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Uptake of PrEP and condom and sexual risk behavior among MSM during the ANRS IPERGAY trial

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ABSTRACT

The double-blind phase of the randomized ANRS IPERGAY trial, evaluating sexual activity-based oral HIV pre-exposure prophylaxis (PrEP), was conducted among high-risk men who have sex with men (MSM). Results showed an 86% (95% CI: 40–98) relative reduction in HIV incidence among participants with tenofovir disoproxil fumarate–emtricitabine vs. placebo. The present pooled analysis aimed to analyze (i) participants' adherence to the prescribed treatment and/or condom use during sexual intercourse and (ii) sexual behavior during the double-blind phase of the study. Four hundred MSM were enrolled in the trial. Every 2 months they completed online questionnaires collecting sexual behavior and PrEP adherence data regarding their most recent sexual intercourse. A total of 2232 questionnaires (M0–M24) were analyzed. Changes over time were evaluated using a mixed model accounting for multiple measures. Irrespective of sexual partner and practice type, on average, 42.6% (min: 32.1–max: 45.8%) reported PrEP use only during their most recent episode of sexual intercourse; 29% (22.9–35.6%) reported both PrEP and condom use; 11.7% (7.2–18.9%) reported condom-use only, and 16.7% (10.8–29.6%) reported no PrEP or condom use with no significant change during the study. Scheduled (i.e., correct) PrEP use was reported on average by 59.0% (47.2–68.5%) of those reporting PrEP use during their most recent sexual intercourse. Overall, 70.3% (65.3–79.4%) and 69.3% (58.3–75.4%) of participants reported, respectively, condomless anal and condomless receptive anal intercourse during their most recent sexual encounter without significant change during follow-up. Overall, on average 83.3% (min: 70.4–max: 89.2%) of participants protected themselves by PrEP intake or condom use or both during the trial, and no increase in at-risk sexual practices was observed. None of these indicators showed significant trend during the follow-up, although we found a tendency toward decrease ($p = .19$) of the median number of sexual partners strengthening the absence of behavioral disinhibition. On-demand PrEP within a comprehensive HIV prevention package could improve prevention in MSM.

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Introduction

The valuable role of antiretroviral therapy in preventing HIV transmission in serodiscordant couples has been clearly demonstrated when the infected partner is receiving treatment (Cohen et al., 2011). However, since the number of new HIV diagnoses continues to grow in the most vulnerable populations, additional prevention strategies are needed. This is particularly true for men who have sex with men (MSM). In France, a 14% increase in new HIV diagnoses was observed between 2011 and 2013 in this population (Cazein et al., 2015). Pre-exposure prophylaxis (PrEP) has shown itself to be a new promising biomedical strategy to prevent HIV acquisition among high-risk HIV-negative people. Several studies have demonstrated efficacy ranging from 44 to 75% when PrEP constitutes part of a comprehensive HIV prevention package (Baeten et al., 2012; Choopanya et al., 2013; Grant et al., 2010; Thigpen et al., 2012). All these studies tested daily tenofovir disoproxil fumarate (TDF) or TDF–emtricitabine (FTC) PrEP regimens and their efficacy was highly correlated with adherence (Blashill, Ehlinger, Mayer, & Safren, 2015). The iPrEx trial, the first PrEP efficacy trial conducted

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among MSM, showed a moderate reduction in HIV incidence of 42%, and a PrEP efficacy of up to 92% when Tenofovir was detectable in blood (Grant et al., 2010). An open-label extension study following iPrEx found that no participants became infected when drug dosage indicated the use of ≥4 tablets per week (Grant et al., 2014). Poor adherence was the main factor associated with low PrEP efficacy in two other daily TDF–FTC regimen trials conducted among women, Fem-PrEP, and VOICE (Corneli et al., 2014; Van Damme et al., 2012).

