSM the most at risk ([6]). Inclusion criteria were similar in the two studies, HIV-negative MSM with a history of unprotected anal sex in the last six months ([5]) or 90 days ([4]).

Data have been collected in 540 participants in PROUD study and 414 in IPERGAY. Three patients in PROUD and 10 in IPERGAY had been excluded for HIV positivity at baseline, indicating a real identification of a high-risk population in both studies. The patients were followed–up for of 243 and 222 person-years in the two groups of PROUD study and for a total of 431 person-years of follow-up in IPERGAY. The strategies used in the two studies summarize the two major schools of thought about PrEP: continued ([4]) versus on-demand ([5]) administration. In the PROUD study, PrEP administration should be either deferred or immediate, but in both cases, it was constituted by a daily drug administration, independently from the prevision of intercourse in the following days. On the contrary, IPERGAY study was designed to administer PrEP in a sexual-activity dependent way, assuming that it would be a mean to heighten the adherence to the proposed therapeutic protocol. Not surprisingly, in both studies some participants either in PrEP or not, also needed post-exposure prophylaxis (PEP). While the double-blind nature of IPERGAY makes understandable the need of PEP in both the arms of the study, the same thing is less obvious in PROUD. In fact, in PROUD, it was well known which people were on PrEP. Consequently, the need of adjunctive PEP might be explained only by a non-adherence to PrEP protocol. If non-adherence was linked to the daily schedule or to insufficient motivation to PrEP taking remains an open issue, but in both cases, the immediate disposability of TDF/FTC and the linkage to a medical center prescriber of PEP had been necessary for the timely formulation of a PEP.

In particular, in PROUD study nearly 18% of participants had at least one prescription of PEP: 12 enrolled in the immediate PrEP arm (for a total of 14 courses of PEP) and 85 participants of the deferred arm (for a total of 174 PEP prescriptions). Of note, at the moment of study enrollment, more than one third of participants declared to have taken PEP in the last 12 months (36%). Thus, the number of PEP prescription was reduced in comparison to the past. In IPERGAY study 14% of patients took PEP during the study period, distributed in the placebo, 25 patients, and the PrEP, 31 patients, arms. In both studies, a certain number of participants acquired HIV infection during the follow-up period: 23 in PROUD and 16 in IPERGAY. The difference between the number of new HIV infections in people on PrEP and other participants was found statistically significant in both studies, with an analogous estimation of the reduction of the risk of HIV infection in PrEP users, equal to 86%. In PROUD study, 20 MSM were diagnosed with a newly acquired HV infection in the deferred arm whilst 3 in immediate arm. Two of those three participants did not attend regularly scheduled visits, and consequently did not have sufficient drug to guarantee a daily assumption. The third was deemed to be already infected at enrollment, with seroconver-

sion demonstrated at week 4 and not yet detectable at baseline due to a recent acquisition. In IPERGAY, 16 HIV infections developed after enrollment, 2 in PrEP and 14 in the placebo arm. Also in this case, the new HIV infections detected in PrEP group occurred in participants non-adherent to the study protocol, in which TDM revealed no drug concentration in plasma and the high number of pills returned was indicative of inadequate PrEP use. Those data show that the major point of weakness of PrEP is not the drug efficacy, but a lack of adherence by study participants. According to these studies data, people that do not have a medical need of TDF/FTC do not take it regularly in 100% of cases, which is understandable, and also expected, as even patients with HIV infection do not reach an adherence to treatment of 100%.

On the other hand, HIV seroconversion occurred also in participants of the studies that had not been assigned to PrEP. In PROUD, six new cases of HIV were diagnosed in the delayed arm, in people who had previously used PEP at least once, suggesting that PEP users are a suitable group on which focalize prevention strategies and PrEP indication (4).

Among participants who became HIV infected despite PrEP prescription, a resistance profile was found only in one case, in the patient who was presumed to be already positive at PROUD study entry and that started TDF/FTC in monotherapy for 4 weeks, till he was diagnosed with HIV. In all other infections that occurred in the PrEP groups no resistance pattern was found, consistently with no-drug taking despite prescription. Moreover, a quite high number of STD has been diagnosed during the two studies. In both studies, bacterial STD has been investigated at every visit in the PROUD study and every six months in IPERGAY, and treated in case of occurrence. Moreover, in IPERGAY free condoms were offered to all study participants. In the PROUD study, 50% of patients on the deferred group versus 57% of patients enrolled in the immediate prescription group acquired a sexually transmitted disease other than HIV. No statistical significance was found in the different frequency of STD in the two groups. However, the datum does not reflect a change in risk behaviors that might in some way be linked to PrEP use, as before study entry (previous 12 months) 64% of participants had at least one diagnosis of sexually transmitted disease. In IPERGAY study too, the number of STD did not differ significantly in the two study groups, with a rate of 41% in PrEP group versus 33% in the placebo group. At screening, 27% of participants received a diagnosis of STD, reflecting also, in this case, a high rate of STD preceding the study entry.