Although PrEP is now recognized internationally as a key element of combination HIV prevention strategies, one of the major concerns that could undermine its benefits regards sexual risk disinhibition and risk compensation (Cassell, Halperin, Shelton, & Stanton, 2006; Cohen, 2010; Eaton & Kalichman, 2007; Hogben & Liddon, 2008; Underhill, 2013). However, previously published results from double-blind randomized placebo-controlled PrEP trials have not shown evidence to support this concern (Baeten et al., 2012; Grant et al., 2010; Guest et al., 2008; Liu et al., 2013; Marcus et al., 2013). The iPrEx trial showed a significant increase in the number of receptive anal intercourse (RAI) partners with a significant increase in condom use among those partners over 144 weeks of follow-up (Marcus et al., 2013). The US CDC safety study, a Phase 2 double-blind randomized trial comparing daily TFD PrEP prescribed to MSM immediately upon study enrollment with daily TDF PrEP prescription 9 months after enrollment, demonstrated a decrease in the number of partners and a significant decrease in the proportion of men reporting condomless anal sex over 24 months of follow-up, irrespective of the trial arm (Liu et al., 2013). In all these trials, participants received risk-reduction and adherence counseling as well as regular sexually transmitted infections (STIs) testing. This comprehensive prevention care may have had an impact on sexual risk behaviors.

To investigate the impact of risk compensation on PrEP users, an open-label randomized trial (PROUD) in sexual health clinics in the UK, compared adherence in MSM prescribed daily TDF–TFC immediately upon trial inclusion, with those whose treatment initiation was deferred until one year after inclusion. Results showed a relative reduction of 86% (90% CI: 64–96), $p = .0001$, in HIV infection in the immediate vs. deferred group, with no increase in STI (McCormack et al., 2015). In a non-research-based context, a 2.5-year follow-up of PrEP use in a US clinical setting among at-risk populations showed no HIV infection, despite a high rate of STI. Furthermore, in the majority of participants, no change or decrease in the number of sexual partners and no change or increase in condom use was observed (Volk et al., 2015).

The ANRS IPERGAY double-blind randomized trial tested the efficacy of a sexual activity-based PrEP regimen in high-risk MSM assuming that an intermittent regimen would result in higher efficacy than a daily PrEP regimen as a result of increased adherence. Participants were randomly assigned to the TDF–TFC or placebo arm. ANRS IPERGAY provided a comprehensive sexual health offer including community-based support, risk-reduction counseling, prevention tools (condoms, lubricants, and syringes if necessary) and regular testing for HIV and other STI. Trial results showed that TDF–FTC led to a relative reduction in infection of 86% (95% CI: 40–98, $p = .0019$) over a median follow-up of 9.3 months (Molina et al., 2015). The objective of the present analysis was to analyze PrEP adherence and sexual risk behavior trends over 24 months of follow-up.

Methods

Study population

The ANRS IPERGAY study is a double-blind randomized combined prevention trial conducted in France and Canada that consisted in providing sexual activity-based antiretroviral prophylaxis for HIV prevention in MSM. Briefly, the trial included HIV-negative male or transgender women who have sex with men, aged ≥18 years, at high risk of HIV acquisition that is reporting anal sex with at least two different partners over the previous 6 months. PrEP was prescribed as follows: 2 pills intake, 2–24 hours before sex followed by 1 pill 24 h and another 48 h after the first drug intake. Participants were offered access to individual-centered risk-reduction counseling, condoms, and lubricants and were regularly tested for HIV and other STI. They completed an online questionnaire every 2 months covering socio-demographic characteristics, alcohol and recreational drug use, sexual behavior, and PrEP adherence during their most recent episode of sexual intercourse. See Molina et al. (2015) for a comprehensive description of the ANRS IPERGAY trial's methodology and results. This study used the January 2015 data-set, and included 400 participants (out of 414 randomized) assigned either to the TDF–FTC ($n = 199$) or placebo ($n = 201$) arm (Molina et al., 2015). The present analyses included 400 participants for whom longitudinal information was available within M0–M24, accounting for 2232 analyzable online questionnaires.

Variables

PrEP adherence outcome. Self-reported PrEP adherence was classified into three categories depending on pill intake: (i) correct PrEP use that is according to protocol

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or taking at least 1 pill within 24 h before *and* 1 pill within 24 h after sex; (ii) suboptimal PrEP use that is taking at least 1 pill 48 h before *or* 48 h after sex; and (iii) no PrEP use that is no pills taken within 48 hours before or after sex.

Sexual behavior outcome. Sexual behavior was assessed using four indicators: (1) the median number of episodes of sexual intercourse in the previous 4 weeks; (2) the median number of sexual partners in the previous 2 months; (3) the frequency of condomless anal intercourse, either insertive or receptive, during their most recent sexual encounter; (4) the frequency of condomless RAI during their most recent sexual encounter.

Sexual practices. Sexual practices reported by participants during their most recent sexual encounter were classified into two categories depending on the HIV-risk level: (i) high exposure: condomless anal sex and (ii) low exposure: no condomless anal sex (i.e., anal sex with condoms or oral sex only).

Statistical analyses

Given the double-blind nature of the ANRS IPERGAY trial, the data of both TDF–FTC and placebo arms were pooled since no significant difference was seen between the arms either in terms of PrEP adherence or sexual behavior (Molina et al., 2015). Descriptive statistical analysis was first carried out for the combination "PrEP and condom use during the most recent episode of sexual intercourse", then on data where correct or suboptimal use of PrEP during the most recent episode was reported. The median number of sexual intercourses, the median number of sexual partners, and also proportions of condom use for last anal intercourse, then specifically for last anal receptive intercourse were described. The longitudinal nature of the descriptive statistics presented in this paper required testing whether a trend over follow-up existed or not. Linear regression was carried out over each outcome with a time term as explanatory variable. Then, the significance of the estimated parameter was tested (e.g., not-significant parameter associated to the time term indicated absence of trend during follow-up). All analyses were performed using Stata/SE 12.1 for Windows (StataCorp LP, College Station, TX, USA) software.

Results

Participants' characteristics

The main characteristics at baseline of the 400 participants with longitudinal data from M0 to M24 included in the study sample are described in Table 1. The median age of MSM was 34.9 [IQR: 29–43] years; 72.3% had a high school or higher educational level; and 84.6% were in active employment. At baseline, MSM had had sexual intercourse a median of 10 [5–16] times in the previous 4 weeks, and a median of 8.3 [5–17] sexual partners in the previous 2 months. Over 70% of MSM reported that their most recent episode of RAI was condomless.

PrEP and/or condom use during most recent episode of sexual intercourse

Observation of PrEP and condom use during participants' most recent episode of sexual intercourse started at M2, since there was no pill intake at M0. The analyses of these outcomes were carried out on 320 participants (out of 400 included in trial) corresponding to 1212 analyzable sexual intercourses between M2 and M24. The 80 participants with missing information were excluded and did not differ significantly from those retained for this part of the analysis, in terms of socio-demographic characteristics and sexual behavior indicators (data not shown). Overall, participants reported that 42.6% of the total number of most recent episodes of sexual intercourses were protected by PrEP as the unique mode of prevention, irrespective of their sexual partner and sexual behavior. Over 28% of most recent episodes of sexual intercourse were without PrEP intake, 16.7% during condomless anal sex (i.e., high-exposure group), and 11.7% during no condomless anal sex (i.e., low-exposure group) (Figure 1). These proportions did not evolve significantly during follow-up low exposure with or without PrEP: $p = .49$ and $p = .38$, respectively; high exposure with or without PrEP: $p = .18$ and $p = .86$, respectively), which highlights the stable high proportion of sexual intercourses protected either PrEP, condom or both, around 83.3% (min: 70.4%, max: 89.2%).

Table 1. Main characteristics of the study sample participants at baseline (ANRS IPERGAY trial, $n = 400$).

	Median [IQR] or *n* (%)
Age	34.9 [29.2–42.8]
Educational level	
<high school	112 (28.1)
≥high school	287 (71.9)
Active employment[a]	
Yes	334 (84.6)
No	61 (15.4)
Median number of sexual intercourses (previous 4 weeks)	10 [5–16]
Median number of sexual partners (previous 2 months)	8.3 [5–17]
Condomless last anal intercourse (insertive or receptive)	241 (71.7)
Condomless last RAI	148 (71.2)

[a]Four missing values.

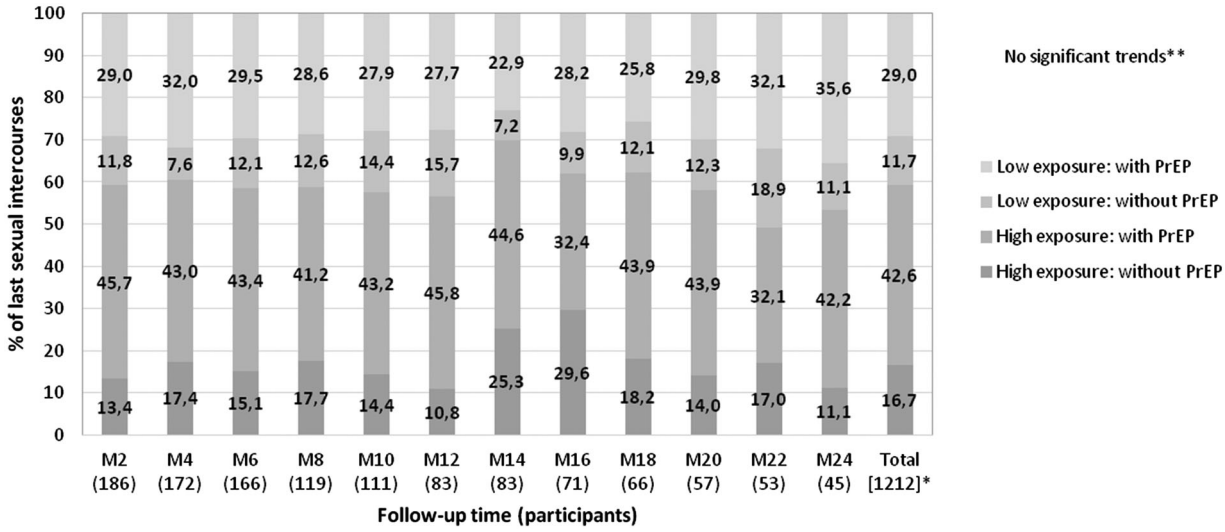


Figure 1. Condom and/or PrEP use reported during the last sexual intercourse (ANRS IPERGAY trial, $n = 320$ participants with at least one analyzable questionnaire between M2 and M24, corresponding to 1212 sexual intercourse analyzed). *Low exposure*: anal sex with condoms or oral sex; *high exposure*: condomless anal sex. *Total: corresponds to the number of sexual intercourses analyzed among the 320 participants between M2 and M24. **Trends were tested for each category: low exposure with PrEP ($p = .49$); low exposure without PrEP ($p = .38$); high exposure with PrEP ($p = .18$); high exposure without PrEP ($p = .86$).

Use of PrEP according to the protocol recommendations

Two hundred and fifty nine participants with available questionnaires between M2 and M24 reported at least once the use of PrEP during most recent episodes of anal sexual intercourse, corresponding to 731 analyzable anal sexual intercourses. We found that correct use of PrEP accounted for 59.0% (min: 47.2–max: 68.5%) on average of the total number of reported episodes, suboptimal use accounting for the remaining 41.0% (31.5–52.8%) (Figure 2). This primacy of reported correct use of PrEP throughout the follow-up period, with no significant trend of the pattern over time (Figure 2, $p = .50$).

Sexual behavior

The longitudinal analysis of the trend of the median number of episodes of sexual intercourse (previous 4 weeks) and the median number of sexual partners (previous 2 months) was performed on the 400 participants included in the present analyses since the follow-up for these indicators started at M0. The median number of episodes of sexual intercourse in the previous 4 weeks remained stable for participants at M0 (median [IIQ] = 10 [5–16]) and M24 (median [IIQ] = 10 [5–20]) with a pattern describing a not-significant trend in the median number of episodes of sexual intercourse ($p = .35$, Figure 3(A)). More fluctuating patterns were observed for our pooled sample with respect to the median number of sexual partners (Figure 3(B)), with a tendency to decrease ($p = .19$) being observed over follow-up, and principally between M2 (10 [4–16]) and M22 (6 [3–17]). We found that condoms were not used in 70.3% (65.3–79.4%) of the most recent episodes of anal intercourse (insertive or receptive). The pooled sample did not show significant trend during follow-up ($p = 0.91$, Figure 3(C)). With respect to RAI, condoms were not used in 69.3% (58.3–75.4%) of most recent episodes. This proportion seemed to remain stable during follow-up, as the trend was not significant ($p = .71$, Figure 3(D)).

Discussion

The ANRS IPERGAY trial, which provides a sexual activity-based PrEP in high-risk seronegative MSM, demonstrated a high protection level against HIV infection (Molina et al., 2015). The present analysis showed that a majority of MSM in the ANRS IPERGAY trial used one of its prevention tools (PrEP and condoms) during sexual intercourse and no increase in at-risk sexual practices was observed during the randomized phase of the study. An interesting finding is the tendency towards decrease in the median number of sexual partners. Several different factors may explain this decrease. Participant's perceptions/beliefs about whether they were taking PrEP or the placebo, as well as the individual-centered risk-reduction counseling, may have had an impact on their sexual behavior. Further analyses will allow us to measure the influence of these

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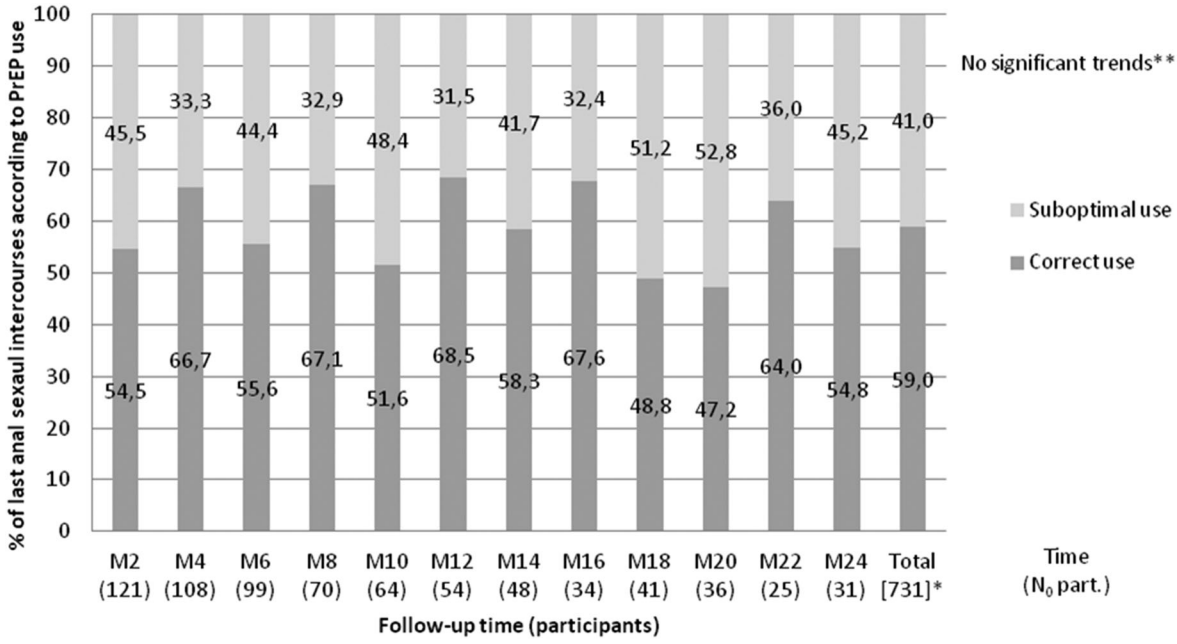


Figure 2. Use of PrEP, reported during the last anal sexual intercourse (ANRS IPERGAY trial, n = 259 participants with at least one analyzable questionnaire between M2 and M24; all of them reported at least on recent episode of anal sexual intercourse protected by PrEP use, corresponding to 731 anal sexual intercourses analyzed). *PrEP correct use*: according to protocol or taking at least 1 pill within 24 h before *and* 1 pill within 24 h after sex; *PrEP suboptimal use*: taking at least 1 pill 48 h before *or* 48 h after sex. *Total: corresponds to the number of anal sexual intercourses protected by using PrEP analyzed among the 259 participants between M2 and M24. **Trends were tested for each category: suboptimal use (p = .50); correct use (p = .50).

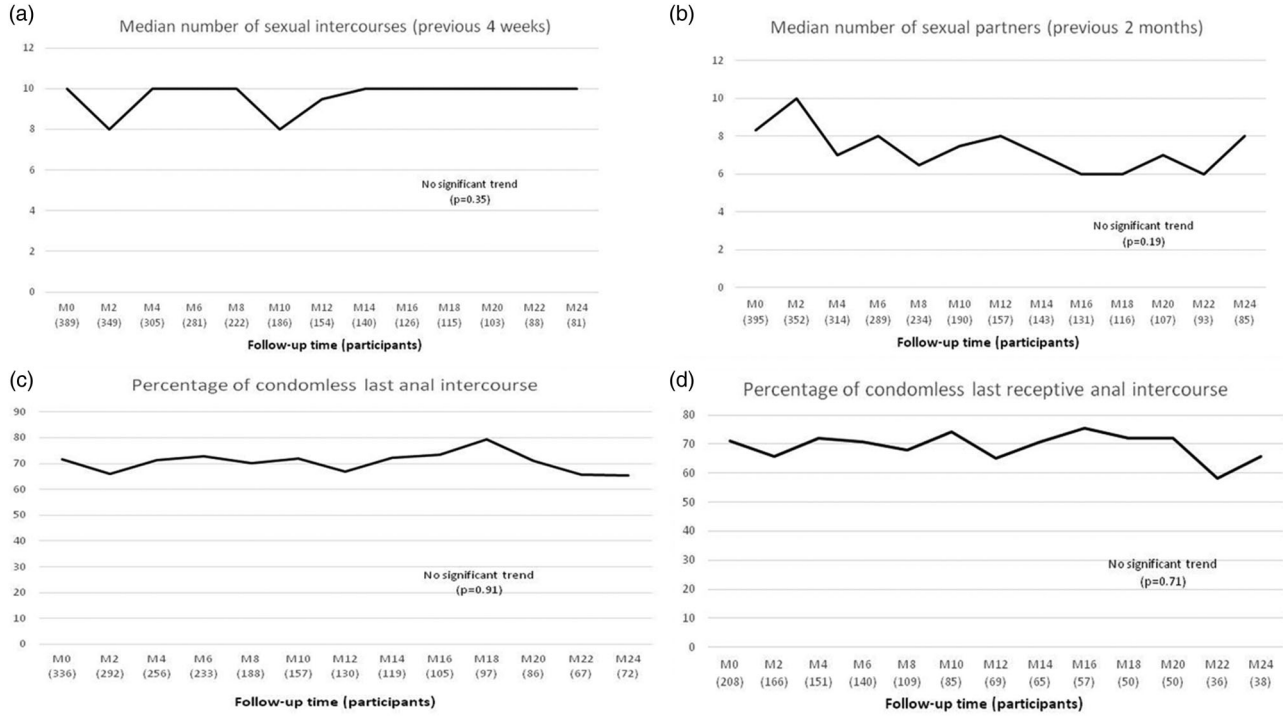


Figure 3. Evolution of median number of sexual intercourse (A), sexual partners (B), condomless last insertive or receptive anal intercourse (C), and condomless last RAI (D) over time (ANRS IPERGAY trial, n = 400 participants).

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socio-behavioral factors on MSM decisions about their sexual health. Data on socio-demographic characteristics revealed that most of the MSM enrolled in the ANRS IPERGAY trial had quite a high education level and were employed, suggesting a good level of knowledge about HIV transmission and prevention strategies. Furthermore, given its innovative nature, ANRS IPERGAY may have attracted MSM who were more aware of the debates surrounding PrEP and/or of results from earlier clinical PrEP trials. Accordingly they do not represent the gay community at large. This may be a common feature of people who choose to participate in clinical research trials, and who may not represent the diversity of affected communities – especially MSM – who might be interested in PrEP use in the real life.

PrEP uptake and/or condom use was reported for over 80% of most recent episodes of sexual intercourse, with a stable pattern without significant trend during the follow-up. PrEP adherence was high, since correct or suboptimal intake was reported for approximately 60% of most recent episodes. To date, all PrEP trials focusing on different at-risk populations including MSM, heterosexual couples, women, and intravenous drug users (IDU) have shown a dose–response relationship between PrEP adherence and protection against HIV transmission (Baeten et al., 2012; Choopanya et al., 2013; Grant et al., 2010; Haberer et al., 2013). As in the Thai IDU PrEP study (Choopanya et al., 2013), the ANRS IPERGAY trial also proposed individualized risk-reduction and counseling (Molina et al., 2015). At each scheduled visit, peer counselors offered a comprehensive package of prevention services, including individual-centered interactive risk-reduction counseling according to the Respect model (Kamb et al., 1998). Moreover, they were also available to meet participants between scheduled visits, if the latter desired. This individualized support might have had a positive impact on retention in the study, as illustrated by the low discontinuation rate observed (12%, Molina et al., 2015) but also on the high level of adherence observed, as demonstrated by pill count, plasma drug level dosage (Molina et al., 2015), and self-reported PrEP use (present results).

Our findings are consistent with other studies showing a similar lack of disinhibition in at-risk practices after initiation of a biomedical prevention strategy within a clinical trial (Baeten et al., 2012; Grant et al., 2010; Guest et al., 2008; Liu et al., 2013; Marcus et al., 2013). The present results were obtained with data collected during the double-blind randomized phase of the ANRS IPERGAY trial, which may have impacted participants' social behavior since they did not know in which arm they were randomized. Another explanation might be that the absence of sexual risk behavior decrease reflects a relative risk compensation difficult to measure since the trial enrolled high-risk MSM. Our results are also in line with those from the PROUD open-label randomized trial which showed no increase in STI, and a high level of protection against HIV infection in MSM immediately prescribed PrEP upon inclusion vs. those for whom prescription was deferred (McCormack et al., 2015). The main difference between PROUD and ANRS IPERGAY trials is that the former utilized a daily PrEP schedule in an open-label phase, the latter a schedule based on sexual activity in a double-blind phase.

Since all the studies highlighted above, including IPERGAY, offered medical staff and/or peer counselors support to participants, it remains difficult to disentangle the relative impact of the PrEP schedule and the individualized support on adherence and on evolution of sexual risk behavior. It has been clearly demonstrated that adherence depends on the quality of the proposed support. Qualitative analyses of data from the iPrEx trial's participants in San Francisco (Gilmore et al., 2013) and Thailand (Tangmunkongvorakul et al., 2012) provided insights into their experience and the individual and contextual factors influencing PrEP use. Among psychosocial factors, quality of health care and the relationship with clinical research staff, as well as individual-centered counseling were all described as facilitating adherence to PrEP, whereas changes in lifestyle routine, side effects, and social stigma were barriers to it. The added value of the ANRS IPERGAY trial was to propose peer-based individualized counseling, included into the comprehensive care package, a strategy which might have helped reinforce participants' motivations to adhere to the treatment schedule. Further analyses are required to measure the effect of individualized counseling on risk behaviors.

The results of the ANRS IPERGAY trial led the data and safety monitoring board to recommend discontinuation of the placebo arm and to offer sexual activity-based PrEP to all participants in an open phase of the trial. There are currently scarce data, outside clinical trials, exploring the impact of PrEP on adherence and on sexual practices of users. A recent qualitative analysis, nested in the ongoing US PrEP demonstration project in MSM, showed that PrEP uptake is being integrated into existing US prevention strategies in this population (Carlo Hojilla et al., 2015). The first results from a PrEP trial in a US clinic, outside of a research setting, have shown the absence of new HIV infection in participants – despite a high rate of STIs – as well as a stable or decrease in the number of sexual partners, and stable or increased condom use in a majority of participants (Volk et al., 2015). Behavioral measures in open-label extension phases of successful PrEP trials will provide useful further information on adherence and changes in sexual

practices in more real-life settings. Furthermore, since results from clinical trials have proved that PrEP can now be considered an integral part of HIV combination prevention, there is a need to develop optimal evidence-based biomedical and behavioral strategies to achieve maximum benefits at a population level.

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