The use of placebo in the control-group in IPERGAY was exactly finalized to avoid a possible augmentation of risky behaviors in PrEP users due to the belief of being HIV-protected. The rate of newly acquired STD was slightly lower compared to PROUD study, but the placebo strategy is not the only responsible mechanism. In PROUD study, the rate of STD was high also in the delayed treatment group, despite people knew they were at risk of HIV infection in case of unprotected intercourse. It is also possible that free condom distribution in IPERGAY may have played a role.

The two studies reached overall the same rate of protection against HIV infection, with a slightly lower number of STD in IPERGAY. But which strategy favored the highest rate of adherence? The retention in care has been similar in the two studies, with 49 (11%) participants who discontinued the follow-up in IPERGAY, versus 40 (7%) in PROUD. The adherence has been checked in the two studies with different tools: by on-line questionnaires preceding every visit (every two months) and additional pill count of the returned study-drug at the moment at the visit in IPERGAY, and by monthly questionnaires either online or on paper in PROUD. Moreover, TDM has been performed in 52 participants who declared to be adherent to PrEP in PROUD study and in the first 113 patients enrolled in IPERGAY. TDM results were compatible with correct assumption in the samples analyzed in both studies: Overall, 88% of participants enrolled in the immediate PrEP arm of PROUD received an adequate number of pills of TDF/FTC to cover all the study period with daily taking, while the remaining 12% did not take enough study-drug. The same estimate is not easy to perform in IPERGAY since the on-demand nature of drug taking. On the basis of questionnaires and pill-counts, the patients who took correctly PrEP were 43%, while 28% declared not to take either TDF/FTC or placebo and the remaining percentage made a suboptimal use of PrEP (29%). Even if it is not possible a direct comparison between the adherence in the two studies, the protocol proposed in PROUD seemed easier to follow by patients, on the basis of the lower number of PEP prescription and the higher retention in care.

Finally, it is interesting to consider the adverse event rate registered with the two different strategies: in PROUD study, a total of 57 adverse events have been registered, of which 13 possibly related to the study drug. No serious adverse event was related to the study-drug. Nausea, headache and arthralgia were the most frequent. Also in IPERGAY study the gastrointestinal adverse events were the more frequent (nausea, vomiting, diarrhea, abdominal pain, and other gastrointestinal disorders). The total number of adverse events with the on-demand TDF/FTC was not statistically different to those in the placebo arm.

The last analogy of the two studies is that an interim analysis of the results of both PROUD and IPERGAY studies demonstrated statistically significant reduction in the rate of new HIV infection among PrEP users that led to early study discontinuation in both.

The two strategies proposed in IPERGAY and PROUD studies share good tolerability and high efficacy (Table 1). None of the participants who correctly took PrEP became HIV infected. PEP users are a high-risk population to whom PrEP should be encouraged. Since the lack of adherence is the major weakness of both PrEP strategies, it is desirable to start PrEP projects in parallel with techniques that enhance motivation and adherence in the population at risk.

CONCLUSIONS

HIV prevention incorporates different interventions, for example behavioral, such as patient and partner education, correct and consistent condom use, or biomedical prevention such as testing and treatment of sexually transmitted diseases, treatment as prevention, circumcision. PrEP, based on TDF and FTC, is a biomedical strategy. The optimal delivery of PrEP to target population needs to be established. Guidelines for initiation and discontinuation of PrEP need to be standardized, and cost effectiveness needs to be evaluated. PROUD and IPERGAY open a new way where the PrEP is an invaluable weapon for reducing the global damage from HIV.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

REFERENCES

1. UNAIDS. FACT SHEET 2016. GLOBAL STATISTIC- 2015. Available online: http://www.unaids.org/sites/default/files/media_asset/20150901_FactSheet_2015_en.pdf (accessed on 01 November 2016)
2. Highest number of new HIV cases in Europe ever. Available online: http://www.euro.who.int/en/media-centre/sections/press-releases/2015/11/highest-number-of-new-hiv-cases-in-europe-ever (accessed on 01 November 2016)
3. UNAIDS. THE GAP REPORT. Available online: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en. (accessed on 01 November 2016)
4. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, Fox J, Taylor S, Antonucci S, Khoo SH, Rooney J, Nardone A, Fisher M, McOwan A, Phillips AN, Johnson AM, Gazzard B, Gill ON. 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.
5. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F, Pintado C, Chidiac C, Chas J, Charbonneau P, Delaugerre C, Suzan-Monti M, Loze B, Fonsart J, Peytavin G, Cheret A, Timsit J, Girard G, Lorente N, Préau M, Rooney JF, Wainberg MA, Thompson D, Rozenbaum W, Doré V, Marchand L, Simon MC, Etien N, Aboulker JP, Meyer L, Delfraissy JF; ANRS IPERGAY Study Group. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015; 373: 2237-2246.
6. HIV in the United Kingdom. 2014 Report. Available online: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf